Rheumatology in Questions

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Preface

Rheumatology is a medical specialty which provides diagnosis, treatment, and follow-up of patients suffering from diseases which can affect, in addition to the musculoskeletal system, every organ of the human body. Therefore, the specialists of this medical field should be adequately trained in all internal medicine fields. On the other hand, physicians from almost all medical specialties should be able to recognize particular manifestations of rheumatic disorders and refer the patient to a rheumatologist in order to institute the appropriate therapeutic modality. In addition, a rheumatologist should be able, after adequate training, to critically evaluate the results and limitations of the immunology laboratory tests. The diagnosis, classification, and definition of prognosis of inflammatory/autoimmune (connective tissue) diseases are assisted by the presence or absence in the serum of antibodies directed against self-antigens (autoantibodies), as well as by the levels of complement and/or other acute phase proteins. Furthermore, the progress of molecular immunology helped to dissect the pathobiology of connective tissue disorders and the identification of critical molecules in the arena of immune-mediated tissue damage in these disorders. Biotechnological development of inhibitors of the identified critical pathogenetic molecules has significantly improved the therapeutic armamentarium of rheumatologists.

The goal of this book is the self-evaluation of rheumatology knowledge of medical students; physicians in internal medicine, rheumatology, physical/rehabilitation medicine, family practice, and orthopedic surgery training; and specialists in practice who desire to refresh their knowledge in the field.

Having the privilege for decades, to preside the Board of Rheumatology in Greece, I have collected questions which were used in the board examinations to evaluate the knowledge of rheumatology candidates. Dr. Evangelia Zampeli, a young contemporary medical doctor, has developed additional questions from the point of view of a recently specialized rheumatologist, in an effort to bridge classical and current evidence-based knowledge in the field with their application in the specialty training. Furthermore, she went carefully over all questions and answers. Professor P. G. Vlachoyiannopoulos, MD, a long-time collaborator, has developed questions and answers addressing basic immunological issues valuable for rheumatologists. All these different questions and their corresponding answers, divided in nine main sections, constitute this handbook.

It should be emphasized that the manual you hold in your hands cannot replace the knowledge that the rheumatologist should gain from studying

rheumatology textbooks or new knowledge published in the journals of the field. Nevertheless, we hope and believe that this manual will be a useful tool for education and continuing learning for physicians of different fields and will fulfill an unmet need in the rheumatology literature.

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Introduction

The manual entitled *Rheumatology in Questions* addresses in the form of questions and answers manifestations of the musculoskeletal system as well as of other organs, differential diagnosis, laboratory and imaging tests, pathology pictures, therapeutic interventions, drug mode of action, and undesired side-effects. Since the etiology of inflammatory/autoimmune (connective tissue) diseases is mediated through the attack of the immune system against self-antigens, two sections with relative questions and answers are included in the manual. One addresses pathogenetic and autoimmune manifestations of the inflammatory/autoimmune diseases and the other summarizes basic immunology knowledge. We believe that the information given in these chapters will help the readers to better comprehend immune-pathogenic mechanisms operating in the expression of inflammatory/autoimmune diseases. Since manifestations of rheumatic diseases are often expressed in the skin, oral mucosa, eyes, and ears, a separate section is devoted to these manifestations. References are provided only for answers providing information which cannot be found in the classical textbooks of rheumatology.

To further reinforce the didactic goal of this manual, representative photos presenting clinical manifestations, imaging findings, and histopathologic features are presented close to the corresponding questions.

Closing this short note, we would like to thank Niki M. Moutsopoulos, DDS, PhD, a mucosal immunologist at the NIH, for reviewing the "Basic Immunology" chapter and Professor Fotini N. Skopouli, MD, FRCP (London), internal medicine/immunology specialist, for reviewing all chapters of the book and for their valuable suggestions and comments. Furthermore, we would like to express our gratitude to Professors M. C. Dalakas, A. A. Drosos, E. Seyahi, F. N. Skopouli, A. G. Tzioufas, and P. V. Voulgari and Drs. C. Kampolis and S. Plastiras for providing photos of their patients and/or their biological materials. Last but not least, we would like to thank our patients who gave us permission to take photos of their clinical manifestations.

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Part I

An Introductory Approach to Autoimmune Disorders

Basic Immunology

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Abstract

Immune system provides the mechanisms for attacking foreign invaders, eliminating autologous toxic substances and offering self-tolerance.

A reductionist approach of the immune system components and their interactions as provided in this chapter will offer knowledge important to better understand the core mechanisms of autoimmune diseases and design therapies targeting their pathogenetic mechanisms.

Immunity is divided into (a) innate (or natural), implemented by macrophages, dendritic cells, granulocytes (neutrophils, basophils, and eosinophils), natural killer cells, the complement system, and the acute-phase proteins, and (b) adaptive, implemented by B and T cells. Immune cells express sensors on cytoplasmic or endosomal membranes or in the cytoplasm, called "pathogen-associated molecular pattern receptors" (PAMPRs), also called pattern recognition receptors (PRRs), and damage-associated molecular pattern receptors (DAMPRs) to sense foreign invaders or damaged tissues and provide defense against them. Natural immunity cells provide a first line of defense, usually successful in eliminating pathogens, but also they limber up the adaptive immune system to take action in case of any failure of defense. The sensors of B and T cells are their antigen receptors (immunoglobulins and T-cell receptors, respectively) which are dissimilar to each other in terms of specificity; each receptor recognizes very specifically one antigen and especially a few peptide residues on it (epitope). However, by taking as a whole the pool of lymphocytes, their receptors offer a vast array of specificities exceeding 10^{11} that is more than the genes of the human body. This implies that not particular genes but rather gene fragments are spontaneously rearranged to make an immunoglobulin or a T-cell receptor gene. One such rearrangement for each peptide chain of the receptor is allowed, so the cells will retain their antigenic specificity as long as they live. Immune cells communicate with each other and approach their targets, either by cell to cell contact using adhesion molecules or by soluble mediators known as cytokines or chemokines, respectively.

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Mechanisms like central (taking place in bone marrow and thymus) and peripheral (taking place in the lymph nodes) tolerance ensure that the immune system will not attack self. Braking of tolerance initiates autoimmune reactivity which may be subclinical but, under certain circumstances, may obtain a clinical phenotype.

1. **Which are the primary and secondary lymphoid organs?**

   Primary or central lymphoid organs are those where lymphocytes are originally generated and educated to discriminate self from non-self; these include the bone marrow and thymus. **Secondary or peripheral lymphoid organs** are the lymph nodes, the spleen, and the lymphoid tissues of the gut, upper and lower respiratory tract, urogenital system, other mucosae, and arteries. Lymphocytes in these tissues are educated to react appropriately to foreign antigens.

2. **Which are the components of the innate immune system?**

   The innate immune system is constituted from:
   - Physical barriers: epithelial surfaces of skin, eye, oral, nasopharyngeal, respiratory, and gastrointestinal tracts
   - Mucosal secretions: sweat, tears, saliva, and gastric acid
   - Antimicrobial peptides, e.g., defensins
   - Pathogen-associated molecular pattern receptors (PAMPRs)
   - Damage-associated molecular pattern receptors (DAMPRs)
   - Cells: polymorphonuclear leukocytes, macrophages, dendritic cells, natural killer cells, and mast cells
   - Proteins: acute-phase proteins, e.g., complement proteins and C-reactive protein
   - Cytokines and chemokines

3. **Which are the main functions of the innate immune system?**

   The innate immune system is evolutionary the oldest defense body mechanism. The immune response that it generates is rapid yet not highly specific, and does not generate an immunological memory.

   Its main functions are:
   - Removal of dead cells and foreign invaders via phagocytosis (macrophages, polymorphonuclear leukocytes, etc.).
   - Recruitment of immune cells of the adaptive immune response.
   - Activation of the complement system cascade which promotes clearance of the foreign invaders, necrotic cells, as well as antigen-antibody complexes.
   - As long as the cells of the innate immune system phagocytose foreign invaders, they present antigens, acting as antigen-presenting cells, to the cells of the adaptive immunity and initiate specific immune responses.

4. **How do innate immune cells recognize foreign invaders?**

   Cells of the innate immune system following exposure to bacterial or viral antigens ingest the foreign pathogen by phagocytosis and structurally conserved microbe-associated molecules, known as pathogen-associated molecular patterns (PAMPs), are recognized by an array of specific sensors present in the plasma, plasma membranes, and host cytosol termed pattern recognition receptors (PRRs). The first classes of cellular PRRs to be identified were the transmembrane sensors called Toll-like receptors (TLRs). The nucleotide oligomerization domain (Nod)-like receptors (NLRs) and the retinoid acid-inducible gene-I (RIG-I)-like receptors (RLRs) are intracellular cytosolic sensors of PAMPs and danger-associated molecular patterns (DAMPs). RLRs are helicases that sense primarily viruses. NLRs can cooperate with TLRs and orchestrate the

inflammatory and apoptotic response. TLRs are expressed on macrophages, dendritic cells, natural killer (NK) cells, B and T lymphocytes, as well as non-immune cells like epithelial and endothelial cells as well as fibroblasts. In humans, 11 TLRs have been identified. Each TLR recognizes different ligands:

TLR1: bacterial lipopolysaccharides
TLR2: bacterial peptidoglycans
TLR3: viral ds-RNA
TLR4: Gram-negative bacteria and host cells
TLRs 5 and 11: *Toxoplasma gondii*
TLR6: mycoplasma
TLRs 7 and 8: ss-RNA
TRL9: DNA of viruses and bacteria

5. **Which is the function of natural killer cells?**

Natural killer (NK) cells control the spread of several types of tumors and viral infections and thus limit the tissue damage. It has been recently shown that NK cells can also play a regulatory role by interacting with dendritic cells, macrophages, endothelial cells, and T cells. NK cells can thus limit or exacerbate immune responses.

6. **Which are the subsets and functions of innate lymphoid cells?**

Recently, innate lymphoid cells (ILCs) were described as a branch of lymphoid lineage. They reside in tissues and are found in abundance in the intestinal lamina propria. Three major subsets of ILCs have been recognized: ILC1, ILC2, and ILC3. The characterization of the three ILC subsets was based on their cytokine production profile. ILC1 subset, as well as NK cells, produces interferon-γ; ILC2 produces IL-5, IL-6, and IL-13; and ILC3 produces IL-17 and IL-22. Thus, their cytokine profile is similar to cytokine profiles of T helper (Th)1, Th2, and Th17/22 lymphocytes. Unlike T and B cells, ILCs do not express antigen-specific receptors derived from recombination-activating gene (RAG)-dependent gene rearrangements and are activated by cytokines produced by other innate immune cells as well as epithelial cells. Recent data suggest that ILCs exist in three differentiation stages as immature, naive, and primed. The immature ILCs express the CD5 molecule, the naive ILCs express the CD45RA molecule, while the primed ILCs express the CD45RO molecule. The ILC subsets have the ability to change phenotype and function according to the signals they encounter in the tissue they reside. The ILCs in addition to their traditional function as antimicrobial cell population play significant role in maintaining tissue homeostasis and as regulators of metabolic processes [1].

7. **Which are the maturation, differentiation, and function of human mast cells?**

Mast cells develop in the bone marrow but migrate as immature precursors that mature in peripheral tissues, especially in the skin, the intestines, and the mucosae of the airways. This cell population is part of the first-line host defense against pathogens that enter the body across epithelial barriers. They are also involved in IgE-mediated allergic responses, since they carry a high-affinity Fc receptor for IgE immunoglobulin but remain inactive until at least two molecules of surface IgE will be cross-linked by binding the antigenic determinants of an allergen.

Mast cells are thought to serve at least three important functions in host defense. First, due to their location near body surfaces, they are able to recruit antigen-specific lymphocytes and nonspecific effector cells, such as neutrophils, macrophages, basophils, and eosinophils, to sites where infectious agents are most likely to be encountered by the host. Second, by recruiting inflammatory cells, they cause intense inflammation which results in increasing the flow of lymph from sites of infection to the regional lymph nodes, where naive lymphocytes are first activated. Third, mast cell-derived leukotrienes (LTs) such as LTC4, LTD4, and LTE4 trigger muscular contraction and contribute to the physical elimination of pathogens from the lungs or the gut.

8. **Which mediators are released from human mast cells?**
   - Reactive oxygen species (ROS)
   - Preformed mediators stocked in the granules: serine proteases (chymase and tryptase), histamine, heparin, serotonin, and ATP
   - Lysosomal enzymes: β-hexosaminidase, β-glucuronidase, and arylsulfatases
   - Newly formed lipid mediators (eicosanoids): prostaglandin D2, leukotriene C4, thromboxane, and PAF (platelet-activating factor)
   - Cytokines: tumor necrosis factor-α (TNF-α), basic fibroblast growth factor (BFGF), stem cell factor (SCF), IL-4, and chemokines

9. **Which are the complement proteins, their production and function?**

   The complement system includes over 30 proteins and/or protein fragments. These proteins or their fragments are in the serum, serosal cavities, and cell membranes. They are generally synthesized by the liver and normally circulate as inactive precursors (pro-proteins). They constitute around 10% of the serum γ-globulins.

   At sites of infection or inflammation, the complement system is sequentially activated through an enzyme-triggered cascade. The complement system, in order to perform its actions, is activated on large surfaces such as pathogen walls or large immune complexes, through three different ways: the **classical**, the **alternative,** and the **lectin pathways**. These pathways depend on different molecules for their initiation:
   - The **classical** pathway involves complement components C1, C2, and C4 and is activated from antigen-antibody complexes binding to C1, which itself has three subcomponents C1q, C1r, and C1s. The pathway forms a C3 convertase (C4b2a), which splits C3 into two fragments: C3b (attaches to the surface of microbial pathogens and opsonizes them) and C3a (activates mast cells to release vasoactive substances such as histamine).
   - The **alternative** complement pathway is activated by lipopolysaccharides on microbial cell surfaces in the absence of an antibody. It can also be triggered by foreign materials and damaged tissues. IgA complexes and the C3 nephritic factor (an autoantibody of C3 convertase) can also activate this pathway. It involves different factors (B, D, H, and I) which interact with each other and with C3b, to form a C3 convertase (C3bBb), which in turn activates more C3, leading to an amplification loop.
   - The **lectin** pathway is activated by the binding of mannose-binding lectin (MBL) to mannose residues on the pathogen surface. This further activates MBL-associated serine proteases, which activate C4 and C2, to form a C3 convertase (C4b2a).
   - The final lytic pathway is initiated by the splitting of C5 into C5b. C6, C7, C8, and C9 unite with C5b forming the membrane-attack complex (MAC), a multimolecular structure that inserts into the membrane creating a functional pore leading to cell lysis.

10. **When do antibody complexes lead to complement activation?**

    Large complexes are formed in great antibody excess and are rapidly removed from the circulation by the mononuclear phagocyte system and are therefore relatively harmless. The pathogenic complexes are of small or intermediate size (formed in slight antigen excess), which bind less avidly to phagocytic cells and therefore circulate longer. The mononuclear phagocyte system normally filters out the circulating immune complexes. Persistence of immune complexes in the circulation and increased tissue deposition occurs when macrophages are overloaded or have an intrinsic dysfunction. In addition, several other factors, such as charge of the immune complexes (anionic versus cationic), valency of the antigen, avidity of the antibody, affinity of the antigen to various tissue components, three-dimensional (lattice) structure of the complexes, and hemodynamic factors, influence the tissue deposition of complexes.

11. **Which are the key regulators of the complement system?**
    - C1 inhibitor: promotes dissociation of C1r2s2 from C1q
    - C4bBP: blocks the formation of C3 convertase in the classical pathway
    - Membrane cofactor protein: blocks C3 convertase in both classical and alternative pathways
    - Decay-accelerating factor: is anchored on cell membranes and promotes C3 convertase dissociation in both classical and alternative pathways

12. **Which one of the activated complement components acts as vasodilator and which as chemoattractant?**

    Proteins C3a, C4a, and C5a act as "anaphylatoxins." They can trigger the degranulation of mast cells and basophils to release histamine resulting in increased vascular permeability and augmented inflammation. In addition, C5a is a powerful chemoattractant for neutrophils and stimulates their degranulation. C5a and C3a also upregulate adhesion molecule expression on endothelial cells.

13. **What is opsonization?**

    Opsonization is an immune process through which specific IgG antibodies or the C3b complement component (acting as an opsonin) bind to the surface of the foreign invader or the necrotic parts of host cells and the complex is being uptaken from the phagocytes through their Fc or C3b receptors (Fig. 1.1).

14. **Which cells can act as antigen-presenting cells (APCs)?**

    Macrophages, dendritic cells, and B lymphocytes can act as professional APCs. The expression of MHC class II molecules along with co-stimulatory molecules and pattern recognition receptors (PRRs) is a defining feature of professional APCs. The nonprofessional APCs include all nucleated cell types in the body and typically express MHC class I molecules.

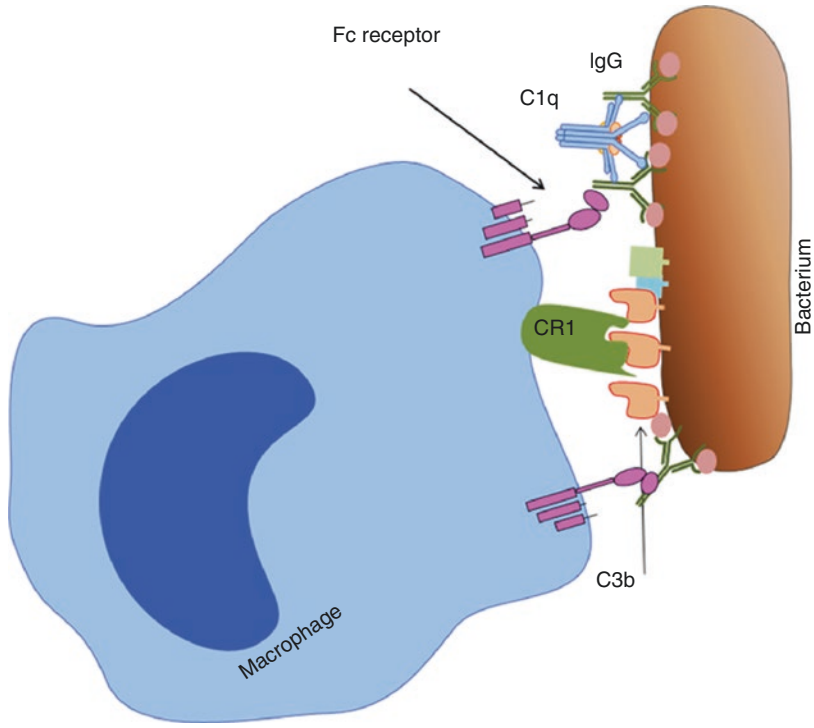

Fig. 1.1 Opsonization**:** Bacteria opsonized by immunoglobulins and C3b complement component are phagocytosed when the Fc portion of antibody and C3b bind to their receptors on the surface of phagocytes

15. **Which cell populations express HLA class I alloantigens and which HLA class II?**

HLA class I molecules: are expressed on nearly all nucleated cells of the body. The antigens they present are peptide fragments endogenous to the cytoplasm of the cell expressing the MHC molecule, and they present them to $CD8^+$ T cells. The resultant T-cell response is cell-mediated killing or suppression of the MHC class I-presenting cell.

HLA class II molecules: are expressed on professional APCs such as dendritic cells, B cells, monocytes/macrophages, and any other activated APCs. The antigens they present are peptide fragments present in lysosomal compartments as a result of phagocytosis or receptor-mediated endocytosis (e.g., bacterial material), and they present them to $CD4^+$ helper T cells. The resultant T-cell response is phagocytic and/or antibody response to eradicate the antigen presented.

16. **Which are the components of the adaptive immune system?**

Main components of the adaptive immune system are two subsets of leukocytes, the T and B lymphocytes; B cells and T cells are derived from the same multipotent hematopoietic stem cells and morphologically are indistinguishable from one another until after they are activated. These cell populations constitute the 20–40% of white blood cells (WBCs); their total mass is about the same with that of the brain or the liver. The majority of lymphocytes are in the lymphoid organs and in the tissues. B lymphocytes, through their products the immunoglobulins, play a major role in humoral immune responses and also can function as antigen-presenting cells. T lymphocytes are the major players in cell-mediated immune responses. The adaptive immune response is relatively slow yet highly specific, and additionally it creates immunological memory; in other words, after an initial response to a specific pathogen, the next encounter with the same antigen leads to an enhanced response to that antigen.

17. **Which are the steps of T-lymphocyte maturation and differentiation?**

T lymphocytes mature and differentiate in the thymus during an antigen-independent stage and later in the peripheral lymphoid organs during an antigen-dependent stage. Distinct stages of maturation and differentiation of T cells in the thymus are marked by the presence of surface molecules, namely, T-cell antigen receptor, CD3 protein complex (which acts as an adaptor to T-cell receptor), and the co-receptors, CD4 and CD8. More details on the developmental stages of T cells are the following:

(a) Upon arrival from the bone marrow, T cells are negative for the T-cell antigen receptor and also negative for CD3, CD4, and CD8 surface molecules; these are called "double-negative T cells" or "double-negative thymocytes." These T cells are still pluripotent.

(b) The double-negative thymocytes give rise to two different cell populations that can be distinguished from each other on the basis of the type of T-cell antigen receptor: the $CD3^+$ $CD4^-CD8^-\gamma\delta$ T cells, which are a minority; these cells possess a T-cell receptor constituted of γ- and δ-chains (the repertoire of these chains is limited); however, the majority of thymocytes become $CD3^+$ $CD4^+$ $CD8^+\alpha\beta$ T cells ("double-positive" αβ T cells).

(c) The $CD3^+$ $CD4^-CD8^-\gamma\delta$ T cells move to the mucosal tissues. The double-positive αβ T cells remain in the thymus, enlarge, and continue to divide.

(d) The large double-positive αβ T cells undergo a stage of small, resting double-positive αβT cells. These cells initially express low levels of αβ T-cell antigen receptors. Most of these cells fail to recognize molecular complexes constituted of self-peptides bound to self-MHCs, and these cells die in the thymus. This process is called "positive selection."

(e) The small double-positive αβ T cells whose receptors recognize molecular complexes constituted of self-peptides bound to self-MHCs ("positively selected" cells), lose either the CD4 or the CD8 coreceptors, and become "single-positive αβ T cells."

(f) During the double-positive stage, but also after that, thymocytes which recognize with high affinity molecular complexes of self-peptides bound to self-MHCs die, and the surviving cells are capable of responding to foreign antigens. This process is called "negative selection."

(g) At this stage rearrangement of α-chain locus begins and the level of expression, as well as the repertoire of surface αβ T-cell receptor, increases. Thymocytes are now either $CD3^+$ $CD4^+$ $CD8^-$αβ T cells or $CD3^+$ $CD8^+$ $CD4^-$αβ T cells, which continue to mature inside thymus for a while and then exit to periphery. These cells are called naive cells since they have not yet recognized an antigen.

(h) Upon recognition of foreign antigen in peripheral lymphoid organs, $CD4^+$ as well as $CD8^+$T cells are differentiated to effector T cells; these are capable of leaving peripheral lymphoid organs and act within tissues.

18. **Which are the main subsets and functions of T lymphocytes?**

T-lymphocyte subsets are:

(a) *$CD3^+CD4^-CD^-$ γδ T cells* home to mucosal tissues. They serve as an early-stage defense mechanism in mucosal surfaces. The actual diversity of γδ T-cell receptor is very limited. They are triggered by alarm signals such as heat shock proteins and several metabolites of pathogenic bacteria. Some subsets of $CD3^+CD4^-CD^-$ γδ T cells do not require antigen presentation through MHC, resembling thus cells of the innate immune system. Yet, they have functions, particularly related to tissue homeostasis and wound healing.

(b) *$CD8^+$ T cells*. These cells are also called "cytotoxic T lymphocytes (CTLs)." They recognize cells infected by viruses (target cells). The target cells express MHC class I molecules in complex with viral antigens. CTLs kill them through a process called apoptosis. $CD8^+$ T cells in order to kill the target cell and reduce the burden of virus release molecules such as perforins, granzymes, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) and express on their surface Fas ligand (Fas-L). Perforins are molecules which penetrate the membrane of infected cells; they are polymerized making holes in the membrane, while granzymes pass through these holes and enter to the target cell; within the target cell, granzymes activate the caspase cascade which eventually leads to programmed cell death known as "apoptosis."

(c) T *helper* (*Th*)*1 cells*. They recognize foreign antigens in complex with MHC class II molecules expressed on the surfaces of professional antigen-presenting cells (APCs). These cells contribute to killing of exclusively intracellular pathogens, such as bacteria entrapped into the phagosomes (mycobacterium tuberculosis is a paradigm), as well as some viruses. The differentiation of naive T cells to Th1 phenotype is controlled by the cytokine interleukin-12 (IL-12). Cytokine signals combined with recognition of foreign antigens drive Th1 . cells to secrete IFN-γ. IFN-γ will stimulate phagocytes to fuse the phagosomes with the lysosomes making the so-called phagolysosomes and thus destroy intracellular parasites.

(d) *Th2 cells*. They primarily stimulate immune responses against extracellular pathogens but also contribute to allergic reactions through stimulation of B cells. They provide help to certain B cells in order to produce IgE antibodies. They also secrete interleukin-4 (IL-4) and interleukin-13 (IL-13). Differentiation of Th2 cells largely depends on APCs which produce IL-4 that differentiates naive T cells to the Th2 phenotype.

(e) *Regulatory T cells (T_{regs})*. These cells are generated when naive cells encounter antigen presented by cells which release transforming growth factor-β (TGF-β). These cells produce also TGF-β and IL-10 and downregulate immune responses. T_{regs} express CD4 and CD25 molecules on their surface as well as the intracellular protein FOXP3 which is a transcription factor.

(f) *Th17 cells*. These cells participate in surveillance of fungi and select extracellular bacteria as well as in the maintenance of barrier integrity. However, Th17 cells can become a pro-inflammatory cell subpopulation. Th17 cells are generated by CD4+ naive T lymphocytes when they recognize antigen expressed by a dendritic cell which produces TGF-β and IL-6. In addition to IL-6 and TGF-β, they are also stimulated by the cytokines IL-23 and IL-1β. Th17 cells contribute to autoinflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, psoriasis, and multiple sclerosis.

(g) *T follicular helper (T_{fh}) cells.* These are $CD4^+$ T cells found within B-cell follicles of secondary lymphoid organs. T_{fh} cells are identified by their B-cell follicle-homing receptor CXCR5 which is constitutively expressed on their surface. T_{fh} cells express CD40L and secrete IL-21 and IL-4. Using the above molecules, T_{fh} cells trigger the formation and maintenance of germinal centers and contribute to the differentiation of antigen-stimulated B cells to plasma cells in order to enhance antibody production.

19. **Which are the B-lymphocyte subsets and their functions?**

B-lymphocyte subsets are as follows:

Follicular B cells constitute the majority of B cells in the blood, lymph node, and spleen and are antibody-producing cells with a great array of specificities. They express surface immunoglobulins with a highly diverse array of specificities; they express also Fc receptors, MHC class II, as well as the surface molecules CD19 (a cell surface molecule in close junction with B-cell antigen receptor which decreases the threshold for antigen receptor-dependent stimulation) and CD23 (also known as FcεRII – a low-affinity receptor for IgE).

Marginal zone B cells constitute the minority of B cells in the blood, lymph nodes, and spleen and are also antibody-producing cells; they serve as a first line of defense against blood-borne pathogens, which reach the marginal zones through the circulation. They express surface immunoglobulin with limited receptor repertoire. These cells exhibit mainly antigen-independent stimulation, but they are also capable of undergoing antigen-dependent stimulation.

B-1 cells predominantly reside in the peritoneal and pleural cavity, produce natural antibodies, and exhibit T-cell-independent activation. B-1 cells have been described in mice, and they overlap partially with $CD5^+$ B cells. B-1 cells have not been described in humans, but $CD5^+$ B cells exist. CD5 is a protein which reduces the severity of the activating signals derived from the B-cell receptors and makes B-1 cells to be activated by exogenous strong signals and not by signals derived from autologous tissues.

Regulatory B cells stop the expansion of pro-inflammatory lymphocytes through the secretion of IL-10, IL-35, and TGF-β while they promote the generation of T_{regs}. The specificity of regulatory B cells and the exact way they differentiate are not known.

20. **Which are the maturation and differentiation steps of B lymphocytes? Which stage is antigen independent and which one is antigen dependent? What is antibody class switching and how is it achieved by B cells?**

The stages of maturation and differentiation of B lymphocytes are recognized by (a) distinct cell surface markers, (b) a specific pattern of immunoglobulin gene expression, and (c) cytoplasmic expression of transcription factors.

Pro-B cells express CD19 and CD10 surface molecules, while they retain the CD43

surface molecule expressed during the stem cell stage. CD43 is a transmembrane cell surface sialoglycoprotein on cells from hematologic lineage and contributes to ligand-receptor-induced T-cell activation. CD10 is a zinc-dependent metalloproteinase that cleaves and inactivates several hormones. During this stage, initiation of the expression of Rag-1 and Rag-2 (recombination-activating gene) proteins and the first recombination of immunoglobulin genes at the heavy-chain locus involving the D-J segment rearrangement take place. Rag-1 and Rag-2 proteins are important factors for the V-D-J rearrangement of immunoglobulin genes. The terminal deoxynucleotidyl transferase (TdT) which catalyzes the non-templated addition of junctional N nucleotides is also mainly expressed during the pro-B stage. Finally, the first C μ-exon of the C locus of the immunoglobulin heavy chain is rearranged with the VDJ segment, and a functional mRNA for the heavy μ-chain is produced and translated to immunoglobulin μ-heavy chain. Only cells that achieve heavy-chain gene rearrangements survive. Pro-B cells do not respond to antigen.

Pre-B cells are the cells which have achieved a productive immunoglobulin μ-gene rearrangement. These cells express immunoglobulin μ-chain on their surface, but they have not rearranged gene segments of the immunoglobulin light chain. The immunoglobulin μ-chain is covalently linked to surrogate light chains, which are invariant; that means they are the same in all pre-B cells. Pre-B cells synthesize also the Igα and Igβ chains of the B-cell receptor. Pre-B cells undergo tremendous proliferation and expansion of the B-cell lineage. The signal for proliferation is not known, but this is probably the process of linking of the surrogate light chains to the immunoglobulin μ-chain. Activation of pre-B cell receptor leads to activation of Bruton's tyrosine kinase (BTK) which delivers signals for survival, proliferation, and maturation of pre-B cells, as well as of the B cells existing beyond this stage. At the pre-B-cell stage, three additional phenomena take place: (a) allelic exclusion, which means any individual B cell expresses an immunoglobulin heavy-chain protein encoded only by one of the two inherited alleles, (b) stimulation of the κ-light-chain recombination, and (c) discontinuation of the surrogate light-chain transcription. Pre-B cell expresses also two surface markers, the CD 43 protein (presented previously) as well as the CD220 protein – an insulin receptor with tyrosine protein kinase activity.

Immature B cells: these cells have already rearranged a κ-light-chain gene, and the κ-light chain associates with the μ-protein; thus, immature B cells express fully assembled IgM immunoglobulin linked to the Igα and Igβ chains of the B-cell receptor, on their surface. Production of κ-protein prevents λ-rearrangement; therefore, λ-rearrangement occurs only in case κ-rearrangement was not productive. This phenomenon is called "light-chain isotype exclusion." If both alleles of κ- and λ-chains failed to rearrange successfully, the B cell will die. The *RAG* gene expression is discontinued, and the cell prevents further rearrangement of the immunoglobulin genes. Immature B cells do not response to antigens. In case their receptors bind strongly to multivalent antigens in the bone marrow, the cells will die or sometimes they may undergo receptor editing – a process of modifying the sequence of light-chain V and J genes – so the cells are not further autoreactive and they can be rescued from programmed cell death. This phenomenon of eliminating strongly self-reactive B cells is called "negative selection." Despite negative selection, there is no complete tolerance at the B-cell level; that means there are always autoreactive B cells in the periphery, but these cells need help from an antigen-specific T lymphocyte in order to respond to a certain antigen. Immature B cells survive the negative selection, leave the bone marrow, and reside in the spleen for a while to complete their maturation before reaching peripheral lymphoid organs.

Mature B cells: these cells divide in several subsets as described previously: follicu-

lar B cells, marginal zone B cells, B1/CD5+ B cells, and regulatory B cells.

Mature B cells which belong to the follicular B-cell subset produce high levels of IgM as well as IgD immunoglobulin using the same VDJ exon and the same κ- or λ-chain to express IgM and IgD surface receptors with the same antigenic specificity. These cells still have not encounter antigen but have the armamentarium to respond to antigen and are called "mature-naive B cells." Follicular B cells receive survival signals delivered by BAFF (called also BLyS) (B-cell activator or B-lymphocyte stimulator).

Marginal zone B cells are similar to B-1 cells described in mice; they express IgM and the CD21 which is the complement C3d receptor, identical to Epstein-Barr virus receptor. Unlike to what happens in mice, CD5+ B cells in humans reside in both the spleen and the lymph nodes.

The stages of maturation of pro-B cells and pre-B cells are antigen independent. One could consider the negative selection observed at the immature B-cell stage as antigen dependent since these cells mature by encountering self antigens in the bone marrow. However immunologists agree that the word "antigen" in this context is used for exogenous antigens. Therefore antigen dependent is only the maturation of naive B cells as soon as they encounter antigens for the first time in the lymph nodes or other lymphoid tissues.

Antibody (or immunoglobulin) class switching is a biological mechanism which allows the antigen-activated B cell (which initially bears IgM surface immunoglobulin by which it recognizes the antigen), to produce immunoglobulins with the same immunoglobulin variable region, but this region is coupled to constant regions belonging to other isotypes, for instance, IgG, with the same antigenic specificity. This happens as soon as the B cell starts to proliferate after antigen recognition and presents (a) antigenic peptides coupled to MHC class II and (b) a molecule called CD40 on its surface. The above constituents are recognized by an antigen-specific T cell through its T-cell receptor and the CD40 ligand, respectively. T cell then releases a mixture of IL-4 and IL-5 which regulate immunoglobulin class switching by the B cell.

21. **In which stages of B-lymphocyte maturation and differentiation is the CD20 molecule expressed?**

The CD20 molecule is expressed on the surface of late pro-B cells and continues to be expressed through all the stages of B-cell development (pre-B, immature B, mature B cells, as well as memory B cells) but not in plasmablasts or in plasma cells. Plasmablasts are immature plasma cells, and plasma cells are the effector B cells which have been transformed to antibody-producing cells.

22. **Which initial observations led to the postulation that antibodies are generated by "constant" and "variant" genes?**

Analysis of amino acid sequence of various immunoglobulins, nearly 50 years ago, revealed that many antibodies of the same isotype shared identical sequences at their C-terminal ends, but they varied considerably at their N-terminal ends, which, as we know today, correspond to the antigen-binding sites of antibodies. This finding led to the postulation that each antibody chain is encoded by at least two genes, one for the "constant" and one for the "variant" region and these genes are combined at the DNA or RNA level constituting a "new" gene. DNA analysis in various tissues using markers of the "variant" (V) and "constant" (C) region revealed that in cells of any other origin except B lymphocytes, these regions were far away from each other within the genome and only in the B-cell DNA the V and C regions were closed, implying that during B-cell maturation and differentiation, a rearrangement of the immunoglobulin genes takes place and V and D regions are physically joint and translated to protein.

23. **Which is the organization of immunoglobulin genes and what are the mechanisms for gene rearrangement for the production of the entire immunoglobulin chains** (Fig. 1.2)?

We know today that three separate loci encode the immunoglobulin gene segments as follows: one locus for all the heavy-chain gene segments (located on chromosome 14), one for the κ-light-chain gene segments (located on chromosome 2), and one for λ-light-chain gene segments (located on chromosome 22). Gene segments lie in series at each locus from the 5′ end to 3′ end, encoding the variable (V) regions; at the 3′ end of the series of the V gene segments, there are series of gene segments encoding the so-called diversity region (D); at the 3′ end of them lie a series of gene segments encoding the so-called joining region (J); and at the 3′ end of them lie a series of gene segments encoding the constant region (C). Light chains lack D regions, but their gene segments are organized in the same fashion, as that of the heavy chains. The heavy-chain locus contains nearly 45 V gene segments each of about 300 base pairs long, the κ-locus contains 30 V gene segments, and the λ-locus contains 45 V gene segments. The κ-light-chain locus has only one C gene segment, and the λ-light-chain locus has four C gene segments; the heavy-chain locus has nine C

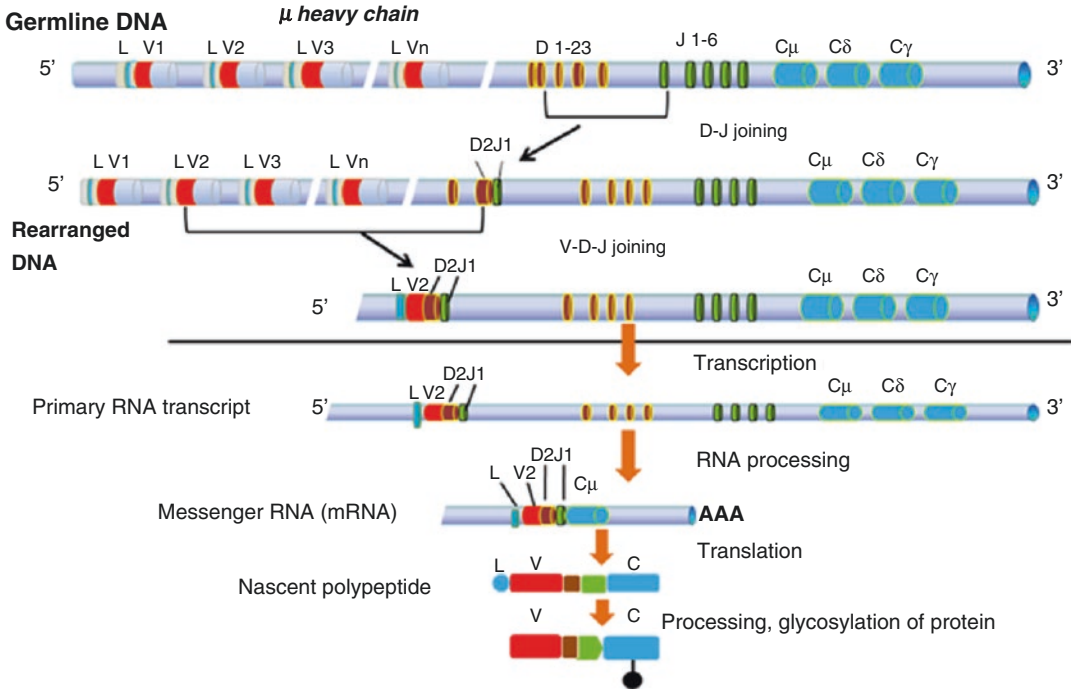

Fig. 1.2 Organization of immunoglobulin genes and mechanisms for gene rearrangement: The organization of the μ-chain gene segments is presented. Gene segments lie in series from the 5′end to 3′end, encoding the variable (V) regions; at the 3′ end of the series of the V gene segments, there are series of gene segments encoding the so-called diversity region (D); at the 3′ end of them lie series of gene segments encoding the so-called joining region (J); and at the 3′ end of them lie series of gene segments encoding the constant region. The VDJ recombination in every individual B cell involves a random selection of one V segment, one D segment (which is absent within the gene segments of the light chains), and one J gene segment to produce the VDJ exon. Therefore, a B cell may rearrange V1D2J2, another B cell may rearrange V2D3J5, etc. Every cell is capable of doing one gene rearrangement for the heavy and one for the light chain. Please note that after the VDJ gene segment rearrangement, the remaining rearrangements are performed at the primary RNA transcript level in order to produce a complete messenger RNA for the entire μ-heavy chain

gene segments each encoding one immunoglobulin isotype (IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgE, IgD). Each of the nine C gene segments is composed of five or six exons.

The VDJ recombination in every individual B cell involves a random selection of one V segment, one D segment (which is absent within the gene segments of the light chains), and one J gene segment to produce the VDJ exon. Therefore, a B cell may rearrange V1D2J2, another B cell may rearrange V2D3J5, etc. To complete the antigen-binding site, a VJ rearrangement among the light-chain gene segments should be also performed. Every cell is capable of doing one gene rearrangement for the heavy and one for the light chain; however, by taking together the whole B-cell population, a huge diversity of antigen receptors is generated. The C regions are located downstream of the rearranged VDJ exon (VJ exon for light chains) lying thousands of base pairs away. This part of the DNA is transcribed to RNA; RNA splicing contributes to deletion of the intervening RNA sequences and eventually brings together the VDJ exon (VJ exon for the light chains) with the C region exons; therefore, an mRNA is formed, which can be translated in the ribosomes to a complete immunoglobulin chain.

24. **Which is the molecular mechanism through which the gene rearrangement for immunoglobulin production operates?**

A thorough understanding of the mechanism of generation of antibody molecules needs to know the following: (a) the nature of recognition signals that drive VDJ recombination, (b) the enzymes involved in this process, and (c) the physical meaning of junctional diversity.

(a) Certain DNA sequences called "recombination signal sequences" (RSSs) are located at the 3′ end of V gene segments, at the 5′ end of each J segment, and at both ends of each D segment. RSSs are highly conserved stretches of seven nucleotides (heptamers) located close to the coding sequence followed by a spacer of 12 or 23 nucleotides also highly conserved; this is followed by a highly conserved stretch of nine nucleotides rich in AT (nonamer). Double-stranded brakes are generated between the eptamer of RSS and the adjacent V, D, or J coding sequence. For the heavy chain, for instance, a DJ recombination occurs first by properly aligning the 3′end of one D and the 5′end of one J segment. This happens because two distinct heptamers come to the right position to be aligned with each other in a way that bridges the gap between the two gene segments. The intervening double-stranded DNA is removed in the form of a circular DNA. Same mechanism operates for recombination of the V with the DJ exon.

The process of VDJ recombination can be divided into four distinct stages:

- *Synapsis*: this is the phenomenon of bringing together two selected coding segments and their adjacent RSSs by a chromosomal looping process; thus, the coding sequences are held appropriately for a recombination event.
- *Cleavage* is the generation of double-stranded brakes at the RSS-coding sequence junctions by enzymatic cleavage. This is implemented by a complex of two enzymes in which one is activated by the other and both act together; these enzymes are the products of the recombination-activating genes 1 and 2 (*RAG-1 and RAG-2*). These enzymes make nicks between coding regions and heptamers in each DNA strand, and the released 3′ OH of the coding end makes a covalent bridge to the phosphodiester bond of the other DNA strand, creating a hairpin.
- *Hairpin opening and reprocessing*: the hairpins are opened up by an endonuclease called "Artemis." Mutations of Artemis in mice are causes of disrupted maturation of

B and T cells leading to the generation of mice with severe combined immunodeficiency (SCID). After opening the hairpins, an enzyme called terminal deoxynucleotidyl transferase (TdT) adds bases to broken DNA ends and contributes substantially to a rather extent antibody diversity.

- *Joining* is the process of ligation of the open ends of hairpins after TdT-induced processing. This process is called "nonhomologous end joining." Several proteins contribute to this process, such as the proteins Ku70 and Ku80 which recruit to the open DNA ends the catalytic subunit of the enzyme DNA-dependent protein kinase (DNA-PK) which catalyzes a repair process. Mice deficient to DNA-PK are presented with the phenotype of SCID mice.

(b) The diversity of B-cell antigen receptors is attributed to two distinct processes: (a) combinatorial diversity which is attributed to the VDJ rearrangements and (b) junctional diversity which is operated by removal or addition of nucleotides at the junctions of the V and D, D and J, and V and J segments, catalyzed by the enzyme TdT as previously described.

25. **What are immunoglobulin idiotype, idiotope, paratope, and isotype** (Fig. 1.3)**?**

Idiotope is the unique set of antigenic determinants (epitopes) of the variable portion of an antibody.

Paratope is a part of five to ten amino acids of an antibody's variable region which recognizes and binds to an antigen. It contains parts of the antibody's heavy and light chains.

Idiotypes are unique genetically controlled determinants which represent the antigenic specificity of the antibody. The idiotypic determinants are located to the immunoglobulin variable region of both immunoglobulin polypeptide chains.

Isotype defines the class of immunoglobulin, as it is determined by the type of its heavy chain. Immunoglobulin isotypes are IgG1, IgG2, IgG3, IgG4, IgIgA2, IgM, IgE, and IgD. Some authors use also the term "isotype" to differentiate the types of κ- and λ-light chains.

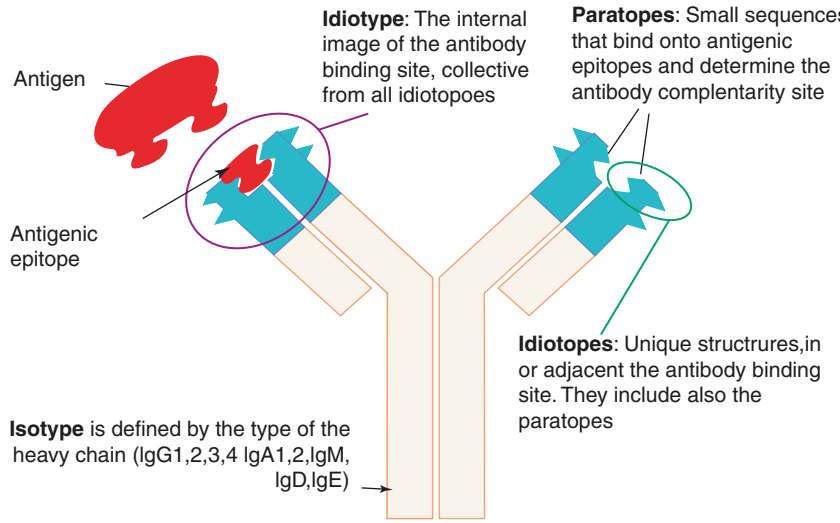

Fig. 1.3 Immunoglobulin idiotype, idiotope, paratope, and isotype: Idiotopes are unique structures in the antibody-binding site or adjacent to this site. The collection of the entire number of idiotopes in a particular site of antibody-binding structure forms the idiotype; therefore, idiotype represents the internal image of the antibody-binding site. Paratopes are small sequences that bind onto antigenic epitopes and determine the antibody complementarity site

26. **What is the function of the Fc portion of immunoglobulin?**

The Fc portion of immunoglobulins (Igs) contributes to the executive actions of antibodies; these actions are mainly dependent on the fact that many body cells possess receptors for the Ig Fc portion. The Fc functions can be classified as follows:

(a) *Transportation of Igs*:

- Polymeric IgA and IgM bind through their Fc portions to Fc cellular receptors, and they are transported across epithelial barriers.
- The Fc portion of the maternal IgG binds to the neonatal Fc receptor in the placenta and facilitates IgG transport to the fetus.

(b) *Opsonization and phagocytosis of bacteria and immune complexes*:

- Antibodies bind to bacterial cell wall polysaccharides and/or proteins and activate complement by interacting with the C1q, with the CH2 areas of the heavy Ig chains. Complement activation leads to the generation of C3b, which also binds to bacterial cell wall. This process is called opsonization. Opsonization is followed by bacterial phagocytosis which can be carried out by binding of the Fc portion of antibody and the C3b complement component to appropriate receptors on phagocytes.
- Immune complexes enable the accumulation of many antibodies together; the CH2 areas of the heavy Ig chain of the antibodies upon binding to the C1q induce complement activation and generation of C3b; subsequently, the Fc portions of Igs alone with the C3b complement component facilitate phagocytosis of immune complexes as previously described, and eventually immune complexes are destroyed.

(c) *The Fc portion of antibodies induces cellular signaling by binding to Fc receptors*:

- Antibody-coated targets bind to Fc receptors on natural killer (NK) cells and activate these cells in order to destroy the target.
- The Fc portion of IgE antibody binds with high affinity to IgE Fc receptors on mast cells and basophils and induces the release of enzymes and vasoactive amines from their granules.
- Ig Fc portion through interaction with the appropriate Fc receptors on phagocytes, in addition to bacterial uptake, induces macrophage, neutrophil, and eosinophil signaling leading to activation of the respiratory burst and induction of foreign cell killing.
- IgA and IgG which are specific for parasites are important for eosinophil binding via interaction with the eosinophil Fc receptors; then eosinophils then attack and kill parasites, by releasing toxic constituents from their granules. This process is known as "exocytosis."

27. **In which fraction of proteins do immunoglobulins belong?**

Several methods to perform serum or plasma protein fractionation exist. The most useful, easy, reliable, and clinically applicable in everyday medical practice is the serum protein electrophoresis, applied by Tiselius in 1937. Serum is applied to a trough (initiation point) on agarose gel or on a cellulose acetate membrane, and constant current is applied with a cathode to the site of the application of the serum. Serum proteins (which used to be called "globulins") are separated by their size and electrical charge through electrical forces and electroendoosmotic forces. Proteins with negative charges such as albumin migrate to the anode, while proteins with positive charges remain close to the cathode. Using this technique, serum proteins can be fractionated in the following fractions (which are depicted as separate zones in electrophoresis), from the anode to the cathode: albumin, α1 globulins, α2 globulins, β1 globulins, β2 globulins, and γ-globulins.

Immunoglobulins migrate to the area of γ-globulins and in fact constitute a large part of the γ-globulin fraction, which appears as a smooth "blush," or smear, close to the cathode. The majority of immunoglobulin mole-

cules move to the cathode, but some of them move slightly toward the anode, so immunoglobulins occupy both sides of the initiation point. IgG moves toward the cathode and occupies the largest part of the γ-globulin fraction, together with IgM and IgD. However, IgA migrates to the anode and occupies the interzone between β- and γ-globulins as well as the β globulin zone.

28. **Based on what markers can lymphocyte populations be characterized as monoclonal?**

A monoclonal T- or B-cell population is defined as a collection of cells derived from a single precursor, and therefore, these cells share common characteristics to each other and also to the precursor cell. In addition, monoclonal B or T cells derive from a pull of immature cells, and thus they may express surface molecules known as "clusters of differentiation" (CDs) which are unusual for healthy, mature cells. Light microscopy may also detect monoclonal B and T cells in case these cells possess morphological changes indicating an aggressive, non-regular phenotype. However, all these changes are suggestive of monoclonality, but they are nonconclusive. The following changes or markers – detected by various methods – indicate monoclonality:

Immunopathological methods:

B cells: a monoclonal B-cell population is defined by a monoclonal immunoglobulin on the surface of B cells. This monoclonal immunoglobulin should include only κ- or λ-light chains. Therefore, monoclonal antibodies to κ- or λ-light chains can differentiate a monoclonal B-cell population, defining B cells baring only immunoglobulins which contain exclusively κ- or λ-chains.

T cells: there is not any immunopathological method to detect monoclonal T cells.

Southern blot to detect B and T cell gene rearrangement: the Southern blot is a sensitive and specific technique to detect monoclonal B- and T-cell populations by detecting precisely the same B- or T-cell receptor gene rearrangement in a collection of B or T cells, respectively. This technique can identify even small monoclonal cell populations compared to the total number of cells under study. Samples appropriate for analysis include fresh cell supernatants, fresh body fluids, or well-preserved frozen tissue sections.

29. **Which are the T and B lymphocyte receptors?**

T-cell antigen receptors are constituted of eight transmembrane polypeptide chains termed α, β, γ, δ, ε, and ζ. Each receptor possesses one α-, one β-, one γ-, one δ-chain, as well as two ε- and two ζ-chains. Chains α and β are covalently linked to each other by a disulfide bridge between cysteine residues, close to the area of their emersion from the cell surface. Each of α- and β-chains contains one variable (V) and one constant (C) domain. Within the V domains, there are regions which differ significantly between individual T cells, and these are called "hypervariable (HV) regions" which come close to each other as the V regions of α- and β-chains are folded; eventually, the HV regions form an area which is complementary to structures constituted of complexes of antigenic peptides with major histocompatibility complex (MHC) antigens; thus, the HV regions are called "complementarity-determining regions" (CDRs). The remaining transmembrane polypeptide chains are not involved in antigen recognition, but in intracellular signaling. They are joined to each other by charged residues as follows: one ε is joined to γ, and one ε is joined to δ-chain, constituting the so-called CD3 complex, while ζ-chains are mutually joined. The CD3 complexes as well as the ζ-chains contain in their intracellular parts conserved sequences of four amino acids of which one is tyrosine; these motifs are called "immunoreceptor tyrosine-based activation motifs" (ITAMs) and facilitate signaling after interaction of the receptor with the MHC-antigenic peptide complex.

B-cell antigen receptor is constituted of membrane IgM or IgD immunoglobulins

associated with two transmembrane invariant chains called Igα and Igβ, which are joined to each other by a disulfide bridge just after their emersion from the cell surface. Thus, the B-cell antigen receptor is the surface immunoglobulin, while Igα and Igβ contain ITAMs in their intracellular domains and facilitate signaling. After class switching, B cells as well as memory B cells express IgG, IgA, and IgE class surface immunoglobulins as antigen receptor.

30. **How can B- and T-cell antigen receptors recognize millions of different antigens?**

In each individual B or T cell, a unique rearrangement of VDJ gene segments occurred and a unique antigen receptor emerged on their surface. Therefore, millions of different B or T cells exist, each expressing an antigen receptor of unique specificity. Thus, by taking B and T cells as a whole, they carry a huge diversity of antigenic receptors. As soon as a B or T cell encounters an antigen, the cell proliferates to make daughter cells identical to the precursor cell. This phenomenon is called "clonal expansion." The B cells differentiate to plasma cells and produce huge amounts of antibodies against the antigen they encountered, while T cells are transformed to "armed effectors T cells" (or simply "effectors T cells"). Then T cells express their executive actions as helper, inflammatory, or cytotoxic cells in the injured tissues. The first encounter of antigen by T and/or B cells in order to successfully activate the cells for proliferation and differentiation should take place in the lymph nodes and other lymphoid tissues because these tissues provide the appropriate "environment" for T- and B-cell activation. Indeed, the lymphoid tissues contain soluble antigens drained by infected tissues, reaching the lymph nodes through the lymphatic vessels; in addition, antigen-presenting cells, such as dendritic cells coming from peripheral tissues and resident macrophages, present antigen "appropriately" to B or T cells; this means that antigen-presenting cells, in addition to antigen presentation, express co-stimulatory molecules and cytokines and provide T or B cells with additional signals for survival, proliferation, and differentiation.

31. **Which are the mechanisms leading to the development of self-tolerance?**

An outline of self-tolerance is as follows:

Tolerance is an antigen-dependent phenomenon. This implies that when immature B or T cells encounter self-antigens in the primary lymphoid organs, such as the bone marrow and thymus, they either (a) die through apoptosis or (b) change their receptor by a mechanism called receptor editing (a process which is applicable for B cells) or (c) become regulatory; that means the cell does not further react to self-antigens (a process which is applicable for CD4+ T cells). The above processes constitute the so-called central tolerance.

In case self-reactive immature lymphocytes will be rescued from death in the thymus or bone marrow and migrate to the periphery, when they encounter self-antigens, they may (a) die through apoptosis, or (b) become anergic throughout life, or (c) be suppressed by regulatory T cells which have developed through central tolerance; (d) finally, lymphocytes may ignore some antigens in the periphery, such as antigens of the testes or the eyes, which lie in immune-privileged sites. These process constitute the so-called "peripheral tolerance."

Mechanisms in detail, inducing tolerance, are as follows:

Central T-cell tolerance:

(a) Thymic medullary epithelial cells express many antigens exposed in the peripheral tissues under the influence of a protein which acts as a transcriptional regulator and promotes the expression of many antigens of peripheral tissues to thymus. This protein is called AIRE (autoimmune regulator); in the absence of AIRE, an autoimmune polyendocrinopathy syndrome is developed, because antigen-specific T cells for endocrine gland

tissues escape central tolerance. AIRE does not explain the expression of so many antigens of the peripheral tissues in thymus, but it is a paradigm of how the system works. Central T-cell tolerance takes place in the thymus through the process of negative selection. This process affects both CD8+ and CD4+ T cells when their T-cell receptors bind with high affinity to "MHC/antigenic peptide" complexes, because in immature T cells, this high-affinity binding induces signals for apoptosis; on the contrary high-affinity T-cell receptor binding in mature cells induces signals for activation and proliferation.

(b) Another option of central tolerance is the transformation of immature CD4+ T cells in the thymus to regulatory T cells.

Central B-cell tolerance is attributed to the following phenomena: (a) B-cell receptor editing; (b) autoreactive B-cell deletion, which is not a very well-understood process; and (c) anergy, when autoreactive B cells recognize autoantigens with low affinity in the bone marrow.

B-cell receptor editing takes place when B cell recognizes multivalent autoantigens with high affinity and receive strong activating signals. In this case, the enzymes RAG-1 and RAG-2 are reactivated, and a Vκ segment upstream of the already rearranged VκJκ unit is joined to a downstream Jκ. This results to deletion of the previously rearranged VκJκ exon, and a new immunoglobulin light chain is expressed which offers a new (probably non-autoreactive specificity) to B-cell surface immunoglobulin (B-cell receptor).

32. **How does peripheral T- and B-lymphocyte self-tolerance develop?**

Peripheral T cell tolerance:

(a) When autoreactive CD4+ T cells encounter antigen in the periphery in the absence of co-stimulatory molecules, they become anergic; that is, they are not activated. There is some evidence that intracellular molecules important for T-cell receptor signaling are ubiquitinated, and the signal for T-cell activation is terminated. Another mechanism for autoreactive T-cell inactivation is the overexpression of CTLA4 surface molecule which belongs to the CD28 family, but when it binds to B7 molecules at the surface of antigen-presenting cells, it prevents B7:CD28 interaction and the T cell fails to be activated. Another molecule which belongs to the CD28 family and like CTLA4 inactivates autoreactive T cells is the PD-1. Ligands for PD-1 are expressed in antigen-presenting cells and other cells.

(b) Suppression of autoreactive T cells by Tregs. The suppressive action of Tregs is mediated by three mechanisms: (a) production of immunosuppressive cytokines IL-10 and TGF-β, (b) overexpression of CTLA4, and (c) consumption of IL-2 – a phenomenon which results in deprivation of effector T cells which also need IL-2 for survival, proliferation, and activation.

(c) Issues regarding CD8+ T-cell tolerance are not very well substantiated.

Peripheral B cell tolerance is attributed to the following mechanisms:

(a) Anergy and deletion which occurs when autoreactive B cells are repeatedly stimulated by autoantigen in lymphoid follicles. They need high levels of the growth factor BAFF/Blys; therefore they are unable to compete normal naive B cells which can differentiate with much less amounts of BAFF/Blys, and eventually autoreactive B cells become anergic or die.

(b) Inhibition of autoreactive B cells by inhibitory molecules as depicted in mice but it is not substantiated in humans. Such molecules are CD22, Lyn, and SHP-1. The ligand for CD22 is not known.

33. **Which are some examples of pro-inflammatory cytokines and the cells that produce them?**

Tumor necrosis factor-α: produced by macrophages, T cells, mast cells, and NK cells. Its main functions are increase of adhesion molecules, stimulation of the production of interleukin (IL)-1 and IL-6, activation of neutrophils, and initiation of acute inflammatory response.

IL-1: produced by macrophages, dendritic cells, neutrophils, and endothelial cells. Its main functions are increase of adhesion molecules and stimulation of hepatocytes to produce acute-phase reactants.

IL-12: produced by dendritic cells and macrophages. Its main functions are to increase IFN-γ production, transform CD4+ T cells to Th1 phenotype, and increase cytotoxic activity of NK cells and CD8+ T cells.

IL-6: produced by macrophages, endothelial cells, and fibroblasts. Its main functions are maturation of B cells and antibody production, differentiation of neural cells, and stimulation of hepatocytes to produce acute-phase reactants.

34. **Which are some examples for the function of Th1, Th2, and Th17 cells and cytokines?**

Th1 cytokines: IFN-γ, IL-2, and TNF. They are produced by CD4+ Th1 cells. Their main functions are cell-mediated immunity and phagocyte-dependent inflammation.

Th2 cytokines: IL-4, IL-5, IL-6, IL10, and IL-13. They are produced by CD4+Th2 cells and innate lymphoid cells-2 (ILC-2). Their main functions are to evoke strong antibody responses (including IgE) and eosinophil accumulation (phagocyte-independent defense) and inhibition of Th1-mediated macrophage activation.

Th17 cytokines: IL-17, IL-22, and IL21. They are produced by Th17 cells. Their main functions are recruitment of neutrophils, induction of antimicrobial peptides in epithelial tissues, and stimulation of inflammation.

35. **Which cells produce chemokines and what is their function?**

Chemokines are produced by leukocytes and by several types of tissue cells such as endothelial cells, epithelial cells, tissue macrophages, fibroblasts, and other cells of the stroma, under the stimulation of cytokines like TNF and IL-1β or under the recognition of pathogen-associated molecular patterns.

Chemokines are divided into two major subfamilies defined as CXC (when two cysteine residues are separated by every other amino acid), which are called α chemokines, and the CC (when two cysteine residues are adjacent), which are called β chemokines. A subgroup of CXC chemokines (for instance, CXCL8, also termed IL-8) with the sequence "glutamic acid-leucine-arginine" (ELR) motif just before the CXC motif support neutrophil migration to infected or damaged tissues. The remaining CC (for instance, CCL2, also termed MCP-1) and CXC (for instance, CXCL10, also termed IP-10) chemokines support the migration of monocytes, lymphocytes, and other immune cells.

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Autoimmune Rheumatic Disorders: Pathogenetic and Laboratory Aspects

2

Abstract

Autoimmune disorders result from the attack of the immune system against self, since patients with these diseases have lost a major characteristic of the immune system, the **immune tolerance** (ability not to react against self). They can affect one organ (**organ-specific**) or many organs (**systemic**). The majority of autoimmune rheumatic diseases are systemic. The disorders occur in genetically predisposed individuals (associated with major histocompatibility antigens and other immunoreactive molecules) when they come across with chemical, physical, or microbial agents in the context of a particular hormonal background (majority are females) and under circumstances that create an incompetence to cope with life stressful events. The autoimmune attack can be mediated by autoantibodies, immune complexes, or T lymphocytes and can result in organ hyperfunction (e.g., hyperthyroidism), hypofunction (e.g., myasthenia gravis), or destruction of the affected organ (e.g., synovium in rheumatoid arthritis). The presence of leukocytosis and acute-phase proteins (C-reactive protein) characterizes the autoimmune disorders as inflammatory (e.g., vasculitis), while their absence as not inflammatory (e.g., systemic lupus erythematosus, SLE). B-lymphocyte hyperactivity, as attested by hyperglobulinemia and a plethora of circulating or tissue-deposited autoantibodies, is a common manifestation in the majority of autoimmune diseases, while different types of T-helper lymphocytes (Th1,Th2, and Th17) operate in different autoimmune diseases. The autoantibodies can be diagnostic (high specificity for a disease, e.g., anti-Sm for SLE), pathogenetic (e.g., DNA-anti-DNA immune complexes activate the complement cascade and induce tissue injury), or predictive for disease development (e.g., rheumatoid factors and anti-cyclic citrullinated autoantibodies).

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1. **On the basis of what facts a disorder can be characterized as autoimmune disease?**

   A disease is termed as autoimmune when (a) antibodies or immune cells recognize self-antigens, (b) these autoreactive antibodies (autoantibodies) and immunocytes result either in hypo- or hyperfunction or tissue injury of the affected organ(s), and (c) transfer of the autoantibodies or autoreactive immunocytes to another human (e.g., maternal autoantibodies to Ro/SSA and La/SSB autoantigens transferred to embryo induce neonatal lupus) or to an experimental animal (e.g., transfer of autoantibodies to acetylcholine receptor (AChR) from a patient to a rabbit induces myasthenia gravis) can produce a similar clinical syndrome.

2. **How are autoimmune diseases classified?**

   The autoimmune diseases can affect one organ of the human body (e.g., autoimmune diseases of the thyroid gland) and are called **organ-specific autoimmune diseases**. Others affect simultaneously or sequentially many organs and are termed **systemic autoimmune diseases**. The majority of autoimmune rheumatic (connective tissue) diseases are systemic autoimmune disorders.

3. **Which are the pathologic results of an autoimmune attack?**
   - Loss of organ function of the affected target tissue: e.g., in diabetes mellitus type I, the β-Langerhans pancreatic cells are destroyed by autoreactice cytotoxic T cells.
   - Suppression of the affected organ function: e.g., in myasthenia gravis, autoantibodies directed against the acetylcholine receptor (AChR) prohibit the transfer of message from the nerves to the muscles, mainly by internalizing the AChR which is destroyed in the phagosome.
   - Hyperstimulation of the affected organ function: e.g., in Graves' disease (hyperthyroidism), autoantibodies directed against the thyroid-stimulating hormone (TSH) receptor mimic the function of TSH, thus providing a constant stimulation of the thyroid gland to produce thyroid hormones, ultimately resulting in the clinical picture of hyperthyroidism.
   - In systemic autoimmune diseases, the immune-mediated events are multiple and complex and can lead to the impairment or destruction of many organs, as is seen in patients with systemic lupus erythematosus.

4. **What is termed hypersensitivity reaction?**

   Hypersensitivity refers to a pathologic immune reaction that is brought about from an immune response after repeated exposure to an antigen. Hypersensitivity diseases include autoimmune diseases, in which immune responses are directed against self-antigens and diseases that result from uncontrolled or excessive responses to foreign antigens. Primary mediators are the adaptive immune system components such as B cells, T cells, and their products, namely, antibodies and cytokines. The term "hypersensitivity" historically defines what we call today "immunity" and was based on the observation that individuals exposed to an antigen are sensitive to respond more aggressively to subsequent exposures to the same antigen. Damage is mediated by the same attack mechanisms that mediate normal immune responses to pathogens. There are four types of hypersensitivity reactions: type I, immediate type; type II, antibody-dependent, cytotoxic; type III, immune complex mediated; and type IV, delayed type.

5. **How do the different types of hypersensitivity reactions occur?**

   Type I hypersensitivity reaction: when genetically predisposed individuals are exposed to an allergen, their dendritic cells, as well as their B cells, recognize the allergen and present antigenic peptides to naive T cells which become T-helper (Th)-2 cells in the periphery and T follicular helper (Tfh) cells in the lymph nodes, both of which secrete the cytokine interleukin-4 (IL-4). Upon activation with IL-4, B cells which have also been exposed to the allergen undergo immunoglobulin (Ig) E class switching and secrete allergen-specific IgE, which binds to the FcεRI recep-

tors on mast cells. Repeated exposure to the allergen leads to allergen-IgE interaction on the surface of mast cells resulting in mast cell activation, with two major consequences: (a) immediate hypersensitivity reaction (minutes after allergen exposure) due to vasoactive amines (histamine, heparin), and lipid mediators, which cause increased vascular permeability and leakage, bronchospasm, and intestinal hypermotility, and (b) late-phase reaction (2–4 h after allergen exposure) due to cytokine secretion, characterized by inflammation due to accumulation of eosinophils and Th2 cells.

Type II hypersensitivity reaction: it takes one of the following patterns: (a) autoantibodies directed against self-antigens lead to opsonization, activation of complement cascade, as well as recruitment of polymorphonuclear leukocytes, macrophages, and natural killer cells, which results in phagocytosis and killing of the target cell; (b) Fc receptor binds antibodies which have recognized either soluble or fixed antigens in various tissues and activates immunocytes bearing Fc receptor; and (c) abnormal functions without inflammation, such as antibody binding and hyperactivation of the thyroid-stimulating hormone (TSH) receptor inducing hyperthyroidism (Graves' disease) or antibody binding to acetylcholine receptor internalizing it into phagosomes where the receptor is degraded and eventually the muscle endplate is deficient of acetylcholine receptors.

Type III hypersensitivity reaction: is induced by autoantibodies which bind to self-antigens and form antigen-antibody complexes (immune complexes). Immune complexes, formed in excess of antigen, are soluble and circulate in the blood, but finally they get entrapped in the capillaries, where they lead to complement system activation and tissue damage. Tissue damage extended in many tissues at the microcirculation level results in disease.

Type IV hypersensitivity reaction: is a cell-mediated immune response which can be implemented either by CD4+ T cells or by CD8+ T cells. CD4+ T cells are activated when they recognize antigenic peptides bound to type II major histocompatibility complex antigens (MHC-II) on the surface of antigen-presenting cells such as dendritic cells or macrophages. Macrophages secrete the cytokine interleukin (IL)-12 which induces maturation and activation of naive CD4+ T cells to become Th1 cells that secrete interferon-γ (IFN-γ) which in turn activates macrophages to secrete the cytokines tumor necrosis factor α (TNF-a), IL-1, and IL-6. These cytokines induce capillary leaking, edema, and fever. In addition, macrophages secrete lysosomal enzymes and reactive oxygen species that induce tissue damage. CD8+ T cells recognize antigenic peptides derived from viral antigens; these peptides are bound to MHC-I molecules on the surface of any nucleated somatic cell which has been infected by viruses. Thus, CD8+ (cytotoxic) T cells kill the virus-infected cells without any additional help and eliminate the reservoir of the virus. To accomplish cell killing, CD8+ T cells secrete perforins and granzymes; the former penetrate the membrane of the target cell and after polymerization form a hole in the cellular membrane; the latter enter the cell through this hole and destroy DNA and intracellular proteins leading to apoptotic cell death.

6. **In which disorders hypersensitivity reactions types I, II, III, and IV predominate?**

It should be emphasized that in inflammatory/autoimmune/allergic diseases, different types of hypersensitivity reactions may operate synchronously. However, in some diseases, a particular type prevails, as, for example:

- Type I: asthma, hay fever, eczema, food allergies, anaphylaxis, and urticaria
- Type II: autoimmune hemolytic anemia/thrombocytopenia, pernicious anemia, Goodpasture syndrome, and pemphigus
- Type III: systemic lupus erythematosus/lupus nephritis, post-streptococcal glomerulonephritis, serum sickness, Arthus phenomenon
- Type IV: chronic delayed-type hypersensitivity reactions to persistent pathogens

(tuberculosis, leprosy, leishmaniasis), to chemical agents (silicosis), contact dermatitis, and rheumatoid arthritis

7. **What is the major pathophysiologic phenomenon observed in patients developing autoimmune diseases?**

The immune system has the ability not to respond to self-antigens. This physiologic phenomenon is called immune tolerance. It is accomplished through central and peripheral mechanisms. In patents with autoimmune diseases, immune tolerance, in other words discrimination of self- and non-self-antigens, is lost.

8. **How can self-tolerance be broken?**

Taking into account that genetic predisposition is a prerequisite for this phenomenon, the following mechanisms/agents have been implicated in breaking self-tolerance:

(a) Disruption of tissue barriers by trauma or infection and release of autoantigens previously hidden from the immune system. A clinical paradigm of this mechanism is the sympathetic ophthalmia. An injury to one eye releases hidden endophthalmic antigens which are recognized from the immune system as foreign and immune response against them is elicited. These autoreactive immune cells then attack not only the injured eye but also the healthy one.

(b) Molecular mimicry. Some pathogens contain epitopes on antigens which resemble epitopes on self-antigens. When an individual is offended by those pathogens, the immune system elicits response not only against the foreign molecules but also against self-antigens. This leads to tissue injury and can induce autoimmune disease. A characteristic example of this mechanism is the one operating in the development of rheumatic fever. Genetically prone individuals after an infection with group A β-hemolytic streptococci develop immune reactivity which recognizes not only the M protein of streptococci but also the autoantigens (myosin/glycogen of the patient's heart muscle and smooth muscle cells of the patient's heart vessels), thereby initiating a type II hypersensitivity reaction against heart structures resulting in their injury.

(c) Activation of the innate immune response through recognition of viral proteins and tissue components released from apoptotic and/or necrotic cells results in induction of autoimmune reactivity (Fig. 2.1a, b).

(d) UV irradiation (induction of apoptosis and release of autoantigens), drugs (acting as haptens), hormones (augmenting immune response), and smoking (induces citrullination of self-proteins stimulating autoimmune responses); all can break self-tolerance and can induce autoimmune disease.

9. **What is the biologic phenomenon of citrullination and in which diseases autoantibodies to citrullinated antigens can be detected?**

Citrullination or deimination is a posttranslational modification of the positively charged amino acid arginine in a protein into the neutral amino acid citrulline. Autoantibodies against citrullinated antigens are primarily detected in the sera of patients with rheumatoid arthritis and infrequently (5%) in the sera of patients with Sjögren's syndrome or systemic lupus erythematosus with arthritis.

10. **What is hapten phenomenon? Provide examples of therapeutic agents commonly inducing it.**

Haptens are chemical moieties too small to elicit immune responses in their free soluble form, because they cannot cross-link B-cell receptors and cannot recruit T-cell help. However, when they are coupled to a carrier protein, they can become immunogenic. An example of a therapeutic agent inducing immune reactions through hapten-carrier phenomenon is heparin causing heparin-induced thrombocytopenia and thrombosis (HITT). In HITT, the immune system develops antibodies against heparin when it is bound to a protein called platelet

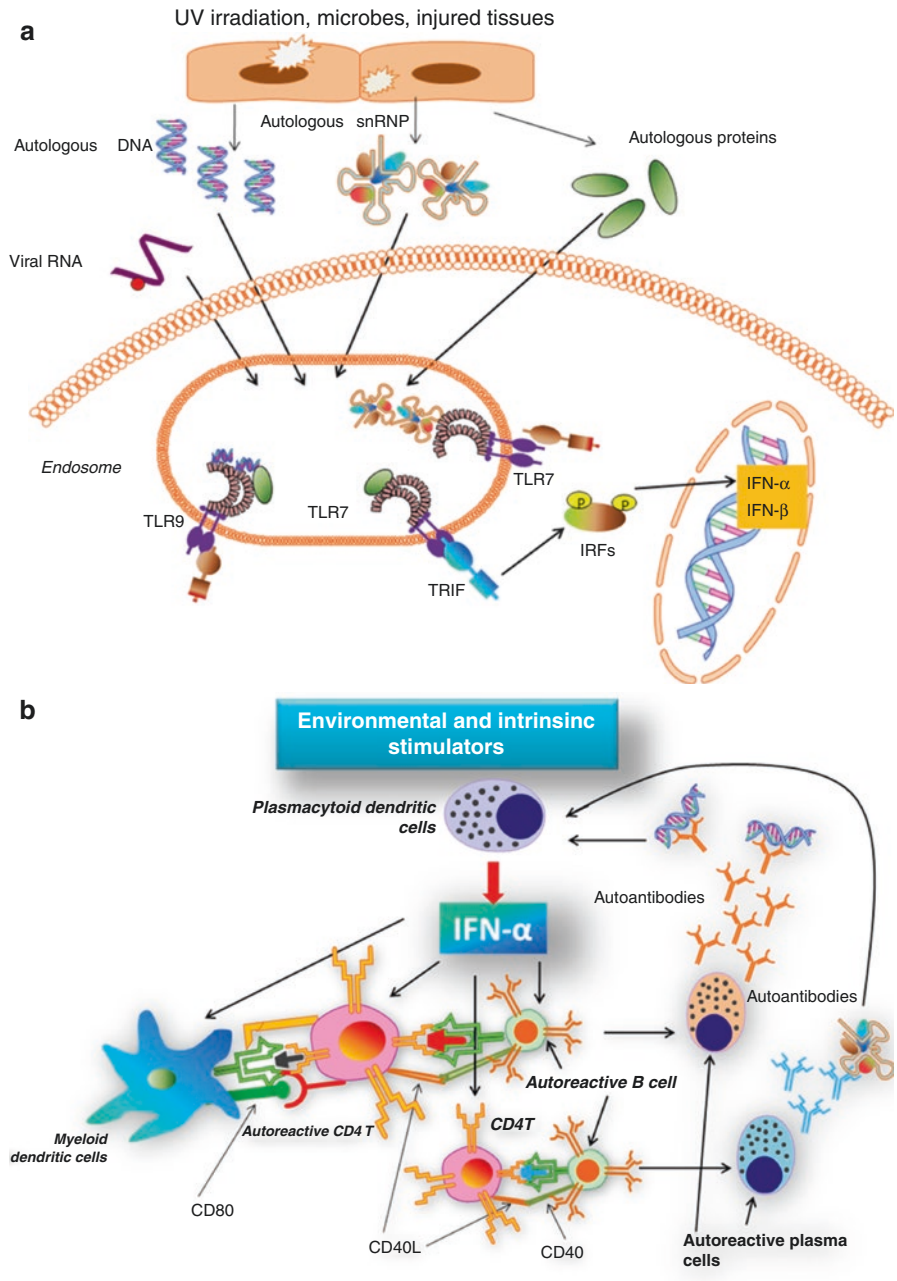

Fig. 2.1 Activation of the innate immune response. (**a**) Several environmental insults, such as UV irradiation, tissue injuries, and viral or bacterial infections, release substances such as autologous DNA, autologous small nuclear ribonucleoprotein particles, and autologous proteins. These substances enter the early endosomes of plasmacytoid dendritic cells and activate the Toll-like receptors (TLRs) which through signaling via transcription factors such as MyD88 (myeloid differentiation primary response protein 88) and TRIF (Toll/interleukin-1 receptor domain containing adapter inducing interferon-β) activate interferon regulatory factor (IRF) which enters the nucleus and stimulates the transcription of genes producing interferon-α and interferon-β (IFN type I). Viral RNAs and C-p-G DNA fragments may also activate plasmacytoid dendritic cells in the same manner. (**b**) IFN I (α and β) stimulate dendritic cells, B cells, and macrophages to express co-stimulatory molecules and activate autoreactive T cells which have been in a stage of immunological ignorance, that is, they did not recognize autoantigens in the absence of co-stimulation. These processes lead eventually to the activation of autoreactive B cells to become plasma cells and produce autoantibodies

factor 4 (PF4). Of note, unfractionated heparin forms more easily complexes with PF4 than the low-molecular-weight heparin. Thus, HITT develops more commonly in patients who are treated with unfractionated heparin. Other examples of medications which can act as haptens are the penicillins which may cause autoimmune hemolytic anemia/thrombocytopenia and hydralazine which in certain individuals can cause drug-induced lupus erythematosus. There are many proteins able to bind haptens. Studies have shown that penicillins make covalent bonds with lysine residues in multiple sites of many proteins. These proteins undergo degradation in the phagolysosomes and then are presented as peptides covalently linked to penicillins on several major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells.

11. **What is autophagy? How does it interfere with the pathogenesis of autoimmune diseases?**

Autophagy is a protective and life-sustaining process by which cellular "debris" are packaged into double-membrane vesicles and degraded by lysosomes. This process of cellular self-digestion is an essential stress response and is cytoprotective by removal or recycling of damaged organelles and proteins that threaten the cell's survival. In the immune system, autophagy regulates processes such as antigen uptake and presentation, removal of pathogens, survival of short- and long-lived immune cells, and cytokine-dependent inflammation.

Genome-wide association studies have linked polymorphisms in autophagy-related genes with predisposition to tissue-destructive inflammatory diseases, such as inflammatory bowel disease and systemic lupus erythematosus. Autophagy's role in regulating the long-term survival of adaptive immune cells has recently surfaced as a defect in multiple sclerosis and rheumatoid arthritis.

12. **Which factors may play a role for the development of autoimmune diseases?**

The effect of environmental factors (microbia, chemical and physical stressors) which break self-tolerance of individuals carrying a genetic predisposition results in autoimmune reactivity. Family and monozygotic twin studies as well as association of autoimmune diseases with certain genes (HLA class I/II and others) have attested for the genetic predisposition of these diseases. Additionally, life stressful events and inability to cope with them, as well as hormones (female predilection), also strongly influence autoimmune disease development.

13. **What is the probability for a monozygotic twin to develop an autoimmune disease if its identical sibling suffers from one?**

Different studies of monozygotic twins have demonstrated that genetics account for about 60% of the disease occurrence, while environmental factors, such as exposure to infectious, chemical, or physical agents, are responsible for the remaining 40%.

14. **What is the major histocompatibility complex (MHC) and what is its role?**

The MHC is a group of genes (to date more than 200 genes) located on chromosome 6 in humans encoding the human leukocyte antigen (HLA). The most important known function of the gene products of the MHC is the processing and presentation of antigens to T cells. Within the MHC region, there are three different subregions encoding for HLA class I (HLA-A, HLA-B, and HLA-C), class II (HLA-DR, HLA-DP, and HLA-DQ), and class III (C2, C4A, C4B, and factor B of complement system; some heat shock proteins, tumor necrosis factor-α [TNF-α], and lymphotoxin) proteins. This means that within each locus (for instance, HLA-DR), there are different gene alleles such as HLA-DR1, HLA-DR2, HLA-DR3,

etc. Each individual inherits one HLA gene for each locus, one from the mother and one from the father.

15. **Which are the HLA class II allele associations with different autoimmune diseases?**
    - HLA-DR2: systemic lupus erythematosus, multiple sclerosis, and negatively correlated with diabetes mellitus type I
    - HLA-DR3: Sjögren's syndrome, myasthenia gravis, systemic lupus erythematosus, and diabetes mellitus type I
    - HLA-DR4: rheumatoid arthritis, diabetes mellitus type I, and pemphigus vulgaris
    - HLA-DRB1-DQA1-DQB1: rheumatoid arthritis, diabetes mellitus type I, and Graves' disease
    - HLA-DR15: systemic lupus erythematosus
    - HLA-DQ2 and HLA-DQ8: celiac disease
    - HLA-DR15: systemic sclerosis

16. **Which other associations besides the HLA have been detected with genomic analysis in autoimmune diseases?**
    - **Rheumatoid arthritis**:

    PTPN22 (protein tyrosine phosphatase, non-receptor type 22)
    IL-23R (interleukin-23 receptor)
    TRAF1 (TNF receptor-associated factor 1)
    CTLA4 (cytotoxic T-lymphocyte-associated antigen 4)
    IRF5 (interferon regulatory factor 5)
    STAT4 (signal transducer and activator of transcription 4)
    CCR6 (chemokine receptor 6)
    PADI4 (peptidyl-arginine deiminase 4)
    - **Ankylosing spondyloarthritis**:

    IL-23R
    TYK2 (tyrosine kinase 2)
    IL-6R (interleukin-6 receptor)
    - **Systemic lupus erythematosus**:

    FcGR3A and FcGR2A (Fc fragment of IgG receptor IIIa, Fc fragment of IgG receptor IIa)
    IRF5 (interferon regulatory factor 5)
    TYK2 (tyrosine kinase 2)
    TLR7 and TLR9 (Toll-like receptor 7, Toll-like receptor 9)
    PTPN22
    CTLA4
    PDCD1 (programmed cell death 1)
    - **Scleroderma**:

    IRF5
    STAT4
    BANK1 (B-cell scaffold protein with ankyrin repeats 1)
    BLK (B-lymphocyte kinase)
    TNFSF4 (tumor necrosis family superfamily member 4)

17. **In which autoimmune disorders T-helper (Th)1, Th2, or Th17 immune response prevails?**

    Approximately 48–72 h after antigenic stimulation, naive T cells (Th0) begin to differentiate into either Th1 or Th2 cells. Which subset emerges depends on the cytokines in the local microenvironment, which are in turn determined by the type of innate response cells that have been activated by the invading entity. Intracellular bacteria and viruses trigger macrophages and dendritic cells to produce interleukin-12 (IL-12). A Th0 that encounters IL-12 becomes irreversibly committed to the Th1 subset.

    Th1-related autoimmune diseases are diabetes mellitus type I, rheumatoid arthritis, Sjögren's syndrome, multiple sclerosis, autoimmune thyroiditis, psoriasis, celiac disease, Crohn's disease, and chronic viral infections.

    On the other hand, extracellular pathogens such as certain bacteria and parasites induce IL-4 production. In the absence of IL-12 but in the presence of IL-4, a Th0 cell generates Th2 effectors.

    Th2-related autoimmune diseases are systemic lupus erythematosus, scleroderma, allergy/atopy/asthma, and ulcerative colitis.

    Th17 development is distinct from that of Th1 and Th2. It is hypothesized that trans-

forming growth factor beta (TGF-β) inhibits the production of IL-12 and IL-4 needed for Th1 and Th2 differentiation, respectively, and together with IL-6 promotes the Th17 differentiation. Once differentiated, Th17 cells require IL-23 and IL-1 to support their survival and proliferation.

Th17-related autoimmune diseases are systemic lupus erythematosus, rheumatoid arthritis, psoriasis, ankylosing spondylitis, inflammatory bowel disease, autoimmune thyroiditis, and scleroderma.

18. **On what basis systemic autoimmune disorders are classified as inflammatory and non-inflammatory?**

Inflammatory systemic autoimmune disorders are characterized by leukocytosis, thrombocytosis, elevated acute-phase proteins (e.g., C-reactive protein), and pro-inflammatory cytokines. This group of diseases encompasses vasculitic syndromes, rheumatoid arthritis, seronegative spondyloarthritis, and juvenile idiopathic arthritis. In noninflammatory systemic autoimmune disorders, leukopenia, thrombocytopenia, and normal acute-phase proteins prevail. Systemic lupus erythematosus, Sjögren's syndrome, scleroderma, and allied conditions belong to this group of disorders.

19. **What is Arthus reaction?**

Arthus reaction is reported after vaccinations containing diphtheria and tetanus toxoid. It is a local type III hypersensitivity reaction. It involves the in situ formation of antigen/antibody complexes after the intradermal injection of an antigen. If the individual has been previously sensitized (has circulating antibodies), an Arthus reaction occurs. Arthus reaction manifests as local vasculitis expressed as a raised erythematous painful nodule due to the deposition of immunoglobulin (Ig) G-based immune complexes in dermal blood vessels and activation of the complement cascade.

20. **What is the biologic phenomenon of autoantibody epitope spreading?**

Autoantibody epitope (determinant) spreading is an acquired biologic phenomenon seen in autoimmunity that involves a continuous acquisition of new self-recognition antigens. Early in the course of an autoimmune disease, patients make antibodies against one epitope, but during the chronic progression of the autoimmune response, they make additional antibodies against moieties in the same molecule (intramolecular epitope spreading) or even against a different molecule (intermolecular epitope spreading), which are closely associated in a tissue (e.g., nucleosome, spliceosome, and ribosome). Autoantibody epitope spreading shifts T-cell autoreactivity from primary initiating self-determinants to secondary determinants.

Examples of autoantibody epitope spreading are the anti-Ro/SSA, anti-La/SSB responses, and the autoantibody spreading in spliceosome from the U1RNP (ribonuclear protein) peptides to Sm (Smith) antigenic molecules.

21. **In which immunoglobulin class rheumatoid factors belong? In the routine test, which autoantibody having rheumatoid factor activity is detected? In which diseases or situations rheumatoid factors can be found in the patient's serum?**

Rheumatoid factors (RFs) are autoantibodies against the Fc portion of immunoglobulin (Ig) (immunoglobulins against immunoglobulins IgM, IgA, and IgG). IgM rheumatoid factor is detected during routine latex agglutination test. IgM is a large pentameric molecule which binds at least ten other Ig molecules and thus demonstrates a strong agglutinability. RFs are found in the sera of two thirds of rheumatoid arthritis, Sjögren's syndrome, mixed connective tissue disease, and idiopathic mixed cryoglobulinemia patients. In the other autoimmune diseases like systemic lupus erythematosus and scleroderma, RFs are found in around one fourth of the patients. It should be noted however that RFs can also be present in the sera of patients with chronic infections (bacterial endocarditis, syphilis, tuberculosis) as well as in the sera of elderly individuals.

22. **What is the prozone phenomenon?**

Prozone phenomenon is a false-negative laboratory result. It is observed when high

antibody titer in the sera under examination interferes with the formation of antigen-antibody lattice, necessary to visualize a positive flocculation test.

23. **What are natural autoantibodies, in which immunoglobulin class do they belong, and what is their physiologic and pathophysiologic role?**

Natural autoantibodies are found in the circulation of all normal individuals. They belong to all immunoglobulin classes (IgM, IgG, and IgA) and are multireactive in the sense that they react with a variety of human components (proteins, cell surface, and intracellular structures).

B lymphocytes, termed B1 cells, are produced initially in the fetus, express particularly IgM antibodies, and have the ability to polyreact with many antigens. The B lymphocytes are committed to the production of natural autoantibodies, which is possibly driven by microorganisms residing in the host, such as bacteria living in the intestine. Natural autoantibodies do not undergo affinity maturation in healthy individuals. They may participate in a variety of physiological activities, such as shaping the B-cell repertoire, immune regulation/homeostasis, and first-line defense against various bacterial cell wall components or parasites. In autoimmune diseases, expansion of natural autoantibody clones may occur, giving rise to development of pathogenic autoantibodies.

24. **Which are the characteristics of pathogenic autoantibodies?**

- Serum titers are high.
- Immunoglobulin (Ig) G isotype predominates.
- Autoantigen specificity is high.
- Somatic mutations occur.

25. **Which antigen(s) recognize the autoantibodies that in the immunofluorescence antinuclear antibody (ANA) test in Hep2 cells give a homogeneous pattern?**

The homogeneous pattern is characterized by diffuse fluorescence of the entire nucleus of cells in interphase and pronounced fluorescence in the condensed chromatin of cells in mitotic phase (Fig. 2.2a). The target antigens can be double-stranded (ds) DNA, single-stranded (ss) DNA, nucleosome, and histones. Intense fine speckled pattern may appear homogeneous as, for example, in case of high titers of anti-Scl70 (topoisomerase I) autoantibodies. Anti-Ku autoantibodies may produce homogeneous immunofluorescence pattern but do not stain the condensed chromatin of cells in metaphase.

26. **Which ANA immunofluorescence patterns are diagnostic?**

- Anti-centromere antibodies: immunofluorescence of the centromere is characterized by staining of 40–60 discrete speckles distributed in the nuclei of cells in interphase, which are localized in the condensed nuclear chromatin in mitotic cells and appear as bars of closely associated speckles (Fig. 2.2b). These autoantibodies are found primarily in patients with limited scleroderma (CREST syndrome: calcinosis, Raynaud's phenomenon, esophageal dysmotility, telangiectasia). However infrequently (<5%), these autoantibodies can be found in the sera of patients with Sjögren's syndrome and autoimmune cholangitis (primary biliary cirrhosis).
- Anti-mitochondrial antibodies: they produce a granular filamentous staining extending throughout the cytoplasm and around the nucleus (Fig. 2.2c). These autoantibodies are found primarily in the sera of patients with autoimmune cholangitis (primary biliary cirrhosis) and infrequently (around 5%) in the sera of patients with limited scleroderma (CREST), Sjögren's syndrome, and overlap syndromes (systemic lupus erythematosus, scleroderma, and Sjögren's syndrome).

27. **Which mitochondrial antigens (M) patients with primary biliary cirrhosis (PBC) recognize?**

Anti-mitochondrial antibodies recognize nine autoantigens (M1-M9) with different

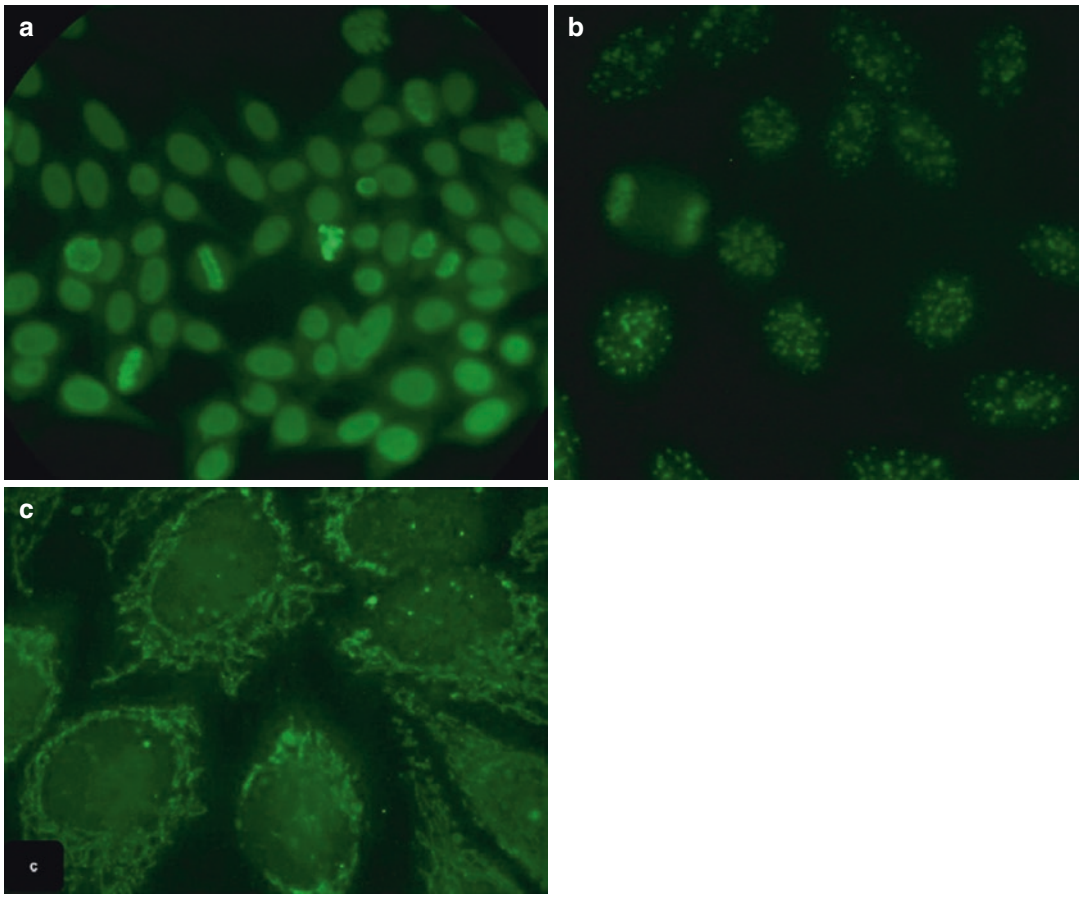

Fig. 2.2 Antinuclear antibody (ANA) immunofluorescence patterns: (**a**) homogeneous pattern (**b**) autoantibodies to centromere (**c**) autoantibodies to mitochondria (*Figure courtesy of Professor Fotini N. Skopouli, MD)*

physical and chemical properties. Reactivity against M2 autoantigen is a specific autoantibody marker in the majority of PBC patients. In contrast autoantibodies against other M-autoantigens can be found in the sera of patients with infectious diseases (syphilis, anti-M1) and undefined collagen diseases (anti-M5) as well as in patients with drug-induced hepatitis (anti-M6).

28. **Which antigen(s) recognize the autoantibodies that in the immunofluorescence ANA test give nucleolar pattern?**

Firstly two main types of nucleolar immunofluorescence staining can be observed using sera of patients with systemic rheumatic disorders, the homogeneous and the speckled. Autoantibodies that recognize the PM/Scl complex (main antigenic components 75 and 100 kD) and Th/To (40 kD ribonucleoprotein) can produce homogeneous nucleolar staining (Fig. 2.3a). Autoantibodies to PM/Scl are found in sera of patients with myositis/scleroderma overlap, while autoantibodies to Th/To can be found infrequently in sera of patients with limited cutaneous scleroderma. Speckled nucleolar pattern is produced from antibodies to RNA polymerases and is found primarily in the sera of patients with systemic sclerosis. Infrequently they can be detected in the sera of patients with mixed connective tissue disease (MCTD). Autoantibodies to Scl70 (topoisomerase I) can produce both staining patterns of the nucleoli and are found primarily in the sera of patients with systemic sclerosis.

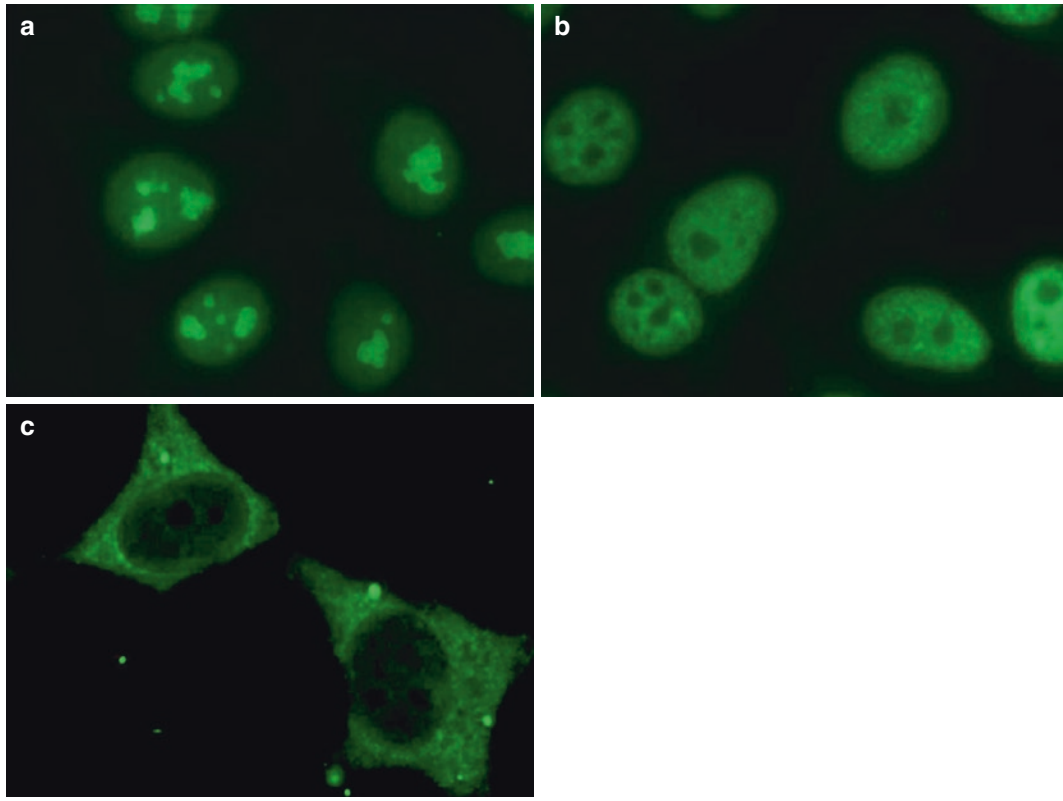

Fig. 2.3 Antinuclear antibody (ANA) immunofluorescence patterns: (**a**) autoantibodies to nucleolar antigens. (**b**) nuclear fine speckled pattern (**c**) cytoplasmic pattern (figure has been developed from the sera of a patient with anti-ribosomal P protein antibodies)

29. **Which autoantibodies give in the immunofluorescence ANA test a rim pattern?**

Autoantibodies against nuclear membrane show, in immunofluorescence, a fine, linear fluorescence pattern of the nuclear membrane with less intense homogeneous staining of the entire nucleus. The target antigens are a family of intermediate filaments comprising lamins and lamin-associated proteins (GP210, lamin A, lamin B, lamin C, Lap 1A, Lap 2).

This rare ANA pattern can be detected infrequently in the sera of overlapping autoimmune disorders such as hepatitis and cholangitis and is variably associated with vasculitis, thrombocytopenia, as well as systemic lupus erythematosus. Low-titer antibodies have been also observed in patients (50%) with chronic fatigue syndrome.

30. **Which autoantibodies give in the immunofluorescence ANA test a speckled pattern?**

Two main immunofluorescence speckled patterns can be seen: coarse and fine speckled. Coarse speckled pattern consists of dense intermediate-sized particles in interphase nucleus together with large speckles. Fine speckled pattern presents fine discrete speckled staining of interphase nuclei. Mitotic cells are not stained (Fig. 2.3b). Coarse speckled pattern is produced from autoantibodies to U1RNP and Sm autoantigens, while fine speckled from autoantibodies to Ro(SSA), La(SSB), RNA polymerases, Ku, and Mi-2 autoantigens.

31. **Which autoantibodies give in the immunofluorescence ANA test a cytoplasmic pattern?**

The cellular cytoplasm contains organelles (e.g., mitochondria, Golgi apparatus, endoplasmic reticulum, and others), different proteins, as well as RNA-protein complexes against which autoantibodies can develop. Anti-mitochondrial autoantibodies to transfer RNAs, as is the anti-histidyl-tRNA synthetase (anti-Jo-1), anti-ribosomal P protein (Fig. 2.3c), and anti-signal recognition particle (anti-SRP), are some of the commonest autoantibodies which produce cytoplasmic immunofluorescence pattern.

32. **Which antigens are detected with direct and indirect Coombs test?**

The direct Coombs test is used to detect immunoglobulins or complement proteins that are bound to the surface of red blood cells (RBCs). The indirect Coombs test detects immunoglobulins against RBCs that are found in the patient's serum and are not bound to RBCs.

33. **In which autoimmune conditions autoantibodies to histones are found?**

Anti-histone antibodies are found in drug-induced lupus patients. Most symptomatic patients (95%) with drug-induced disease due to procainamide, hydralazine, and quinidine will have elevated immunoglobulin (Ig) G anti-histone levels, while most asymptomatic will have IgM anti-histone antibodies. Patients with drug-induced lupus due to minocycline, statins, or propylthiouracil will have less frequently positive anti-histone antibodies (40%). Antibodies to histones are also frequently (50–80%) found in systemic lupus erythematosus patients depending on disease activity status. The anti-histone antibodies are directed to different histones in drug-induced lupus and in systemic lupus erythematosus.

34. **In which autoimmune diseases anti-nucleosome antibodies can be detected?**

Anti-nucleosome antibodies were firstly indirectly described when the lupus phenomenon was observed in 1948. Today, with the use of specific assays, anti-nucleosome antibodies are found in systemic lupus erythematosus patients with active disease, in patients with drug-induced systemic lupus erythematosus as well as in some scleroderma patients. In systemic lupus erythematosus patients, they correlate directly with renal disease, and in anti-dsDNA negative systemic lupus erythematosus patients, they inversely correlate with serum complement levels. In antiphospholipid syndrome patients, their presence predicts systemic lupus erythematosus development.

35. **Toward which proteins and/or phospholipids the anti-phospholipid antibodies are directed?**

Anti-phospholipid antibodies (aPL) comprise a group of antibodies that recognize *negatively charged* phospholipids including cardiolipin, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, and phosphatidic acid *neutrally charged* phospholipids including phosphatidylethanolamine, phosphatidylcholine, platelet-activating factor (PAF), sphingomyelin, a phospholipid-binding protein co-factor, called β2 glycoprotein 1 (β2GP1), and the protein prothrombin [1].

36. **What is lupus anticoagulant and how does it affect prothrombin and activated partial thromboplastin time?**

Lupus anticoagulant (LA) is an immunoglobulin binding to phospholipids and cell membrane proteins. The term is a misnomer as LA is in fact a prothrombotic agent. The term "anticoagulant" refers to its in vitro properties, since in laboratory tests, this immunoglobulin increases activated partial thromboplastin time (aPTT) which cannot be corrected by addition of normal plasma, whereas in vivo it interacts with platelet membrane phospholipids, increasing adhesion and aggregation of platelets. Prothrombin time (PT) is not affected by the presence of LA. If PT is prolonged, it might indicate a high level of LA, but it can also be due to

prothrombin (factor II) deficiency, which is associated with bleeding tendency rather than hypercoagulability. Prolonged aPTT is seen in half of patients with LA; however, a normal aPTT does not exclude LA presence.

37. **Why is Venereal Disease Research Laboratory (VDRL) test positive in patients with antiphospholipid syndrome?**

The VDRL test measures antibodies against negatively charged phospholipids, such as cardiolipin. Antibodies recognizing negatively charged phospholipids can cause agglutination, similar to what is seen in patients with syphilis. A false-positive VDRL test, in other words a positive test in patients without syphilis, can therefore be found in patients with antiphospholipid syndrome.

38. **Which autoantibody specificities can be found in the sera of patients with necrotizing autoimmune myositis?**

Anti-signal recognition particle (anti-SRP) and anti-3 hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGC) antibodies.

39. **Which autoantibody specificities account for fetal loss?**

Anti-β2GPI, lupus anticoagulant (LA), anti-cardiolipin, anti-Ro/SSA, anti-La/SSB, and anti-thyroglobulin antibodies.

40. **Which are the constituents of Ro/SSA and La/SSB autoantigens?**

Ro/SSA and La/SSB autoantigens are constituents of ribonucleoprotein complexes with small noncoding RNAs ("Y RNAs"). The antibodies to Ro/SSA recognize two distinct proteins with different molecular weights (52 kDa and 60 kDa) and cellular locations. The 52 kDa protein is an interferon-inducible protein located in the cytoplasm. The 60 kDa protein binds to small noncoding RNAs ("Y RNAs") located in the nucleus. The Ro/SSA protein functions as an RNA chaperone that binds to defective cellular and viral RNAs to hasten their degradation, while the La/SSB protein functions as a termination factor for RNA polymerase III.

41. **In which disease autoantibodies to Ro52 and Ro60 are found?**

Ro52: systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, anti-Jo-1 positive myositis, and primary biliary cirrhosis.

Ro60: systemic lupus erythematosus and Sjögren's syndrome.

42. **In which systemic lupus erythematosus patients anti-ribosomal P antibodies can be found?**

Anti-ribosomal-P autoantibodies are found in the sera of systemic lupus erythematosus patients with neuropsychiatric manifestations, mainly psychosis and epilepsy.

43. **In which autoimmune disorder autoantibodies against PM/Scl autoantigen are found?**

Anti-PM/Scl antibodies are found in the sera of polymyositis-scleroderma overlap syndrome patients.

44. **What autoantibody specificities can be detected in the sera of patients with dermatomyositis (DM) without myositis (amyopathic)?**

Autoantibodies against melanoma differentiation-associated protein 5 (anti-MDA5), but only in 20% of patients with clinically amyopathic DM, usually associated with rapidly progressive interstitial lung disease (ILD).

45. **In which autoimmune disorders antibodies to Hsp-65 can be found?**

Heat shock protein 65 (Hsp-65) is a mycobacterial protein that has common structural elements with several human host proteins. Through molecular mimicry, antibody production to mycobacterial HSP65 has been associated with diabetes mellitus type I, autoimmune thyroiditis, Crohn's disease, rheumatoid arthritis, autoimmune hepatitis, primary biliary cirrhosis, and scleroderma. Hsp65 is also implicated in multiple vasculitis-associated systemic auto-

immune diseases such as Kawasaki disease, Behçet's disease, and Takayasu arteritis.

46. **Perinuclear immunofluorescence pattern of neutrophils develops from antibodies directed against myeloperoxidase, the so-called pANCA. Which other autoantibodies may give the same pattern and in which patient's sera can they be detected?**
   - α-Lactoferrin
   - α-Elastase
   - α-Cathepsin G

– They can be found in the sera of patients with ulcerative colitis, sclerosing cholangitis, and rheumatoid arthritis.

47. **What is the role of complement activation in systemic autoimmune diseases?**

Complement proteins belong to the innate immune system. They recognize and eliminate foreign invaders either by killing them or by stimulating phagocytosis by opsonization. Activation of the complement plays a significant role in the pathogenesis of systemic autoimmune diseases. Activation of the classical pathway is the cornerstone in immune complex-mediated diseases such as systemic lupus erythematosus, cryoglobulinemic vasculitis, and post-streptococcal glomerulonephritis. In the recent decade, increasing evidence suggests that the alternative complement pathway is involved in several systemic autoimmune diseases such as ANCA-associated vasculitis, leading to new therapeutic options (monoclonal antibodies against C5 or C5a have shown to be effective in experimental models of ANCA-associated vasculitis and antiphospholipid syndrome). In the IgA-dominant Henoch-Schönlein purpura, activation of the lectin pathway has been shown to contribute to more severe disease.

48. **Which autoimmune conditions can develop in patients with C4 null allele?**

C4 has two allotypes, A and B. Deficiency in the C4A allotype is associated with systemic lupus erythematosus, diffuse systemic sclerosis (negative for anti-topoisomerase I antibody), and limited systemic sclerosis. A deficiency in the C4B allotype is associated with diffuse systemic sclerosis (positive for anti-topoisomerase I antibody), diabetes mellitus type I, and rheumatoid arthritis.

49. **Which autoimmune conditions are characterized by low complement C3 and C4 levels?**

Systemic lupus erythematosus, post-streptococcal glomerulonephritis, subacute bacterial endocarditis, cryoglobulinemia (types II and III), bacterial sepsis (pneumococcal, Gram negative), viremia (especially hepatitis B), and hypocomplementemic urticarial vasculitis.

50. **What does CH50 test evaluate?**

The hemolytic complement assay (CH50) assesses the integrity and function of the classical pathway of complement activation. Patient serum is added to standardized suspension of sheep red blood cells coated with rabbit anti-red blood cell antibodies, resulting in immune complex formation which in turn activates the classical pathway, resulting in lysis of the sheep red blood cells. CH50 is the reciprocal of the serum dilution that lyses 50% of the sheep red blood cells.

51. **Which are the physicochemical characteristics of C-reactive protein?**

C-reactive protein (CRP) is localized in the serum protein electrophoresis between the beta and gamma zones producing beta/gamma zone fusion (Fig. 2.4). It is a pentameric protein comprised of five individual subunits non-covalently linked, in cyclic symmetry in a single plane and belongs to the family of pentraxins (together with serum amyloid P). CRP is produced by hepatocytes, when they receive message from IL-6 and other pro-inflammatory cytokines. CRP serum levels rise within 2–4 h after tissue injury, infection, or inflammation and peak within 24–72 h. In the absence of inflammatory stimuli, CRP levels fall rapidly with a

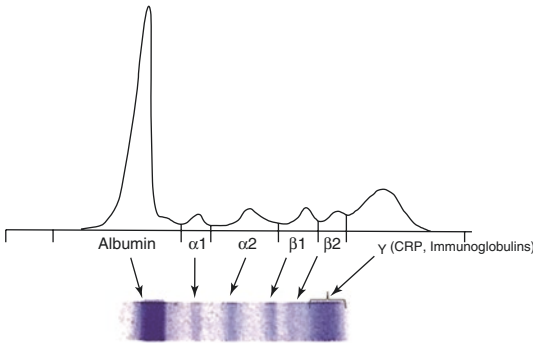

Fig. 2.4 Serum protein electrophoresis: the serum proteins are separated on an agarose gel or cellulose acetate membrane with the application of electric current. Negatively charged proteins (albumin) move faster toward the anode, while γ-globulins possessing a weaker charge move backward from the application site, separated primarily by endo-osmotic forces

half-life about 18 h. It can act as an opsonin by binding to phosphatidylcholine expressed on the surface of dead or dying cells and some bacteria and in that way activates the classical complement pathway (C1q), leading to their opsonization, by generating C3b complement component on cell surfaces.

52. **Which are the characteristics of the three cryoglobulin types?**

Cryoglobulins are immunoglobulins (Ig) or immunoglobulin-containing complexes that precipitate from serum and plasma at low temperatures (<37 °C) and become soluble again upon rewarming.

Type I cryoglobulins: are composed of a single monoclonal Ig, IgM being the most common Ig class. Their quantity is typically very high (cryocrit > 5%) and precipitation occurs rapidly upon cooling (<24 h). This type of cryoglobulins is associated with underlying lymphoproliferative disorders (multiple myeloma, Waldeström's macroglobulinemia, chronic lymphocytic leukemia, B-non-Hodgkin's lymphoma, amyloidosis).

Type II cryoglobulins: are "mixed" cryoglobulins composed of a monoclonal Ig (usually IgM) that acts as an antibody (e.g., rheumatoid factor) against polyclonal Ig (typically IgG). Their quantity is usually intermediate (cryocrit 1–5%), and their precipitation may take a few days to occur. They are associated with hepatitis C infection (90%), Sjögren's syndrome, and lymphoproliferative processes.

Type III cryoglobulins: are "mixed" cryoglobulins similar to type II; the immunoglobulin with rheumatoid factor activity is polyclonal Ig directed against another polyclonal Ig. Their quantity is usually small (cryocrit < 1%) and their precipitation is slow (takes up to 7 days). They are associated with hepatitis C infection (90%), other infections (HIV, HBV, EBV, CMV, *Coxiella burnetii*, parvovirus, and tuberculosis), autoimmune diseases (Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis), and lymphoproliferative processes.

53. **Which proteins can become amylogenic?**

In primary amyloidosis (AL), amyloid fibrils derive from the N-terminal region of the immunoglobulins' light chains (λ more often than κ) produced by a monoclonal population of plasma cells in the bone marrow. In chronic inflammatory conditions, serum amyloid A (SSA) protein precipitates in the tissues and induces the picture of secondary amyloidosis. Other amyloid proteins include calcitonin (ACal) which is associated with medullary carcinoma of the thyroid, atrial natriuretic factor (AANF) associated with senile amyloidosis of heart atria, prolactin (APro) associated with prolactinoma, β-amyloid (Aβ) associated with Alzheimer's disease, and transthyretin which is responsible for familial amyloidosis.

54. **What factors do not allow the fast precipitation of red blood cells (RBCs) in the test tube and provide a within normal limit erythrocyte sedimentation rate (ESR)?**

Four factors affect ESR: size, concentration and shape of RBCs, and plasma protein composition.

Size of RBCs: microcytes sink slower – lower ESR.

Concentration of RBCs: if high numbers of RBCs, they sink slower – lower ESR.

Shape of RBCs: sickle cells and spherocytes sink slower – lower ESR.

Plasma protein composition: increased levels of albumin cause RBC to sink slower – lower ESR, while increased γ-globulins and fibrinogen cause RBCs to sink faster-higher ESR.

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Part II

Autoimmune Rheumatic (Connective Tissue) Diseases

Inflammatory Arthritides

3

Abstract

Inflammatory arthritides are systemic diseases characterized by synovial inflammation as well as cartilage and bone destruction, accompanied by increased levels of acute-phase reactants. They can be seropositive or seronegative based on the presence or absence of rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies, respectively. Rheumatoid arthritis (RA) is the prototype seropositive arthritis. RA is characterized by extensive synovitis resulting in articular cartilage erosions and joint destruction and presents as symmetrical arthritis of small and large joints along with a wide spectrum of extra-articular manifestations.

Seronegative spondyloarthropathies include psoriatic arthritis (PsA), ankylosing spondylitis (AS), enteropathic arthritis, post-infectious (reactive) arthritis, adult-onset Still's disease, juvenile idiopathic arthritis, and juvenile spondyloarthropathy. Type and location of articular involvement, extra-articular and systemic manifestations, as well as findings from joint imaging are important in distinguishing different types of arthritis. Sacroiliac joint and spine involvement alone or accompanied by asymmetrical arthritis of large peripheral joints and enthesitis are seen more often in seronegative spondyloarthropathies. Psoriasis and psoriatic nail changes are frequently encountered in PsA patients. Keratoderma blennorrhagicum, conjunctivitis, and uveitis are some of the extra-articular manifestations of reactive arthritis. Enteropathic arthritis, seen in patients with Crohn's disease or ulcerative colitis, can affect the spine, sacroiliac joints, and large peripheral joints. *Tropheryma whipplei*, parvovirus 19, hepatitis B and C virus infection, *Borrelia burgdorferi*, and disseminated gonococcal infection are associated with arthritis, which is sometimes difficult to distinguish from inflammatory arthritis. Rheumatic fever, a sequel of group A streptococcal pharyngitis, manifests with febrile migratory polyarthritis, myocarditis, valvular heart disease, erythema marginatum, and chorea.

H.M. Moutsopoulos et al., *Rheumatology in Questions*, https://doi.org/10.1007/978-3-319-71604-6_3

1. **What is rheumatoid arthritis?**

   Rheumatoid arthritis is a chronic, systemic, autoimmune disease. Its main site of pathology is the joint synovium. Inflammation of the synovium leads to cartilage erosion and joint deformities. Extra-articular manifestations may accompany joint disease, yet arthritis is the major manifestation of rheumatoid arthritis.

2. **What is the role of genetic factors in the pathogenesis of rheumatoid arthritis?**

   The precise pathogenic mechanisms underlying rheumatoid arthritis (RA) are not yet fully understood. However, an increasing number of studies show that the interaction between genetic and environmental factors and the continuous activation of innate and adaptive immune systems trigger an abnormal autoimmune response. Large-scale genome-wide association studies (GWAS) on patients with RA have linked more than 30 genomic risk loci and single nucleotide polymorphisms (SNPs) to RA susceptibility; however, the genetic risk loci identified to date only account for approximately 60% of the total heritability of RA.

   Class II major histocompatibility antigens/human leukocyte antigens (HLA-DR), as well as non-HLA genes, have been implicated in the pathogenesis of RA. Apart from susceptibility to RA, some genes are implicated in disease outcome and prognosis. HLA-DRB1 gene plays an important role in antigen presentation to T cells and is a well-known genetic risk factor for RA. Valine and leucine amino acids at position 11 in the HLA-DRB1 locus are identified as additional susceptibility factors for a more severe RA course and radiographic progression. Of note, certain gene profiles have also been associated with response or non-response to therapy. Recently, it has been demonstrated that the HLA-E 01:01/01:01 genotype may be associated with decreased RA risk and superior response to anti-TNF agents. Contrariwise, the HLA-E 01:03 variant may account for a lower probability of achieving disease remission.

   In the last few years, growing interest has been shown in elucidating, besides genetic factors, epigenetic mechanisms which could be implicated in the final interpretation of the encoded genetic information. Epigenetic factors respond to external stimuli and form bridging links between the environment and the genes [1, 2].

3. **What is the role of environmental factors in the pathogenesis of rheumatoid arthritis?**

   Various environmental factors have been postulated to be implicated in the pathogenesis of rheumatoid arthritis (RA). Of those, tobacco smoking is the most widely studied and recognized environmental risk factor for RA development.

   – Smoking and smoking intensity are associated with increased risk of seropositive RA (rheumatoid factors and/or anti-citrullinated protein antibodies (ACPA)-positive). The increased risk of seropositive RA in smokers is associated with the presence of rheumatoid epitope (HLA-DRB1), confirming the genetic-environmental interaction between the alleles of the rheumatoid epitopes and tobacco. Besides triggering disease in genetically susceptible individuals, smoking has also been shown to have a negative impact on RA course and severity as well as on response to treatment.
   – Female hormones have been controversially implicated in RA susceptibility. In a recent study, it has been shown that oral contraceptives, as opposed to smoking, decrease the risk of RA, especially of ACPA-positive RA.
   – Several infectious agents have been studied as possible environmental factors implicated in RA development. *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, causative agents of periodontitis, which is twice more frequent in RA patients than in the general population, have aroused as a potential risk factor for the development of RA. They induce activation of citrullinating enzymes and produce chronic inflammation and erosive

destruction of periodontal bone. Periodontal disease, like RA, has been associated with HLA-DRB1.
– Exposure to crystalline silica and silicone breast implants are well-defined risk factors for RA [3–6].

4. **Which are the main immunopathological mechanisms involved in the pathogenesis of rheumatoid arthritis?**

The inflamed synovium in rheumatoid arthritis is characterized by distinct features:
– Fibroblast-like synoviocytes (FLS, synovial fibroblasts or type B synoviocytes) physiologically inhabit the intimal lining of the synovium and control the composition of the synovial fluid and the extracellular matrix (ECM) of the joints' lining. In rheumatoid arthritis (RA), FLS proliferate, acquire a pathogenic phenotype, and mediate inflammation which leads to destruction of the joint. RA FLS secrete enzymes able to destroy the ECM (such as matrix metalloproteinases, MMPs), aggrecanases and cathepsins, which favor resorption of ECM and promote cartilage destruction. RA FLS are also potentially important promoters of bone erosion, since they are able to secrete receptor activator of nuclear factor-κB ligand (RANKL), which promotes osteoclast differentiation. The invasiveness of RA FLS is stimulated by local pro-inflammatory factors (interleukin (IL)-1 and IL-6, TNF, reactive oxygen and nitrogen species) whose formation is triggered by local hypoxia, growth factors (platelet-derived growth factor, PDGF), and ECM proteins. Another pathologic feature of RA FLS is their enhanced, compared to FLS of healthy individuals, ability to secrete many cytokines, chemokines, and proangiogenic factors, thus exerting a potent immunoregulatory function through interaction with immune cells.
– Neoangiogenesis with endothelial activation and a massive invasion of inflammatory cells (macrophages, dendritic cells, lymphocytes, and mast cells) in the synovial sublining. Lymphocytes – B and T cells – infiltrate the synovium in different patterns: diffusely, in the form of aggregates (small aggregates consist mainly of T lymphocytes; in large aggregates, B cells are the dominant cell population), forming germinal centers which contain follicular dendritic cells and high endothelial venules (formed early in the disease process), which are responsible for ectopic neoangiogenesis.
– T helper (Th)17/T regulatory (Treg) cell imbalance. RA has been classically identified as a Th1-mediated disease, yet recently the role of Th17 and Treg is being extensively investigated. Th17 cells represent a distinct effector T-cell subset, which are found in the inflamed rheumatoid synovium and produce the IL-17 family members, IL-21, and IL-22. IL-17 has been shown to play a leading role in pannus growth, RANKL-independent osteoclastogenesis, and synovial neoangiogenesis. Treg cells are found in abundance in the hyperplastic rheumatoid synovium and that their number increases in parallel with the worsening of inflammation. On the other hand, circulating Treg cells are reduced during inflammation which seems to be a compensatory mechanism to counteract local inflammation.
– Immunohistochemical analysis of synovial tissue specimens has shown that the numbers of CD38+ plasma cells and CD22+ B cells in RA synovium are increased in early seropositive rheumatoid arthritis [1].

5. **Which are the early synovial pathology findings in rheumatoid arthritis patients?**
   – A band-like mucoid swelling of the synovial adventitia, with increased acid glycosaminoglycans
   – More frequent occurrence of vasculitis
   – Less marked infiltration of lymphocytes and plasma cells
   – Absence of gross fibrin infiltration and granulocyte infiltration
   – Absence of diffuse fibrosis and hyalinosis

6. **What are fibrillar collagen type II (CII) antibodies, and in which rheumatoid arthritis phenotype can they be found?**

Fibrillar collagen type II (CII) is a major protein of the hyaline cartilage. Antibodies to CII (anti-CII) form immune complexes and induce the production of pro-inflammatory cytokines from mononuclear and polymorphonuclear granulocytes. Increased anti-CII levels are detected in a subgroup of rheumatoid arthritis (RA) patients mainly at the time of diagnosis. In these patients, the presence of anti-CII antibodies has been shown to associate with an acute inflammation (increased C-reactive protein, erythrocyte sedimentation rate) and clinically relevant markers (swollen joint count and disease activity score (DAS)28), which nevertheless is transient and lasts up to 6 months after diagnosis, in contrast to anti-citrullinated peptide antibody (ACPA)-positive RA patients. Anti-CII antibodies are positively associated with HLA-DRB1*01 and HLA-DRB1*03 and negatively with smoking, opposite associations as compared to ACPA. Although anti-CII antibodies are not yet diagnostically useful, the early anti-CII detection predicts a more favorable RA phenotype regarding inflammatory outcome [7].

7. **What is pannus?**

The synovium is the primary site of the inflammatory process in rheumatoid arthritis. In normal joints, it is a thin (only 1–3 cells thick) lining that serves as a source of nutrients for cartilage since cartilage itself is avascular. In rheumatoid arthritis, the inflammatory cytokine milieu causes the synovial lining cells (fibroblast-like and macrophage-like synoviocytes) to proliferate. The inflamed synovium becomes greatly hypertrophied (8–10 cells thick) and develops villous projections that invade and erode the cartilage and bone, leading to destruction of the joint. This inflamed, hypertrophied synovium is called pannus.

8. **What are the characteristics of rheumatoid arthritis synovial fluid?**

The synovial fluid in rheumatoid arthritis is an exudate, with white blood cell counts ranging from 5000 to 50,000/mm^3 and with a neutrophil predominance. The protein level is elevated, while the fluid glucose level may be lower than that of the serum. Crystals are absent and cultures are negative. Synovial fluid rheumatoid factor can be positive, and complement (C3, C4) levels can be lower than the serum complement levels. The presence of cells called "ragocytes," which are granulocytes that have phagocytized immune complexes, can be found in the inflammatory synovial fluid from rheumatoid arthritis patients and may indicate an unfavorable disease prognosis.

9. **Which joints are more commonly affected in rheumatoid arthritis** (Fig. 3.1)**?**

Most patients with rheumatoid arthritis have symmetrical arthritis involving primarily the metacarpophalangeal (MCP) joints, the proximal interphalangeal (PIP) joints, the wrists (with a predilection for

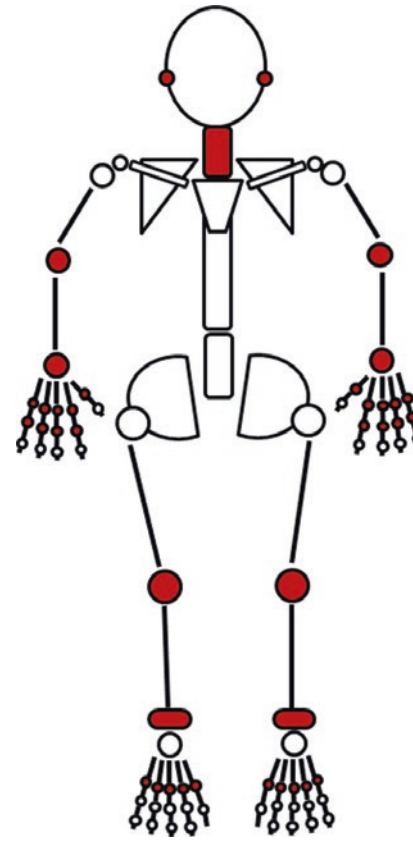

Fig. 3.1 Rheumatoid arthritis: schematic representation of the affected joints

ulnar styloid and triquetrum), and the metatarsophalangeal (MTP) joints. Larger joints tend to become involved after the involvement of the small joints. The cervical spine can be involved with the C1–C2 (atlantoaxial) joint being the most commonly affected level.

10. **How can disease activity score (DAS)28 be calculated in rheumatoid arthritis?**

The number 28 refers to the joints assessed: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees.

- Count the number of swollen joints (out of the 28).
- Count the number of tender joints (out of 28).
- Measure erythrocyte sedimentation rate and/or C-reactive protein levels.
- Global assessment of health by the patient in a scale from 1 (very good) to 10 (very bad).
- Feed these information into a mathematical formula.
- DAS28 $\leq$ 2.6 = disease in remission, DAS28 >2.6 to $\leq$3.2 = low disease activity, DAS28 >3.2 to $\leq$5.1 = moderate disease activity, and DAS28 > 5.1 = severe disease activity.

11. **Which are the typical radiographic features of rheumatoid arthritis-affected joints** (Fig. 3.2)**?**

The radiographic hallmarks of rheumatoid arthritis are:

Soft tissue swelling: fusiform and periarticular. It represents a combination of joint effusion, edema, and tenosynovitis, and it can be the very early sole radiographic finding.

Osteoporosis: initially juxta-articular and later generalized (affected additionally by corticosteroid therapy and limited joint movement).

Joint space narrowing: typically symmetrical.

Marginal erosions: due to erosion by pannus.

Late changes include:

- Subchondral cyst formation: destruction of the cartilage presses synovial fluid into the bone.
- Subluxation causing:

Ulnar deviation of the metacarpophalangeal joints

Boutonniere and swan neck deformities

- Deformities: hitchhiker's thumb deformity, hammertoe deformity, and hallux valgus.
- Carpal instability: scapholunate dissociation and ulnar translocation
- Radiographic findings in cervical spine involvement include:

Atlantoaxial subluxation

Erosion and fusion of apophyseal and facet joints

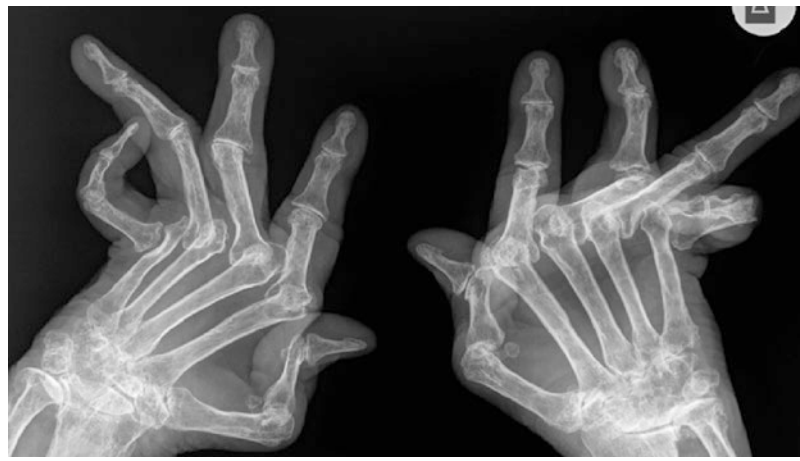

Fig. 3.2 Advanced seropositive rheumatoid arthritis: hand X-ray showing marked subluxation of the fingers with ulnar deviation of the metacarpophalangeal joints, bone cysts, and diffuse osteopenia. Hitchhiker's thumb deformity is best seen on the left hand. The carpal bones are fused with cystic lesions and sclerosis (*Figure courtesy of Professor Alexandros A. Drosos, MD*)

Erosion of spinous processes
Osteoporosis and osteoporotic fractures

12. **Asymptomatic patients with autoantibodies to immunoglobulins (rheumatoid factor) and citrullinated peptides (ACPA). What is the probability that they develop rheumatoid arthritis?**

    A study of healthy relatives of rheumatoid arthritis patients has shown that the positive predictive value was 64% when both ACPA and rheumatoid factor were positive and 58% when only ACPA autoantibodies were present [8].

13. **Which are (according to incidence) the extra-articular manifestations of rheumatoid arthritis?**

    Extra-articular manifestations can develop prior or during the clinical course of the disease. Anemia (of chronic disease), Sjögren's syndrome, pleurisy, pericarditis, and subcutaneous and lung nodules are some of the extra-articular manifestations of rheumatoid arthritis. B-cell lymphoma development occurs in rheumatoid arthritis patients three times more frequently than in age-, sex-, and race-matched healthy individuals. In untreated or poorly responding to therapy rheumatoid arthritis patients, AA amyloidosis can develop. AA amyloidosis, vasculitis, and Felty's syndrome these days are seen very infrequently.

14. **Which are the most common mortality causes of patients with rheumatoid arthritis?**
    - Cardiovascular disease
    - Interstitial lung disease
    - Infections
    - Lymphoproliferative disorders
    - Treatment/drug related, e.g., nonsteroidal anti-inflammatory drugs causing upper gastrointestinal tract bleeding

15. **Which clinical manifestation(s) in rheumatoid arthritis patients can lead to sudden death?**
    - Subluxation of the odontoid process into medulla oblongata
    - Unrecognized coronary artery disease leading to sudden cardiac death

16. **Is the incidence of cardiovascular disease increased in patients with rheumatoid arthritis, and if so, what are the underlying causes?**

    Rheumatoid arthritis by itself is considered an independent risk factor for cardiovascular disease (CVD), associated with at least 1.5-fold increased risk for a fatal coronary event compared to age- and sex-matched general population. Rheumatoid arthritis patients present evidence of advanced preclinical carotid atherosclerosis compared to healthy controls, to a magnitude similar to that observed in diabetes mellitus patients. Rheumatoid arthritis patients present an increased burden of traditional CVD risk factors including hypertension, dyslipidemia, smoking, insulin resistance, obesity/altered body composition, and physical inactivity, but all this accounts only partly for the excess CVD mortality. The systemic inflammatory burden and chronic activation of the immune system present in rheumatoid arthritis play a major role in the atherosclerotic process. The extent to which traditional CVD risk factors and rheumatoid arthritis-related parameters (inflammatory burden, activity/remission, and treatment modalities) interact and/or contribute to increased CVD incidence remains inconclusive. Nevertheless, besides effectively inducing rheumatoid arthritis remission, it is of equal importance to optimally control classical CVD risk factors in rheumatoid arthritis patients.

17. **Which are the cutaneous manifestations of rheumatoid arthritis patients, and do these patients constitute a particular disease subgroup?**
    - Raynaud's phenomenon is present in around 5–10% of rheumatoid arthritis patients and can predict an aggressive disease course.
    - Rheumatoid nodules are subcutaneous nodules found in 10–20% of rheumatoid arthritis patients, who are typically seropositive and have severe disease (Fig. 3.3).

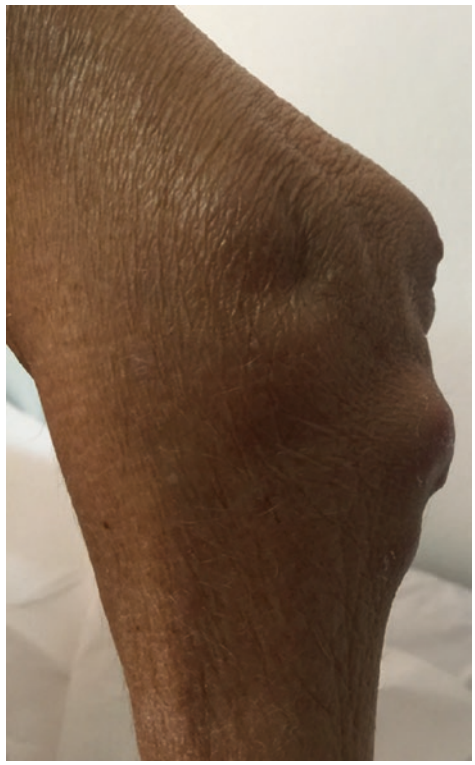

Fig. 3.3 Rheumatoid nodules: subcutaneous nodules on the extensor surface of the elbow in a 58-year-old female patient with long-standing seropositive rheumatoid arthritis

- Small-vessel vasculitis can develop when the rheumatoid arthritis articular disease is in remission and can present with a clinical picture ranging from purpuric lesions to ulcerative-necrotic cutaneous lesions.
- Pyoderma gangrenosum and Sweet's syndrome are both infrequent neutrophilic dermatoses that can be seldomly seen in rheumatoid arthritis patients.

18. **Which organs (according to incidence) rheumatoid vasculitis affects?**

Primarily the skin. Major manifestations include palpable purpura, ischemic ulcers, and digital gangrene. Digital infarctions may accompany other manifestations of vasculitis or may occur alone as isolated digital arteritis, in which case the prognosis is relatively favorable. Mononeuritis multiplex is another classic presentation of rheumatoid vasculitis. Weight loss, pleurisy, pericarditis, ocular inflammation, splenomegaly, hepatomegaly, and Felty's syndrome have also been reported in association with rheumatoid vasculitis.

19. **Exudate pleural effusion with low sugar level. Infections have been ruled out. What is the underlying autoimmune disease?**

Rheumatoid arthritis.

20. **In which rheumatoid arthritis patient subpopulation rheumatoid nodules can be seen in the lungs?**

Lung nodules are seen in rheumatoid arthritis patients that have worked as coal miners (Caplan's syndrome/rheumatoid pneumoconiosis) as well as in rheumatoid arthritis patients exposed to silica dust or asbestos.

21. **Which are the clinical, laboratory, and other characteristics of rheumatoid arthritis patients demonstrating anti-Ro/SSA antibody positivity?**

Anti-Ro-/SSA-positive rheumatoid arthritis patients have the same articular and extra-articular manifestations as anti-Ro-/SSA-negative patients. However, they are predominantly females with lower rheumatoid factor titers in their sera and a higher incidence of round cell infiltrates in the minor salivary gland biopsy specimens compared to rheumatoid arthritis patients without anti-Ro/SSA. Finally, anti-Ro-/SSA-positive rheumatoid arthritis patients more frequently experience side effects with D-penicillamine treatment [9].

22. **What is the kidney pathology which can develop in rheumatoid arthritis patients?**

Rheumatoid arthritis has been associated with a variety of kidney disorders principally due to chronic inflammation and drug exposure/toxicity. From kidney biopsies performed on rheumatoid arthritis patients, the most commonly observed renal pathologies are mesangial proliferative glomerulonephritis, membranous nephropathy, immunoglobulin A nephropathy, minimal change disease,

pauci-immune glomerulonephritis, analgesic nephropathy, interstitial nephritis, and AA amyloidosis.

23. **How common is Felty's syndrome? In which rheumatoid arthritis subgroup does this syndrome develop?**

Felty's syndrome is rheumatoid arthritis in combination with splenomegaly and leukopenia. It is seen in less than 1% of rheumatoid arthritis patients who are seropositive (rheumatoid factor positive) and have subcutaneous nodules and other extra-articular manifestations. It has been shown that in most of these rheumatoid arthritis patients there is an association with the alloantigen HLA-DR4.

24. **Is the risk for periodontitis increased in rheumatoid arthritis patients?**

Yes. According to the nation-wide studies from the United States, individuals who fulfill the rheumatoid arthritis classification criteria present four times higher risk to develop periodontitis compared to individuals who do not fulfill the criteria [10].

25. **Is there a link between osteoporosis and rheumatoid arthritis?**

Rheumatoid arthritis has been found to be associated with osteoporosis, not only because rheumatoid arthritis patients are treated with corticosteroids but also because the rheumatoid arthritis-related inflammatory burden can by itself add to the risk of developing osteoporosis. When rheumatoid arthritis synovitis becomes persistent, then the bones around the joints become thinned, and this is known as localized secondary osteoporosis.

26. **How does pregnancy affect the course of rheumatoid arthritis?**

Clinical symptomatology of rheumatoid arthritis improves during pregnancy in 50–70% of patients. Disease relapse, however, can be often seen some months postpartum. Rheumatoid arthritis patients with an active disease during the third trimester are more likely to have preterm births and small-for-gestational age babies. Infertility is not increased in rheumatoid arthritis patients, and there is no significant increase in maternal or fetal complications except for risks related to rheumatoid arthritis therapy [11].

27. **Palindromic rheumatism. What is the clinical picture and which disease will these individuals develop eventually?**

Palindromic rheumatism is a type of recurrent episodes of inflammatory arthritis. The arthritis symptoms disappear between attacks and the affected joints return to normal. Men are equally affected with women between the ages of 20–50 years. Over time 35–50% of the affected individuals will evolve to rheumatoid arthritis, particularly those who possess in their serum rheumatoid factor and/or anti-citrullinated peptide antibodies (ACPA) positivity. It is worth noting though that recognition of ACPA epitopes and isotypes in patients with palindromic rheumatism is different than those in rheumatoid arthritis [12].

28. **What is the remitting, seronegative, symmetrical synovitis with pitting edema (RS3PE) syndrome?**

It is a syndrome that affects mostly men above the age of 60 years. It has an acute onset and a benign course, since it remits by less than 36 months and does not relapse. It presents with edema of the dorsum of the hands and feet, symmetrical synovitis of small joints, and flexor tendinitis. Rheumatoid factor is negative, and the patients respond quickly to low-dose corticosteroids. X-rays of the affected joints do not present any pathological signs.

29. **What did we learn from the genetic studies of ankylosing spondylitis?**

The genetic background constitutes an over 90% risk for the development of ankylosing spondylitis. Genetic studies strongly suggest that ankylosing spondylitis develops from the interaction of the mucosal immune system with the intestinal microbiome, an interplay

which leads to excess IL-23 production and initiation of the inflammatory process. Genetics also play a significant role in ankylosing spondylitis parameters such as disease activity, joint fusion rate, and the development of extra-articular manifestations [13].

30. **What is the hypothesis regarding the role of human leukocyte antigen (HLA)-B27 in the pathogenesis of ankylosing spondylitis?**

A genetically susceptible (HLA-B27 alloantigen-positive) individual when exposed to microbial triggers is postulated to clinically express ankylosing spondylitis. There are four different related hypotheses:

- *Arthritogenic peptide hypothesis*: suggests that the HLA-B27-specific autoimmune response may be directly initiated for structurally unique peptide-MHC complexes, depending on the amino acid composition of the antigen peptides.
- *Molecular mimicry hypothesis*: suggests that a cross-reactive peptide derived from an infecting bacterial pathogen stimulates T cells, which subsequently respond to an HLA-B27-associated "self-peptide" or to peptides derived from HLA-B27 directly.
- *Free heavy-chain hypothesis*: HLAB-27 heavy-chain can form stable homodimers without associated β2 microglobulin on the cell surface. These homodimers can trigger a direct activation of natural killer cells causing IL-17 and TNF-α release.
- *Unfolded protein hypothesis*: HLA-B27 appears to exhibit a tendency to misfold and a predilection for forming dimers or multimers in the endoplasmic reticulum. This causes a stress response, resulting in the release of inflammatory cytokines (IL-23) and stimulation of Th17 cells. Furthermore, endoplasmic reticulum aminopeptidase 1 (ERAP-1) is involved in the loading of MHC molecules in the endoplasmic reticulum, and abnormal loading may contribute to misfolding of HLAB-27. Both ERAP-1 and IL-23 receptor polymorphisms have been implicated in the genetic risk for developing ankylosing spondylitis.

31. **Which peripheral joints are affected by ankylosing spondylitis?**

Ankylosing spondylitis affects primarily the sacroiliac joints and the joints of the spine. However, approximately 30% of ankylosing spondylitis patients will develop peripheral arthritis. The hips, the shoulders, and the knees are most commonly involved (Fig. 3.4). Rarely arthritis of the sternoclavicular, temporomandibular, and cricoarytenoid joints or the pubic symphysis occurs. Involvement of the thoracic, costovertebral, sternocostal, and manubriosternal joints can also rarely occur.

32. **Which are the causes of Achilles tendinitis (Fig. 3.5)?**

The commonest cause of Achilles tendinitis is repetitive and intense tension on the

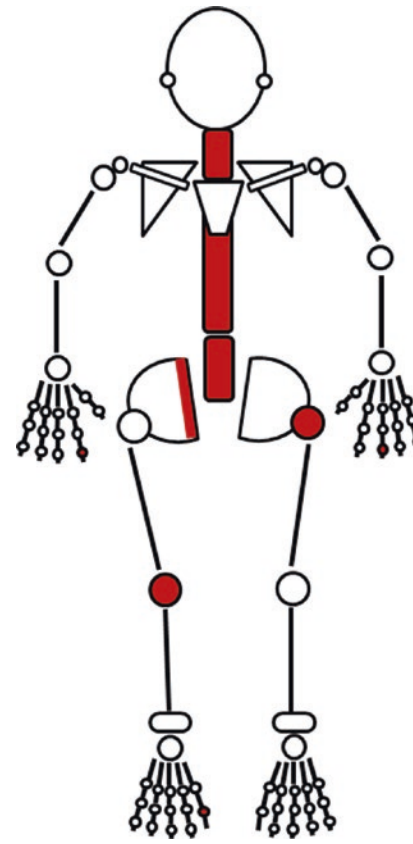

Fig. 3.4 Ankylosing spondylitis: schematic representation of the affected joints

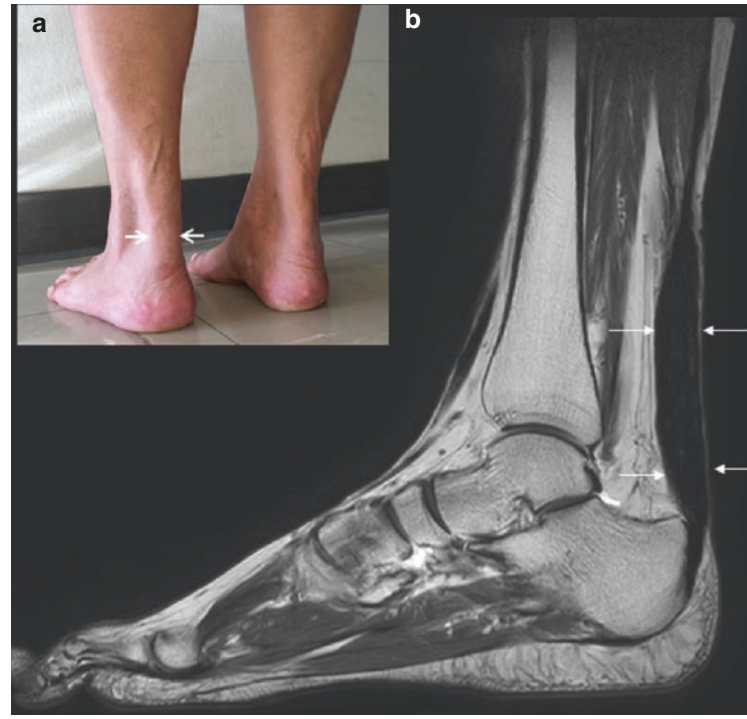

Fig. 3.5 Achilles tendinitis: (**a**) in a 55-year-old female with psoriatic arthritis who presented with a painful left foot. On clinical examination, a painful and swollen Achilles tendon was palpated (white arrows). (**b**) Magnetic resonance imaging (proton density, modified Dixon) revealed diffuse fusiform thickening in the whole length of the Achilles tendon (anteroposterior diameter 15 mm, normal <6 mm) with no tear or enthesitis (white arrows) (*Figure courtesy of Professor Alexandros A. Drosos, MD)*

tendon as occurs in individuals who exercise strenuously. Inflammation of the tendon enthesis is another etiology of Achilles tendinitis. Patients with HLA-B27-related diseases like ankylosing spondylitis, reactive arthritis, and psoriatic arthritis can manifest Achilles tendinitis. Patients with hereditary connective tissue disorders can also develop Achilles tendinitis.

33. **Which are the spine and pelvis radiological findings in patients with ankylosing spondylitis?**

Sacroiliac joints: involvement is usually bilateral and symmetric. Initially involves the synovial-lined upper two thirds of the sacroiliac joint. The earliest radiographic change is erosion of the iliac side of the sacroiliac joint. Progression results in an initial "pseudo-widening" of the sacroiliac joint space with bony sclerosis eventually followed by complete bony fusion of the joint (Fig. 3.6a). In early sacroiliitis when plain X-rays may appear normal, magnetic resonance imaging (MRI) will show inflammation and edema.

Spine: an early MRI finding is the so-called shinny corners (Romanus lesion) which represent the insertion of the annulus fibrosus to the corners of the vertebral bodies. Andersson lesion is the inflammatory involvement of the intervertebral discs by spondyloarthritis that presents as noninfectious spondylodiscitis in a few ankylosing spondylitis patients and can mimic infection. Gradual ossification of the outer layers of the annulus fibrosus forms intervertebral bony bridges called syndesmophytes. Squaring of the vertebral bodies, bilateral syndesmophytes, fusion of the apophyseal joints, and calcification of the spinal ligaments result in the complete fusion of the vertebral column giving the appearance of "bamboo spine" (Fig. 3.6b). In advanced stages of the disease – especially if poorly treated – these changes result in loss of natural spinal curvature, thoracic kyphosis, loss of lumbar lordosis, buttock atrophy, and forward bending of the neck (Fig. 3.6c).

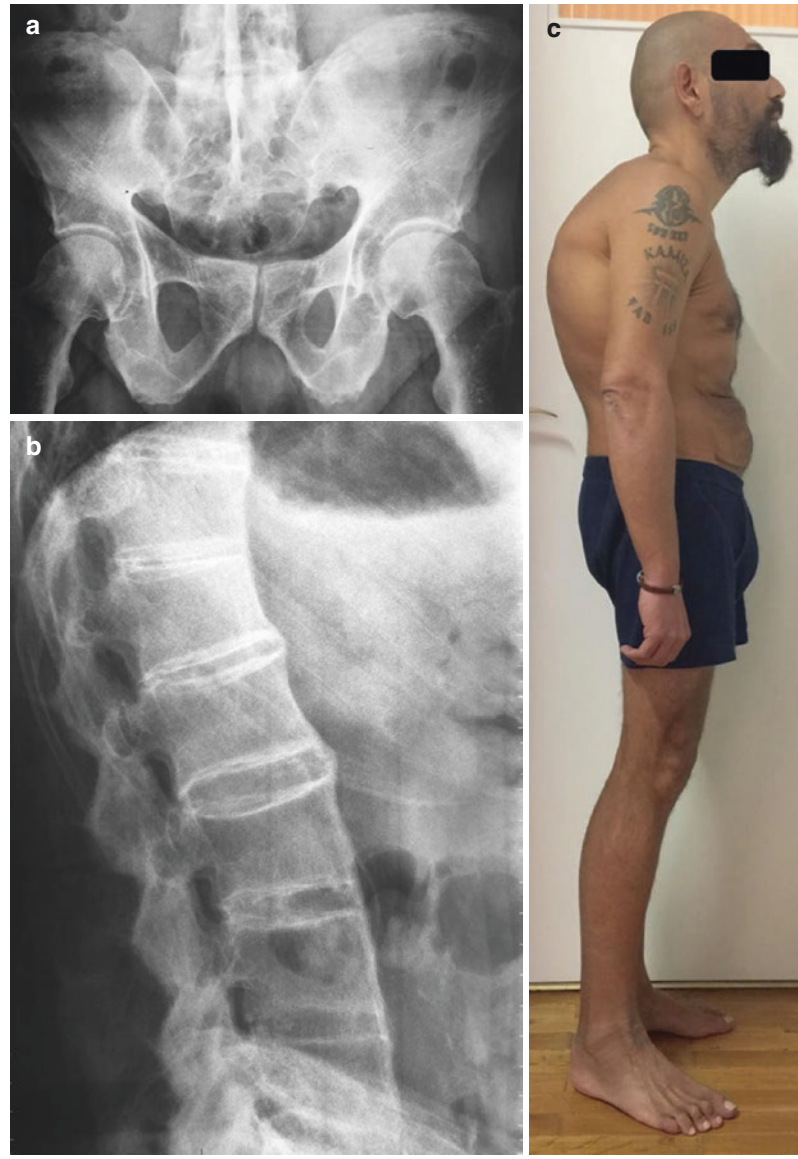

Fig. 3.6 Fused sacroiliac joints in a 48-year-old male patient with advanced untreated ankylosing spondylitis. (**a**) Plain pelvis X-ray showing complete bony fusion of both sacroiliac joints. (**b**) Lateral X-ray view of lumbar spine of the same patient showing large syndesmophytes and calcification of the anterior longitudinal ligament giving the appearance of "bamboo spine." (**c**) The patient's clinical picture shows loss of lumbar lordosis, buttock atrophy, and exaggerated thoracic kyphosis with a forward neck bending

34. **Which are the magnetic resonance imaging findings seen in patients with sacroiliitis?**

The presence on magnetic resonance imaging (MRI) of bone marrow edema in subchondral bone is considered to be the finding that determines the presence of active sacroiliitis (Fig. 3.7). If structural lesions are seen in the sacroiliac joints on MRI, these may further contribute toward the diagnosis of inflammatory lesions of ankylosing spondylitis.

35. **Compare magnetic resonance imaging with radiography in detecting structural lesions of the sacroiliac joints in patients with axial spondyloarthritis.**

Magnetic resonance imaging (MRI) appears to be superior to radiography in detecting erosions and joint space narrowing. In contrast, MRI is inferior to radiography in detecting joint sclerosis [14].

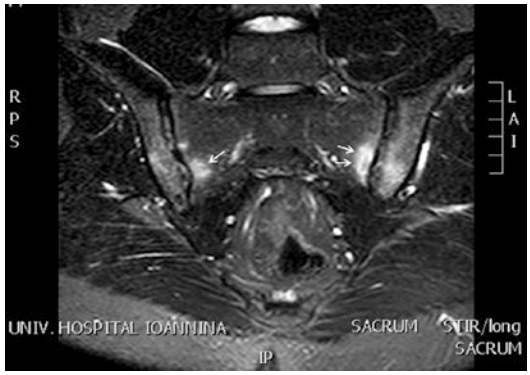

Fig. 3.7 Sacroiliitis: magnetic resonance imaging (STIR sequences in coronal view) of the sacroiliac (SI) joints in a 28-year-old male with low back pain. Diffuse bone edema with high signal of the SI joints bilaterally (arrows) is evident, more prominent on the left side (*Figure courtesy of Professor Alexandros A. Drosos, MD*)

36. **What is the lung pathology which can be seen in ankylosing spondylitis patients?**

Ankylosing spondylitis patients can rarely present with pulmonary apical fibrocystic disease. In the early phase of the disease, lung involvement may be unilateral. In the majority of cases though, as disease progresses, involvement becomes bilateral and fibrobullous nodules coalesce to form cysts and cavities, while fibrosis and bronchiectasis are also common. Fungal or mycobacterial superinfection of the cysts and cavities is not uncommon. *Aspergillus fumigatus* is the most common pathogen isolated. Moreover, a restrictive ventilatory impairment can also be seen in patients with ankylosing spondylitis due to restricted thoracic cage expansion (ankylosis of the thoracic spine, fusion of the costovertebral joints, and anterior chest wall involvement).

37. **How can one differentiate, based on symptomatology, low back pain due to degenerative arthritis versus spondyloarthritis?**

The low back pain of spondyloarthritis (inflammatory) is usually characterized by morning stiffness, subsides with movement, and worsens with rest in contrast to low back pain of degenerative arthritis which worsens with movement.

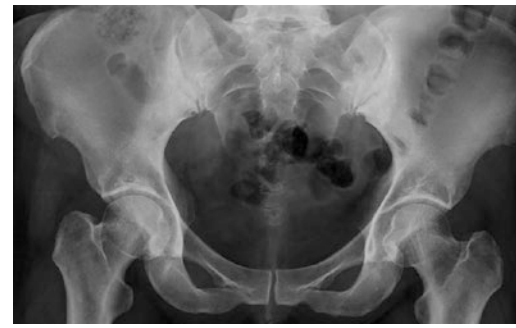

Fig. 3.8 Osteitis condensans ilii: a multiparous 41-year-old female presented with low back pain. X-rays of the pelvis showed sclerosis of the iliac side of the sacroiliac (SI) joints bilaterally (more pronounced on the left side) without joint space narrowing of the SI joints. This finding is considered diagnostic for osteitis condensans ilii (*Figure courtesy of Professor Alexandros A. Drosos, MD*)

38. **What is osteitis condensans ilii and how does it differ from sacroiliitis?**

Both entities can present with low back pain, but radiologically they have quite different appearance. Osteitis condensans ilii is a disorder seen in multiparous women. Firm sclerosis, in a triangular shape, usually bilaterally, is seen at the iliac part of the sacroiliac joint, while the sacrum and joint space are intact (Fig. 3.8). In patients with sacroiliitis erosions and sacroiliac joint space narrowing, bilaterally or unilaterally are the cardinal X-Ray manifestations.

39. **How does physical strain, (e.g. sports) affect the appearance of bone marrow edema of the sacroiliac joints seen by magnetic resonance imaging?**

Low grade bone marrow edema is reported in the sacroiliac joints of up to 25% of healthy individuals and mechanical back pain patients, challenging the imaging discrimination from early spondyloarthritis. In a recent study comparing two cohorts of healthy hobby runners and professional ice hockey players, the frequency of bone marrow edema on magnetic resonance imaging (MRI) was determined before and after a competitive run and before and after a competitive season respectively. Bone marrow edema was identified in 3 to 4 quadrants on average for both groups of

athletes and the posterior lower ilium was the most affected region in all of these athletes, followed by the anterior upper sacrum.

Therefore, it should be noted that physical strain can cause the presence of low-grade bone marrow edema, especially clustered in the posterior lower ilium or anterior upper sacrum, and this is not sufficient to confirm axial spondyloarthritis in these individuals [15].

40. **What is diffuse idiopathic skeletal hyperostosis?**

Diffuse idiopathic skeletal hyperostosis (DISH) also known as Forestier's disease is characterized by ossification of ligaments of the spine, especially the anterior longitudinal ligament of the spine. It is a noninflammatory disease that commonly occurs in obese, diabetic males over 50 years of age. Plain X-ray of the spine shows large osteophytes, flowing hyperostosis, and calcification of the anterolateral aspect of at least four continuous vertebral bodies (Fig. 3.9). The absence of ankylosis of facet joints and erosions of sacroiliac joints differentiate DISH from ankylosing spondylitis.

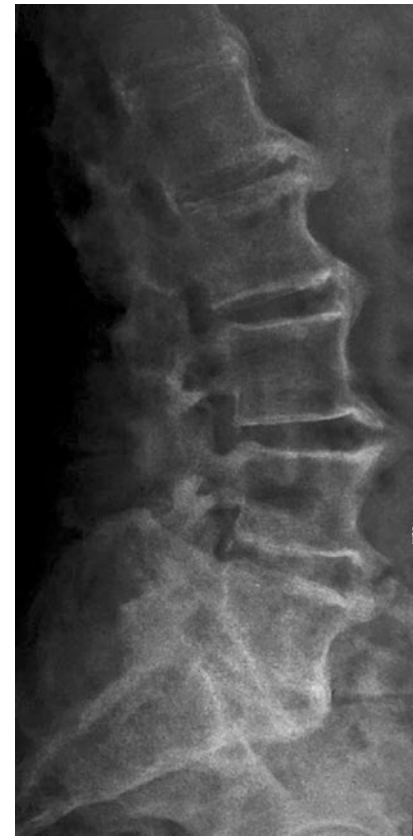

Fig. 3.9 Diffuse idiopathic skeletal hyperostosis: lateral X-ray view of the lumbar spine from a 70-year-old patient revealing flowing ossification along the anterior aspects of more than four contiguous vertebrae, while disc spaces are preserved

41. **Which joints can be affected in patients with psoriatic arthritis?**

Psoriatic arthritis can affect any joint (large and small) of the body. Large joints of the lower extremities are more often affected. One joint, e.g., the knee (monoarthritis), small number of joints (<3 joints, oligoarthritis) (Fig. 3.10), or multiple joints (polyarthritis) can be affected simultaneously. Fingers or toes can be affected and resemble the appearance of sausages, a condition called dactylitis. Sacroiliitis, more often asymmetric, can also be a psoriatic arthritis manifestation.

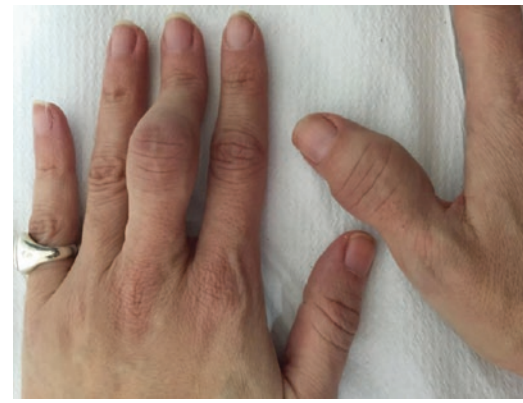

Fig. 3.10 Oligoarticular psoriatic arthritis: a 42-year-old female patient with arthritis affecting the left third proximal interphalangeal joint and the first right distal interphalangeal joint

42. **What is the relation between the onset and flares of psoriasis with the development of psoriatic arthritis?**

In the majority (70%) of patients, psoriasis precedes arthritis by an average of 7 years. Arthritis precedes or occurs simul-

taneously with psoriasis in one third of the patients. In patients with simultaneous onset of skin and joint disease, flares of both diseases are usually coexisting. However, for the majority of patients, the skin and arthritis run nonsynchronous courses.

43. **Which are the characteristic nail changes in patients with psoriatic disease?**
   - Oil drop or salmon patch: translucent yellow-red discoloration in the nail bed which resembles a drop of oil under the nail plate.
   - Pitting: loss of parakeratotic cells from the surface of the nail plate.
   - Beau's lines: transverse lines in the nails due to intermittent inflammation causing growth arrest lines.
   - Leukonychia: areas of white nail plate due to foci of parakeratosis within the body of the nail plate.
   - Subungual hyperkeratosis: excessive proliferation of the nail bed and hyponychium. This may lead to onycholysis (Fig. 3.11a).
   - Onycholysis: the nail plate separates from its underlying attachment to the nail bed. The nail plate whitens and may detach. Secondary infection may occur.
   - Nail plate crumbling: the nail plate weakens due to disease of underlying structures (Fig. 3.11b).

44. **Which parameters predict radiologic disease progression in psoriatic arthritis?**

Severe disease at presentation and elevated C-reactive protein levels.

45. **Which medical conditions coexist commonly with psoriatic arthritis?**

Obesity, type II diabetes mellitus, hyperuricemia, hypertension, fatty liver, increased incidence of metabolic syndrome and risk of premature atherosclerosis, and cardiovascular disease.

46. **Which clinical entities can lead to arthritis mutilans?**

Psoriatic arthritis and multicenter reticulohistiocytosis.

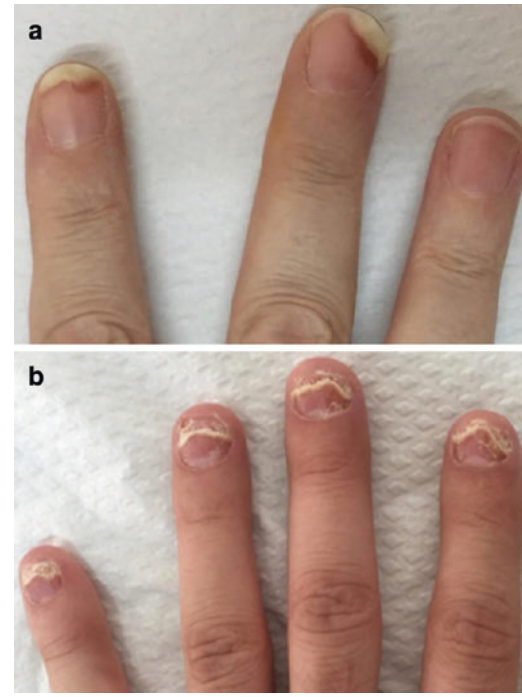

Fig. 3.11 Nail psoriasis: (**a**) a 48-year-old female patient with psoriatic arthritis presents separation of the nail plate from the underlying nail bed and hyponychium affecting the nails of the second and third right fingers, a form of nail psoriasis termed onycholysis. (**b**) A 31-year-old male patient with psoriatic arthritis presents with nail plate crumbling in all fingernails

47. **In which rheumatic disorders dactylitis can be a manifestation?**

Dactylitis occurs in seronegative arthritis, psoriatic arthritis, ankylosing spondylitis, and post-infectious (reactive) arthritis.

48. **Which are the rheumatologic manifestations in patients with inflammatory bowel disease?**

In inflammatory bowel disease, rheumatologic manifestations are frequent and include peripheral arthritis, axial involvement, and peripheral enthesitis. Secondary osteoporosis and hypertrophic osteoarthropathy may also occur. Axial involvement ranges from low back pain to true ankylosing spondylitis. Two types of peripheral arthritis can be seen in inflammatory bowel disease patients: type I, pauciarticular usually nondestructive arthritis affecting large joints and usually associated with active bowel disease, and type II, polyar-

ticular affecting small joints and tending to run a course independent of the bowel disease.

49. **What is the course of arthritis in patients with inflammatory bowel disease?**

Typically, the course of arthritis follows that of the inflammatory bowel disease; flares and remission of both pathologies coincide.

50. **Which bowel diseases are associated with inflammatory arthritis?**
- Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
- Microscopic colitis
- Whipple disease
- Gluten-sensitive enteropathy (celiac disease)

51. **What extraintestinal manifestations can occur in patients with inflammatory bowel disease and inflammatory arthritis?**
- Pyoderma gangrenosum
- Erythema nodosum
- Anterior uveitis and episcleritis
- Aphthous stomatitis
- Sensorineural hearing loss

52. **Which are the rheumatologic manifestations of Whipple disease?**

Whipple disease is a chronic, multisystem infection caused by *Tropheryma whipplei*. The disease usually affects middle-aged men. The most common symptoms arise from the gastrointestinal tract and are expressed with diarrhea and weight loss. In three quarters of patients, arthritis is the initial manifestation and can precede by a mean of 6 years the other disease symptoms. The classic disease scenario is long-term, unexplained, seronegative oligoarthritis or polyarthritis with a palindromic or relapsing course, although chronic destructive polyarthritis and spondyloarthritis have been repeatedly reported. The diagnosis of the disease in the majority of patients is set with periodic acid-Schiff staining of the proximal small bowel biopsy specimens which reveals the bacterial structures as inclusions within the tissue macrophages. Today polymerase chain reaction for *T. whipplei* DNA from tissue or blood is the diagnostic tool used in patients in the early stages of the disease or with atypical Whipple disease.

53. **Which microbial species are responsible for the development of post-infectious arthritis?**
- Urogenital: *Chlamydia trachomatis* and *Ureaplasma urealyticum*
- Enterogenic: salmonella species, shigella species, yersinia species, and campylobacter species
- Others: *Clostridium difficile*, *Neisseria gonorrhoeae*, streptococcus (post-streptococcal reactive arthritis), *Giardia lamblia*, mycoplasma, and *Borrelia burgdorferi*

54. **Migratory arthritis. In which medical disorders is it observed?**

Migratory arthritis is the arthritis which affects, over a period of days, one joint after the other. Disorders which present with migratory arthritis are systemic gonococcal infection, rheumatic fever, sarcoidosis, systemic lupus erythematosus, Lyme disease, and bacterial endocarditis.

55. **Which are manifestations of post-infectious arthritis (reactive arthritis)?**
- Fever and shaking chills (rigors).
- Joint pain and stiffness, typically of the knees, ankles, and feet. Wrists, fingers, and other joints are affected less often. Spondylitis and dactylitis can also develop.
- Warmth and redness around the joint.
- Commonly inflammation of the tendons (tendinitis) or at places where tendons attach to the bone (enthesitis).
- Mild conjunctivitis sometimes difficult to detect and more infrequently anterior uveitis can develop.
- Painless oral mucosal ulcers and skin rash can infrequently develop in patients with post-infectious arthritis.

56. **Which are the mucocutaneous lesions seen in association with post-infectious (reactive arthritis)?**

Keratoderma blennorrhagicum consists of prominent hyperkeratotic scaling lesions of the palms and soles (Fig. 3.12). Circinate balanitis is a painless, serpiginous ulceration of the glans penis. Both lesions are mostly associated with urogenital reactive arthritis. One fourth of patients with reactive arthritis develop painless oral ulcers.

57. **What are the differences in the synovial fluid findings between patients with rheumatoid arthritis and seronegative arthritis?**

In the synovial fluid from an inflamed joint of a rheumatoid arthritis patient, in contrast to synovial fluid from a joint of a patient with seronegative arthritis, rheumatoid factors and decreased complement (C3 and C4) levels may be found.

58. **Which viral infection, in the initial phase, can give the picture (arthralgias, fever, urticarial rash, low complement levels) of serum sickness?**

Hepatitis B infection.

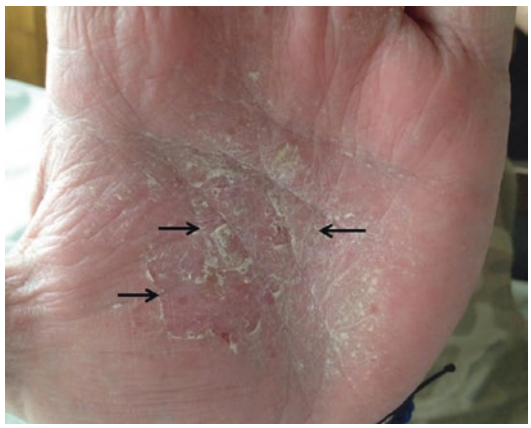

Fig. 3.12 Keratoderma blennorrhagicum: a 27-year-old male patient with chronic post-infectious arthritis. Palmar vesicopustular waxy lesions coalescing to form larger crusty plaques with desquamating edges are evident (arrows)

59. **Which are the rheumatologic manifestations of parvovirus 19 infection?**

In adults, the virus can cause an inflammatory arthritis that is difficult to be differentiated from rheumatoid arthritis. The arthritis affects symmetrically the wrists, hands, knees, and ankles. Joint symptoms last usually for 1–3 weeks, although in 20% or more of the affected individuals, arthritis may persist for months to years. Adults, in contrast to infected children, often do not experience fever nor do they develop cutaneous rashes. In some patients, the arthritis can be debilitating and requires prednisone to control symptoms. The presence of circulating IgM antiviral antibodies connotes an acute viral infection. The IgM antibody should eventually clear and convert entirely over to IgG antibody. If the arthritis does not get better, other types of inflammatory arthritis should be considered.

60. **Which rheumatic manifestations can be seen in patients with chronic hepatitis C?**

Hepatitis C virus (HCV) is lymphotropic and can trigger a B-cell expansion which causes a wide spectrum of autoimmune/lymphoproliferative disorders. These extrahepatic manifestations become clinically manifest in 40–70% of the HCV-infected patients and can be classified as rheumatic. These include arthralgias, arthritis, fatigue, fibromyalgia, cryoglobulinemic vasculitis, and chronic sialadenitis (Sjögren's-like syndrome).

61. **What is the clinical picture of arthritis occurring in patients with rheumatic fever versus the clinical picture seen in patients with rheumatoid arthritis?**

The arthritis in patients with rheumatic fever is acute and migratory. Typically it affects large joints like knees, ankles, elbows, and wrists. The affected joints can be red, hot, or swollen. The arthritis responds usually well to aspirin and does not leave any cartilage or bone defects. In adult rheumatic fever patients, tenosynovitis is common and sometimes

severe and resembles disseminated gonococcal disease. In contrast rheumatoid arthritis is a chronic polyarthritis which affects symmetrically small and large joints and can cause permanent joint destruction and deformity.

62. **Which parts of the heart are affected by rheumatic fever and which are the sequelae?**

In patients with rheumatic fever, all parts of the heart (endocardium, pericardium, and myocardium) can be affected. The hallmark of rheumatic carditis is valvular lesions. The most commonly affected valve is the mitral either alone or together with the aortic valve. The early valvular damage is usually valve regurgitation. After repeated recurrences of rheumatic fever, the valvular leaflets get thickened, scarred, and calcified, pathologies which lead to valvular stenosis.

63. **Which are the major and minor diagnostic criteria for adult-onset Still's disease?**

- Major criteria: fever (>39 °C) lasting for more than 7 days, arthralgias/arthritis of more than 2-week duration, characteristic salmon-like rash, and leukocytosis (>10 × 10^9/L with >80% neutrophils)
- Minor criteria: sore throat, lymphadenopathy, hepatosplenomegaly, abnormal liver function tests, negative rheumatoid factor and antinuclear antibodies

Diagnosis requires at least five diagnostic criteria, two of which being major.

64. **Which are poor prognostic factors for adult-onset Still's disease course?**

Patients with chronic polyarticular disease generally have worse prognosis and more disability than patients with only systemic manifestations. Nevertheless, adult-onset Still's disease could be life-threatening, especially in patients with systemic disease complicated with hemophagocytic (macrophage activation) syndrome, acute respiratory distress syndrome, or disseminated intravascular coagulation.

65. **What is macrophage activation syndrome?**

It is a secondary (reactive) syndrome which can occur in patients with adult-onset Still's disease and systemic juvenile idiopathic arthritis and in patients with active Epstein-Barr or cytomegalovirus infection. It is a life-threatening condition and presents with:

High fever
Hepatosplenomegaly
Very high serum ferritin levels
Elevated liver function tests
Pancytopenia
Hypertriglyceridemia
Consumptive coagulopathy
Central nervous system involvement

Diagnosis is confirmed by a bone marrow aspiration which shows phagocytosis of hemopoietic cells by macrophages.

66. **Which are the main types of arthritis in juvenile idiopathic arthritis and which are the immunologic characteristics of each type?**

- Oligoarticular (<4 large joints): usually antinuclear antibody positive
- Polyarticular: resembles rheumatoid arthritis, is rheumatoid factor and anti-citrullinated peptide positive, and has worse prognosis
- Systemic: characterized by high fever, throat pain, rash, leukocytosis, and elevated acute-phase proteins

67. **Which are the clinical/pathological characteristics of multicentric reticulohistiocytosis?**

Multicentric reticulohistiocytosis is a rare disease affecting more females than males (3:1). Constitutional symptoms such as fever, malaise, weight loss, and itching are commonly present. Mucocutaneous manifestations typically manifest with reddish-brown papules and nodules in the hands, fingers (Fig. 3.13a), around the nails, as well as in the oropharyngeal and nasal mucosal surface.

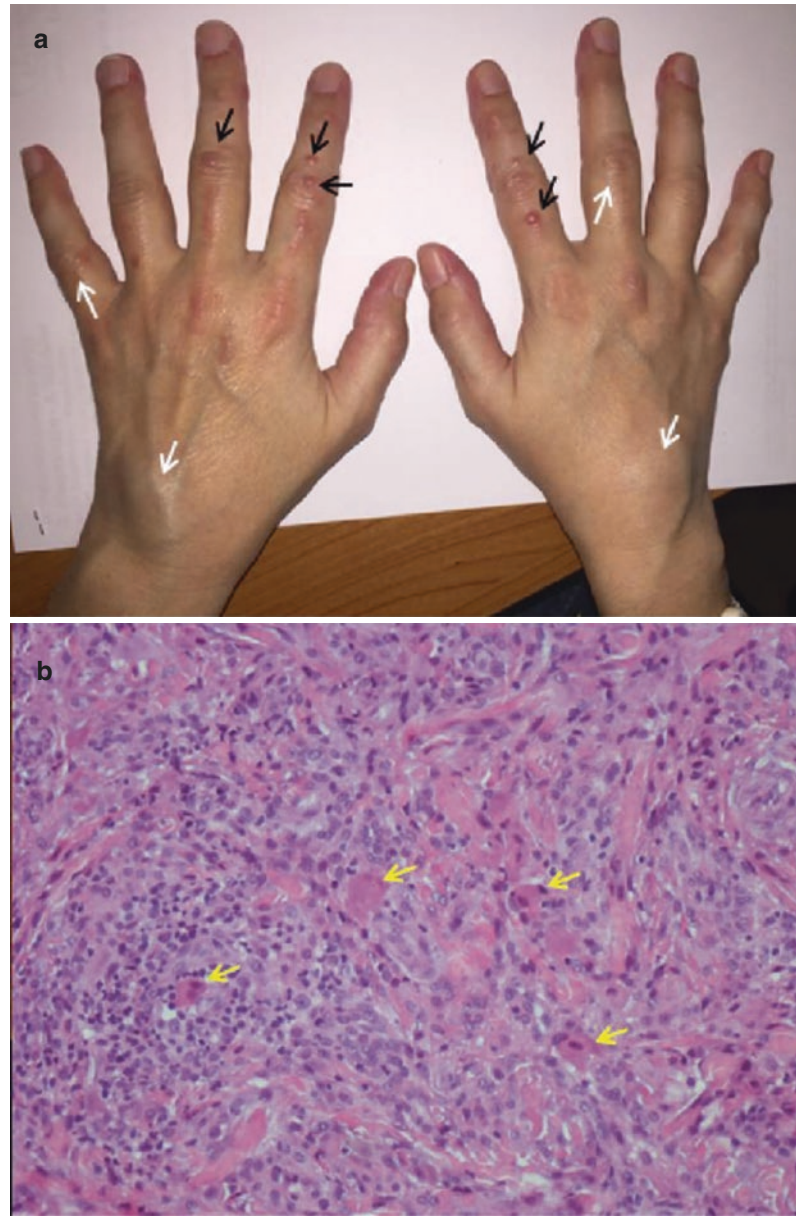

Fig. 3.13 Multicentric reticulohistiocytosis: (**a**) a 33-year-old female presented with fever, joint pain, morning stiffness, and multiple, red-brown, non-tender, cutaneous nodules ranging from 1 to 5 mm, localized on both hands (*black arrows)* along with symmetrical arthritis of the proximal interphalangeal and wrist joints (*white arrows*). (**b**) Biopsy of the nodules demonstrated abundant infiltration of the dermis by histiocytes and scattered multinucleated giant cells (large histiocytes) with finely granulated eosinophilic cytoplasm (H&E ×200, yellow arrows)

Biopsy of the lesions characteristically shows eosinophilic histiocytes and multinuclear giant cell infiltrates with opalescent appearance, fine vacuoles, and PAS-positive granules (Fig. 3.13b). In some patients, arthritis remits spontaneously, while in 1/3 of the patients, it can progress to destructive (mutilans) arthritis. In the latter group of patients, arthritis can be symmetrical and debilitating, usually affecting the interphalangeal finger joints but also the hips and knees. The diagnosis of multicentric reticulohistiocytosis can be easily suspected when a patient presents with the typical skin lesions associated with erosive arthritis.

68. **Which form of exercise the physician should recommend to a patient with arthritis, and why?**

Exercise can reduce articular pain and stiffness and increase range of motion and muscle strength. It can also lead to weight

loss, which will reduce stress on painful joints. The best exercises for people with arthritis are those that place the least stress on the joints, such as exercising in water, swimming, walking, stretching, and using weight machines as well as stationary cycling. Before beginning any new exercise program, the patient should consult the physician.

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4 Systemic Lupus Erythematosus, Antiphospholipid Syndrome, and Mixed Connective Tissue Disease

Abstract

This chapter presents essential knowledge on systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and mixed connective tissue disease (MCTD). These diseases share common features in the sense that they are systemic, can be overlapping, and present with nondestructive arthritis.

SLE is the prototype immune complex-mediated disease in humans. There is a strong but not absolute, genetic predisposition for its development. Patients' serum contains autoantibodies against nuclear antigens (ANA) as well as other autoantibodies (e.g., anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-U1RNP or anti-Sm, antiphospholipids, anti-ribosomal proteins). Some of them are diagnostic biomarkers, while others predict particular clinical manifestations. Such examples are anti-Ro/SSA antibodies which are associated with a photosensitive, annular/polycyclic, and psoriasiform/papulosquamous rash, anti-dsDNA antibodies with SLE nephritis, anti-ribosomal P with psychosis, antiphospholipids with thromboses and recurrent abortions, and anti-histones with drug-induced SLE. IgG anti-Ro/SSA or anti-La/SSB antibodies cross the placenta and affect the fetus which develops anti-Ro-related rashes, thrombocytopenia, and rather infrequently cardiomyopathy which leads to complete heart block (neonatal lupus).

APS is an acquired, autoimmune thrombophilia, characterized by the presence of antiphospholipid antibodies and expressed mainly by thrombotic events, pregnancy morbidity, autoimmune hemolytic anemia, or thrombocytopenia. Thrombotic events reoccur usually in the same vascular bed (arterial or venous) and can range from isolated thromboses to massive pulmonary emboli or concurrent thromboses in many organs (catastrophic APS). The heart is involved in terms of coronary artery disease or valvular, noninfectious vegetations (Libman-Sacks endocarditis), while the kidney by thrombotic microangiopathy of the glomeruli or chronic renal vascular lesions.

H.M. Moutsopoulos et al., *Rheumatology in Questions*, https://doi.org/10.1007/978-3-319-71604-6_4

MCTD is a disease characterized by Raynaud's phenomenon, puffy hands, and arthritis/arthralgias. Acrosclerosis, esophageal dysmotility, myositis, lung fibrosis, and pulmonary hypertension can manifest in patients with MCTD, along with high titers of anti-U1RNP antibodies. The outcome is unpredictable, but many patients after years evolve to systemic sclerosis.

1. **Does inheritance play a role in the development of systemic lupus erythematosus?**

   Population-based studies have shown two to three times increased relative risk to develop systemic lupus erythematosus in individuals with particular HLA class II genes (HLA-DR2, HLA-DR3). The strongest evidence that systemic lupus erythematosus is genetically determined comes from familial aggregation studies. An identical twin of a patient with systemic lupus erythematosus carries a 25–50% chance of developing systemic lupus erythematosus, while a nonidentical twin has a risk of 2–5%, the latter still being greater than that in the general population. First-degree relatives of a patient with systemic lupus erythematosus carry a six times higher risk of developing systemic lupus erythematosus. Furthermore, inherited deficiencies of early complement components (C1q, C2, C4) increase five to ten times the risk of systemic lupus erythematosus development.

2. **Which clinical or laboratory manifestations predict that a patient not fulfilling diagnostic criteria will evolve to systemic lupus erythematosus, and when?**

   The presence of malar rash, oral ulcers, elevated anti-dsDNA, and decreased serum C4 complement levels predict that an individual not fulfilling at that time systemic lupus erythematosus diagnostic criteria will evolve to systemic lupus erythematosus within the next 2–5 years, but not necessarily with major organ involvement.

3. **Which are the most common autoantibodies encountered in patients with systemic lupus erythematosus, and what are their main clinical associations?**
   - Antinuclear antibodies (ANA): are not specific for systemic lupus erythematosus, and less than 5% of individuals presenting ANA positivity will actually develop systemic lupus erythematosus. Yet, 98% of systemic lupus erythematosus patients will demonstrate elevated ANA titers.
   - Anti-dsDNA: highly diagnostic for systemic lupus erythematosus and correlate with disease activity, in particular lupus nephritis.
   - Anti-Sm (Smith): highly diagnostic for systemic lupus erythematosus and do not correlate with disease activity.
   - Anti-Ro/SSA: encountered also in patients with subacute cutaneous lupus erythematosus (SCLE), Sjögren's syndrome, neonatal lupus (especially anti-Ro52), neuromyelitis optica spectrum diseases, and photosensitivity.
   - Anti-La/SSB: encountered primarily in patients with Sjögren's syndrome and patients with SCLE.
   - Anti-ribosomal P: highly specific for systemic lupus erythematosus with psychiatric disease (lupus psychosis, epilepsy).
   - Antiphospholipids: associated with inhibition of in vitro coagulation tests (lupus anticoagulant), thrombosis, recurrent fetal loss, and thrombocytopenia.
   - Anti-histones: encountered in systemic lupus erythematosus and drug-induced lupus erythematosus patients.

4. **In a febrile systemic lupus erythematosus patient, which simple lab test(s) will point to fever being due to bacterial infection and not to disease exacerbation?**
   - White blood cell count: leukocytosis
   - Elevated serum CRP levels (more than 15–20 times above normal value)
   - Elevated serum procalcitonin levels

5. **A patient with arthralgias, skin rash, leukopenia (WBC < 4000/mm^3), and negative antinuclear antibodies (ANA). What is the**

possibility that this patient has another autoantibody, which one, and why?

Anti-Ro/SSA autoantibodies. Patients in whom the only autoantibodies present are anti-Ro antibodies may have a falsely negative ANA test using the traditional human epithelial cell line-2 (HEp-2) substrate, because Ro60 immunoreactivity may be lost during the preparation of the cells and because Ro52 is a cytoplasmic, rather than a nuclear autoantigen. This patient might also have positive antithyroid peroxidase or anti-thyroglobulin antibodies.

6. **Which laboratory parameters should be periodically evaluated in order to follow systemic lupus erythematosus disease activity?**

Laboratory parameters used to follow disease activity in systemic lupus erythematosus patients include complete blood count, erythrocyte sedimentation rate, serum creatinine, liver enzymes, urine analysis, serum C3 and C4 levels, and anti-dsDNA autoantibody levels.

7. **Which are the demographic and clinical findings which predict that an acute exacerbation (flare) will occur in a systemic lupus erythematosus patient?**

Young age of systemic lupus erythematosus onset (<25 years), proliferative lupus nephritis at diagnosis, oral ulcers, increased anti-dsDNA levels >50%, leukopenia and thrombocytopenia, anti-Sm antibody positivity, and use of immunosuppressive agents for severe systemic lupus erythematosus are all factors that can predict a lupus flare.

8. **Which are the commonest morbidity and mortality causes in patients with systemic lupus erythematosus?**

The commonest causes of morbidity in patients with systemic lupus erythematosus are infections, hypertension, cardiovascular disease, osteoporosis, cytopenias due to immunosuppressive agents, and malignancies. The most frequent causes of mortality in patients with systemic lupus erythematosus are active systemic lupus erythematosus, cardiovascular disease, thromboses, and serious infections.

9. **Which are the most common infections seen in immunosuppressed systemic lupus erythematosus patients?**

Microbial septicemia, *Pneumocystis carinii* pneumonia, varicella zoster virus infection, and tuberculosis.

10. **When does varicella zoster infection develop in systemic lupus erythematosus patients, and which are the risk factors for generalized infection?**

Varicella zoster virus infection can occur in systemic lupus erythematosus patients treated with immunosuppressive agents, when the disease is in remission. Usually the course of varicella zoster virus infection is benign; however seldomly, and especially in cases of sciatic nerve involvement, generalized varicella zoster virus infection can develop. Varicella zoster virus infection by itself does not seem to exacerbate systemic lupus erythematosus. Discontinuation of immunosuppressive agents is recommended, and antiviral therapy should be instituted.

11. **Which are common causes of anemia in systemic lupus erythematosus?**

Anemia of chronic disease, iron deficiency anemia, autoimmune hemolytic anemia, and seldomly myelodysplasia.

12. **Which conditions usually coexist with autoimmune hemolytic anemia in systemic lupus erythematosus patients?**

Renal involvement, thrombocytopenia, and less often thrombotic episodes.

13. **What is the clinical picture of Jaccoud's arthropathy? In which autoimmune patients can it be seen?**

Jaccoud's arthropathy was first described in patients with rheumatic fever, but it can be seen in patients with systemic lupus erythematosus and Sjögren's syndrome. Presents with correctable deformities of the metacarpophalangeal and metatarsophalangeal joints which is the result of soft tissues abnormalities such as laxity of ligaments, fibrosis of the capsule, and muscular imbalance, rather than joint bony destructions (Fig. 4.1).

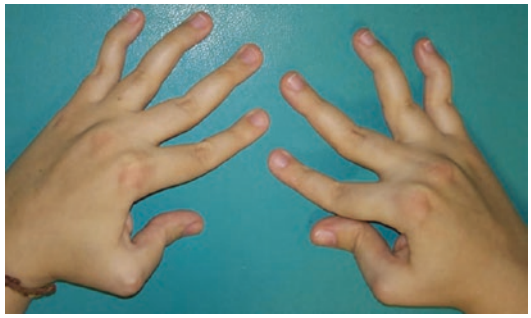

Fig. 4.1 Jaccoud's arthropathy: a 28-year-old female with long-standing systemic lupus erythematosus presents with correctable deformities of the metacarpophalangeal and proximal interphalangeal joints which is the result of soft tissues abnormalities such as laxity of ligaments, fibrosis of the capsule, and muscular imbalance, rather than joint bony destructions

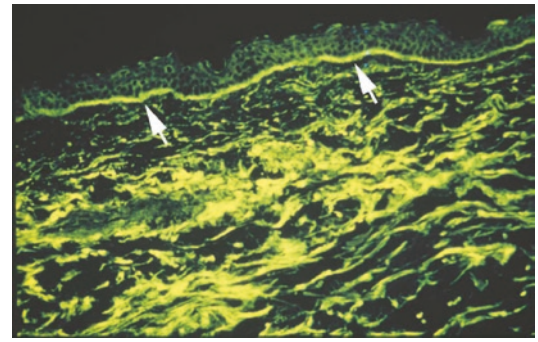

Fig. 4.2 Lupus band test: direct immunofluorescence staining of clinically healthy and unexposed to sun skin from systemic lupus erythematosus patient revealed deposits of immunoglobulins and complement components along the dermo-epidermal junction (arrows)

14. **What is lupus band test? In which skin area is it performed? What is its diagnostic and prognostic use?**

The lupus band test is a diagnostic procedure performed on a skin biopsy specimen that detects, with direct immunofluorescence staining, deposits of immunoglobulins and various complement components along the dermo-epidermal junction in lupus erythematosus patients. Detection of these deposits in the skin of patients with lupus erythematosus demonstrates a linear band at the basement membrane zone, hence the name lupus band test. Biopsy tissue is taken from clinically healthy skin of systemic lupus erythematosus patients preferably unexposed to sun. It is positive in about 70%–80% of sun-exposed non-lesional skin specimens obtained from patients with systemic lupus erythematosus and in about 55% of systemic lupus erythematosus cases if sun-protected non-lesional skin is analyzed. In contrast to systemic lupus erythematosus patients where the lupus band test is frequently positive in both involved and uninvolved skins, in patients with cutaneous lupus, only the lesional skin shows a positive lupus band test (Fig. 4.2). Moreover, a positive lupus band test may serve as a prognostic indicator in patients with an established diagnosis of lupus erythematosus, as it correlates with severe extracutaneous disease, mainly lupus nephritis, and with anti-dsDNA antibodies.

15. **Which are the cutaneous manifestations of systemic lupus erythematosus?**

The skin manifestations of systemic lupus erythematosus can be divided into nonspecific (nondiagnostic) and specific (diagnostic).

- *Nonspecific* manifestations include:
  - Raynaud's phenomenon (Fig. 4.3)
  - Non-scarring alopecia (Fig. 4.4)
  - Livedo reticularis (Fig. 4.5)
  - Skin vasculitis
- The *specific* cutaneous systemic lupus erythematosus manifestations are divided into acute, subacute, and chronic:
  - **Acute systemic lupus erythematosus cutaneous** manifestations include:
    Butterfly rash (maculopapular eruption in the central face area around the nose) (Fig. 4.6)
    Photosensitivity eruptions in sun-exposed areas
    Papular erythematous rashes in the arms and legs
    Bullous eruptions with erosions and mouth/hard palate ulcers (Fig. 4.7)
  - **Subacute cutaneous lupus erythematosus (SCLE)** typical skin rashes include:
    Annular/polycyclic and psoriasiform/papulosquamous rashes (Fig. 4.8). The lesions typically occur in photosensitive distribution. Common locations of

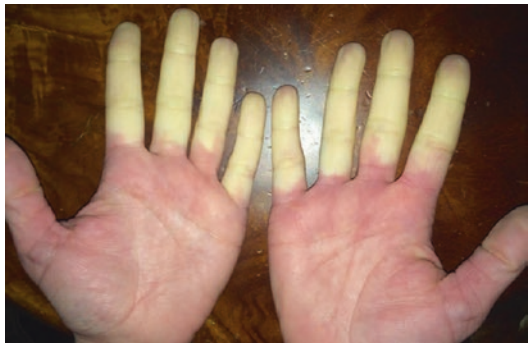

Fig. 4.3 Raynaud's phenomenon in a 40-year-old male patient with systemic lupus erythematosus who upon stress develops white coloring of the fingers

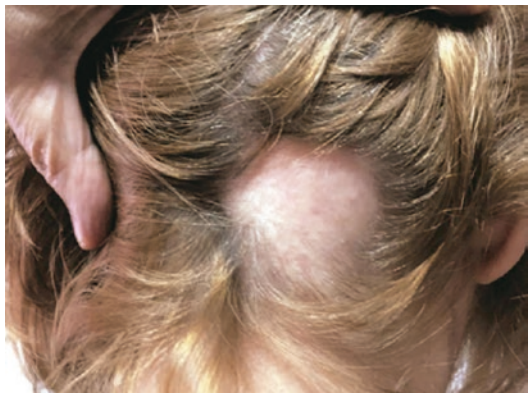

Fig. 4.4 Non-scarring scalp alopecia in a 52-year-old female patient with systemic lupus erythematosus

SCLE rash include the neck, the shoulders, the upper chest, the upper back, and the extensor surface of the hands. In the majority of patients, sun exposure exacerbates the disease.

– **Chronic cutaneous manifestations** in systemic lupus erythematosus patients include discoid rashes which are painless disc-shaped erythematous plaques with areas of follicular hyperkeratosis. When the lesions progress, they result in cutaneous atrophy, either in loss or increase of skin pigmentation (Fig. 4.9), and depressed scars can develop. If the discoid lesions are on the scalp, they result in scarring alopecia (Fig. 4.10).

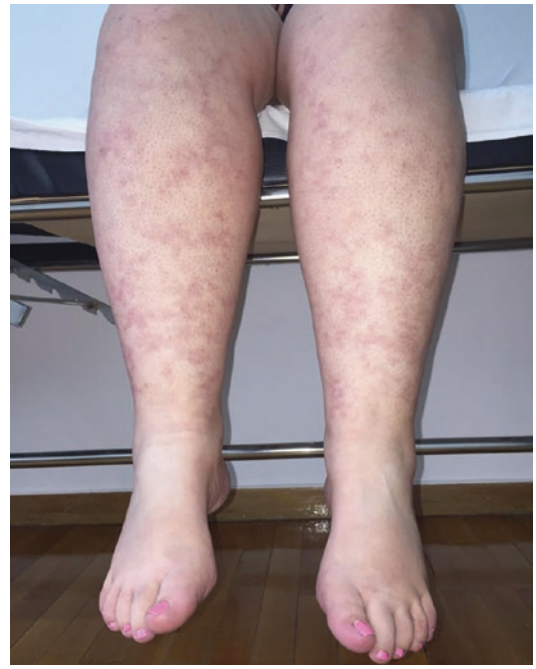

Fig. 4.5 Livedo reticularis in a 20-year-old female with systemic lupus erythematosus and antiphospholipid syndrome

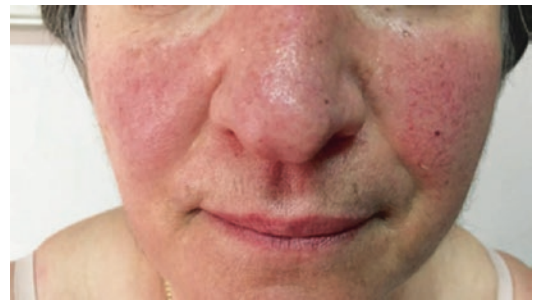

Fig. 4.6 Butterfly rash in a 50-year-old woman with systemic lupus erythematosus

16. **What is the histopathologic classification used for systemic lupus erythematosus renal biopsies?**
    – **Class I: minimal mesangial lupus nephritis (LN) –** normal-appearing glomeruli by light microscopy (LM) with immune deposits confined to the mesangium visible by immunofluorescence (IF).
    – **Class II: mesangial proliferative LN** – mesangial proliferation (of any degree)

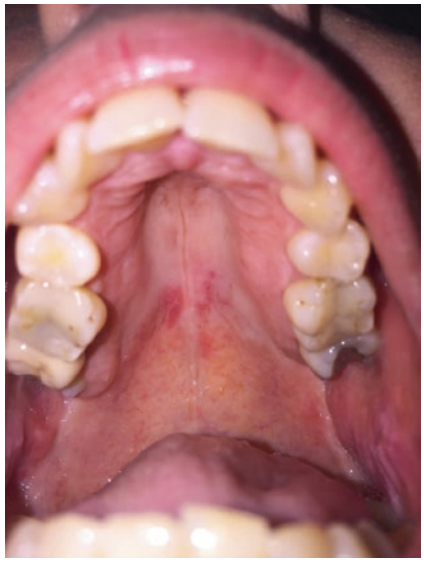

Fig. 4.7 Painless hard palate ulcer in a 40-year-old lady with exacerbating systemic lupus erythematosus

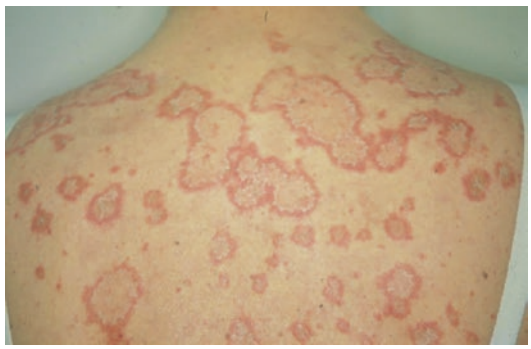

Fig. 4.8 Subacute cutaneous lupus erythematosus in 21-year-old female patient with an annular/polycyclic and psoriasiform/papulosquamous rash on the back after sun exposure

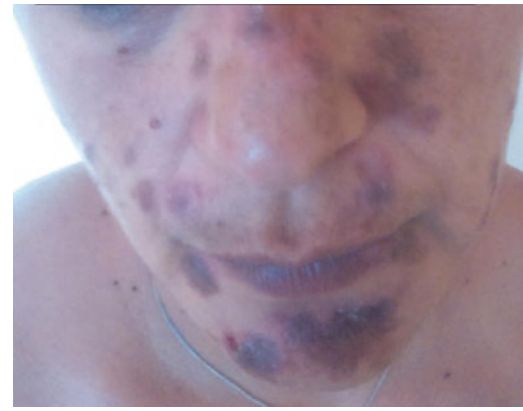

Fig. 4.9 Discoid lupus erythematosus: a 36-year-old female patient with multiple chronic hyperpigmented discoid lesions on the face

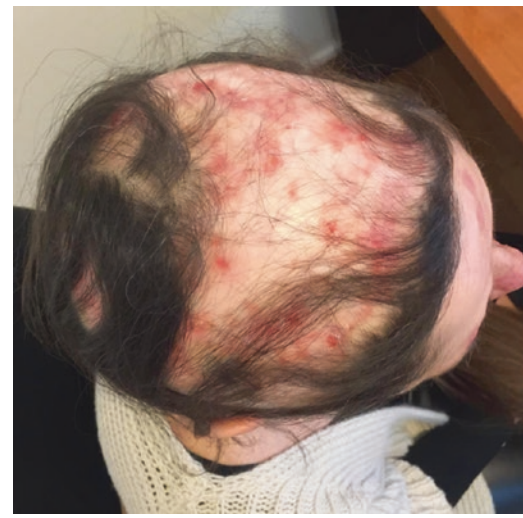

Fig. 4.10 Scarring scalp alopecia: a 34-year-old female with systemic lupus erythematosus and multiple discoid scarring scalp lesions

visible by LM and mesangial deposits by IF. Minute subendothelial or subepithelial immune deposits may rarely be visible by IF or electron microscopy (EM) , but not by LM, whether or not there is endocapillary proliferation.

- **Class III: focal LN** – focal, segmental, or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.
- **Class IV: diffuse LN** – subendothelial immune deposits visible by LM with or without mesangial alterations involving ≥50% of all glomeruli.

– Class IV is subdivided into diffuse segmental (IV-S, segmental defined as a glomerular lesion that involves less than half of the glomerular tuft) when ≥50% of the involved glomeruli has segmental lesions, and diffuse global (IV-G) when ≥50% of the involved glomeruli have global lesions.

– Lesions in classes III and IV are further characterized as purely active (A), as purely chronic (C), and as a combination of active and chronic lesions (A/C).
  – **Class V: membranous LN** – global or segmental subepithelial immune deposits involving ≥50% of the glomerular tuft in ≥50% of glomeruli. Class V lupus nephritis may occur in combination with class III or IV.
  – **Class VI: advanced sclerosing LN** – ≥90% of glomeruli are globally sclerotic with no evidence of ongoing activity.

17. **Where do immune complexes deposit in the membranous and where in the membranoproliferative lupus nephritis?**

    In the membranoproliferative lupus nephritis (class III, class IV), the immune complexes deposit subendothelially, while in the membranous lupus nephritis subepithelially (Fig. 4.11).

18. **Which lupus patients have lower incidence of lupus nephritis?**

    Drug-induced lupus and subacute cutaneous lupus erythematosus patients.

19. **Which are the adverse predictors of remission and relapse of lupus nephritis?**

    Adverse predictors of remission are severe proteinuria and delayed initiation of therapy from the time nephritis was clinically diagnosed. Predictors of earlier relapse for patients entering remission include a longer time to remission and a history of central nervous system involvement.

20. **Which are poor prognostic factors for lupus nephritis?**

    Hypertension, renal failure, massive proteinuria, and high activity score of lupus nephritis on renal biopsy specimen are all associated with poor renal prognosis.

21. **Which are the clinical and laboratory findings distinguishing toxemia of pregnancy from lupus nephritis flare?**

    The distinction between severe toxemia of pregnancy (preeclampsia/eclampsia) and active lupus nephritis can be difficult, since both conditions may present with hypertension, thrombocytopenia, hemolytic anemia, and compromised renal function with protein-

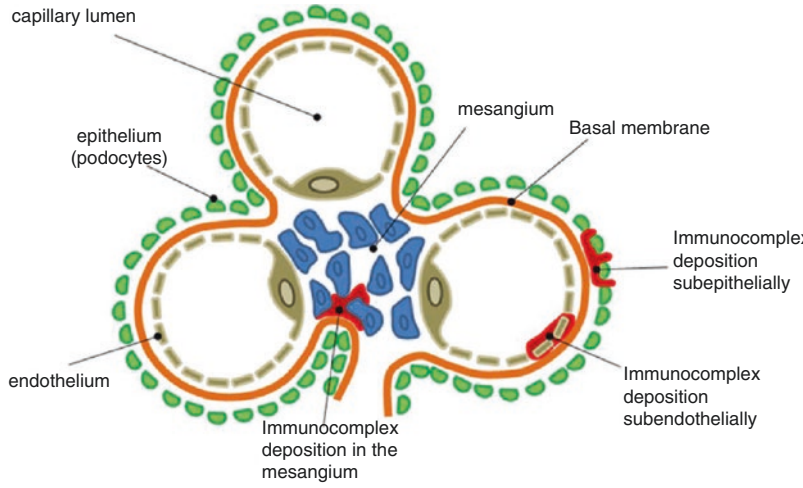

Fig. 4.11 Lupus nephritis: a schematic representation of the renal pathology. Deposition of immune complexes (ICs) in the mesangium occurs in patients with mesangial glomerulonephritis (GMN), and deposition of ICs under the endothelium is observed in patients with proliferative GMN, while deposition under the epithelium is found in patients with membranous GMN

uria. The absence of other clinical manifestations indicative of systemic lupus erythematosus activity (arthritis, rash, leukopenia), as well as the lack of white blood cells, red cells, and casts in the urine and stable anti-dsDNA autoantibodies, decreased urine calcium, and increased serum uric acid levels, makes the diagnosis of eclampsia more likely. Serum complement levels are not helpful in distinguishing the two conditions, since they can be decreased during a lupus flare as well as in patients with pregnancy toxemia.

22. **Which are the transient and which are the permanent lesions in newborns with neonatal lupus?**

Neonatal lupus is associated with the transplacental passage of maternal anti-Ro/SSA and anti-La/SSB antibodies. The most frequent manifestations seen in affected neonates are rash (lesions of discoid lupus or subacute cutaneous lupus), hepatic dysfunction, and thrombocytopenia. The cutaneous, hepatic, and hematologic manifestations are transient, generally resolving in 2–6 months after delivery. The most serious manifestation of neonatal lupus is cardiomyopathy which leads to complete heart block (CHB). Heart block typically begins in utero during the second or third trimester initially as first- or second-degree atrioventricular block and then can progress to third-degree block. CHB, if established, appears to be irreversible, and the neonate may require a permanent pacemaker. The long-term prognosis of children with neonatal lupus is guarded since some of them will develop later in their life other autoimmune disorders.

23. **Which anatomic heart sites can be affected from systemic lupus erythematosus?**

Pericardium, coronary arteries, heart valves, myocardium, and endocardium.

24. **Which valves are commonly affected from Libman-Sacks endocarditis and what are the sequelae?**

Libman-Sacks endocarditis is a noninfectious endocarditis, also called verrucous or marantic, that can occur in systemic lupus erythematosus and antiphospholipid syndrome patients with active disease of long duration. The valvular vegetations (Fig. 4.12) are composed of fibrin, neutrophils, lymphocytes, and histiocytes and more frequently produce valvular regurgitation, while stenosis occurs infrequently. The ventricular and atrial surface of the mitral valve is typically and more often affected. These vegetations infrequently embolize. Verrucous endocarditis is also seen in patients with hypercoagulable states and malignancy.

25. **Pulmonary arterial hypertension is a serious complication of systemic lupus erythematosus. Which risk factor(s) can predict this complication in systemic lupus erythematosus patients?**

Early recognition of pulmonary arterial hypertension (PAH) is not easy due to lack of specific symptoms. Recent meta-analyses showed that the presence of anti-U1RNP, anti-Sm, and antiphospholipid antibodies in the sera of systemic lupus erythematosus patients (especially Asian in origin) is a risk factor for PAH development, warranting careful monitoring and screening for PAH of systemic lupus erythematosus patients with these autoantibody reactivities [1, 2].

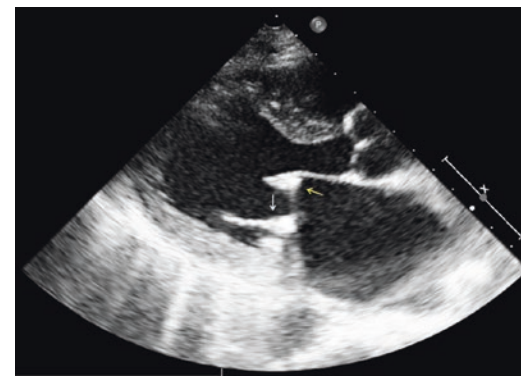

Fig. 4.12 Libman-Sacks vegetations: a 40-year-old woman with systemic lupus erythematosus and antiphospholipid syndrome demonstrating serious mitral valve insufficiency. Transthoracic two-dimensional echocardiogram revealed thickening and calcification of the posterior mitral valve leaflet (white arrow) and Libman-Sacks vegetation (yellow arrow) (*Figure courtesy of Ioannis Moyssakis, MD*)

26. **Which neurologic manifestations can be seen in systemic lupus erythematosus patients?**

Cognitive impairment is the most frequent manifestation, followed by seizures. Additional manifestations include peripheral neuropathies, acute confusional state, headache, and depression. Central nervous system involvement can also manifest as lupus retinopathy. Lupus retinopathy is a microangiopathy of retinal vessels, particularly associated with vasculitis or anticardiolipin antibodies; it is associated with active systemic disease (mostly lupus nephritis), and retinal lesions during fundus examination (Fig. 4.13) are of critical importance, both visually and prognostically.

Less common manifestations are psychosis, movement disorders, myelopathy, optic neuritis, cerebrovascular accidents, cranial neuropathies, and aseptic meningitis.

27. **How common are strokes in systemic lupus erythematosus patients?**

Strokes in systemic lupus erythematosus patients are twice more common compared to the incidence of strokes in the general population. Usually strokes occur within the first year after systemic lupus erythematosus diagnosis. Thus, as soon as the diagnosis of systemic lupus erythematosus is established, the physicians should search for stroke risk factors and apply the necessary measures to eliminate them [3].

28. **In which systemic lupus erythematosus patients posterior reversible encephalopathy syndrome (PRES) can occur, and what is its clinical course?**

This syndrome has been rarely described in systemic lupus erythematosus patients. Several risk factors have been postulated for the development of PRES in systemic lupus erythematosus, such as younger age, high disease activity, lymphopenia, hypertension, dyslipidemia, renal function impairment, and immunosuppressive therapy (including high doses of corticosteroids alone or in combination with cyclophosphamide). The onset of the neurologic symptomatology can be acute or subacute. The patients present with altered mental status and headaches and can develop seizures or vision loss. Magnetic resonance imaging findings are

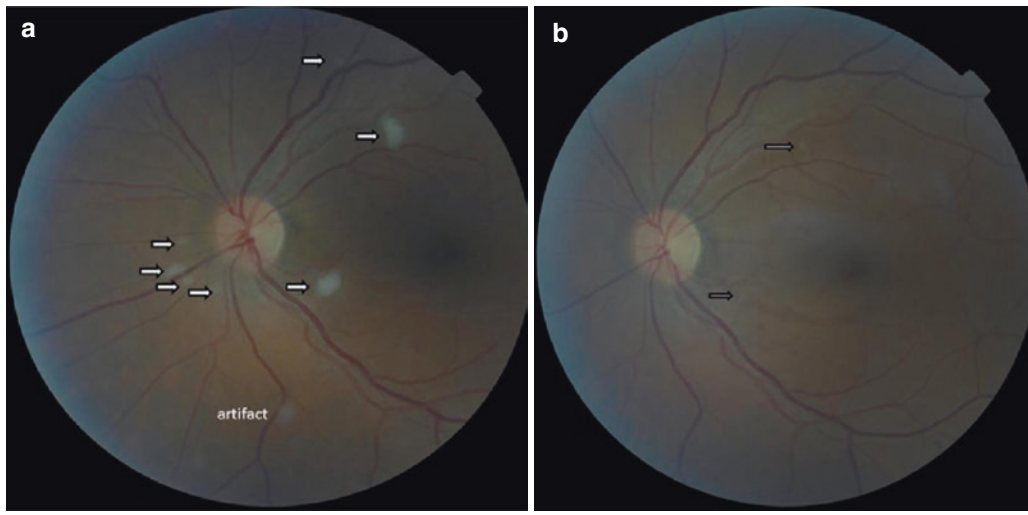

Fig. 4.13 Lupus retinopathy: a 58-year-old nonhypertensive, nondiabetic female patient with systemic lupus erythematosus and lupus nephritis who presented with fever, microscopic hematuria, and a generalized vasculitic rash. (**a**) Funduscopic examination revealed cotton wool spots (grayish-white slightly elevated lesions which look like clouds) in the superficial retina (arrows) in both eyes. (**b**) Cotton wool spots regressed after treatment with methylprednisolone and cyclophosphamide intravenous pulses (*Figure courtesy of Professor Athanasios G. Tzioufas, MD*)

characteristic and reveal white matter changes mostly in the parieto-occipital areas bilaterally. These findings differentiate posterior reversible encephalopathy syndrome from other central nervous system complications of systemic lupus erythematosus. The clinical and imaging abnormalities of the syndrome resolve within 1–4 weeks without any sequelae [4].

29. **Which are the cerebrospinal fluid findings in a systemic lupus erythematosus patient with central nervous system disease?**

Examination of cerebrospinal fluid (CSF) from a systemic lupus erythematosus patient primarily aims to rule out central nervous system (CNS) infection. However, the presence in the CSF of high immunoglobulin (Ig) G index (connotes intrathecal IgG production), oligoclonal Ig bands, low complement C4 component and normal sugar levels all attest toward the diagnosis of CNS involvement from systemic lupus erythematosus.

30. **Which are the predictors of poor outcome in systemic lupus erythematosus patients with neuropsychiatric manifestations?**

The number of previous neuropsychiatric events and the coexistence of antiphospholipid syndrome.

31. **Which are the clinical and laboratory findings in patients with mixed connective tissue disease?**

Patients with mixed connective tissue disease (MCTD) express manifestations of different systemic autoimmune connective tissue diseases but do not fulfill classification criteria for any of them. The most common clinical manifestations include Raynaud's phenomenon, puffy (swollen) hands (Fig. 4.14), and arthritis/arthralgias. Acrosclerosis, esophageal dysmotility, myositis, interstitial lung disease, and pulmonary hypertension can manifest in patients with MCTD, while severe renal and CNS diseases are uncommon. High levels of anti-U1RNP antibodies are the laboratory hallmark of MCTD, and these patients characteristically lack other specific autoantibodies (e.g., anti-Sm, anti-dsDNA).

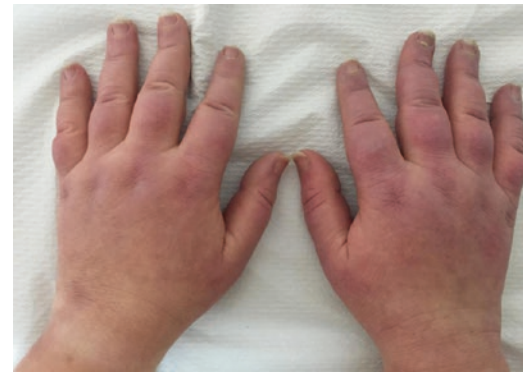

Fig. 4.14 Mixed connective tissue disease: puffy (swollen) hands in a 33-year-old female patient diagnosed with high titers of anti-U1RNP antibodies

32. **What is the clinical course of a patient with mixed connective tissue disease?**

The clinical course of mixed connective tissue disease (MCTD) is variable. Some patients can run a rather benign course, while others experience a severe and progressive disease. Arthritis, fatigability, and shortness of breath on exertion can predict higher mortality. Pulmonary hypertension contributes to premature death of patients with MCTD [5].

33. **What is termed overlap syndrome?**

Patients with an overlap syndrome meet the diagnostic criteria for more than one systemic autoimmune disease. Although features of two diseases may occur simultaneously, usually manifestations of one disease predominate clinically. Sjögren's syndrome is the most common overlapping systemic autoimmune disease, and it can be seen with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, mixed connective tissue disease, autoimmune thyroiditis, primary biliary cirrhosis, mixed cryoglobulinemia, and hypergammaglobulinemic purpura.

34. **In which medical situations should the suspicion of antiphospholipid syndrome be raised?**

Antiphospholipid syndrome should be ruled out as a possible underlying diagnosis in patients with:

- Arterial thrombosis in an individual younger than 50 years of age
- Recurrent miscarriages not explained by other causes (anatomic, hormonal, genetic)
- Recurrent venous thromboses, when genetic factors are ruled out
- Both arterial and venous thromboses
- Thromboses at unusual vascular sites

35. **What is termed primary and secondary antiphospholipid syndrome?**

Primary antiphospholipid syndrome (Hughes syndrome) is defined by the presence of antiphospholipid autoantibodies, thrombotic events, and/or pregnancy morbidity in the absence of another associated autoimmune disease. Up to 10% of individuals with primary antiphospholipid syndrome will evolve to systemic lupus erythematosus within 10 years of diagnosis. Systemic lupus erythematosus or other patients with autoimmune diseases and antiphospholipid autoantibodies who develop a thrombotic event are defined as having secondary antiphospholipid syndrome.

36. **Which are the clinical and renal histological lesions in antiphospholipid syndrome patients with nephritis?**

Renal involvement occurs in as many as 25% of patients with the primary antiphospholipid syndrome (APS). Clinically APS-associated nephropathy presents with hypertension, microscopic hematuria, and proteinuria (usually mild) and if untreated leads to renal insufficiency. The spectrum of renal pathology in APS includes renal artery thrombosis, renal infarction, renal vein thrombosis, and a small vessel vaso-occlusive nephropathy defined as "antiphospholipid antibody-associated nephropathy." This nephropathy is characterized by acute lesions, thrombotic microangiopathy, and chronic lesions such as fibrous intimal hyperplasia, organizing thrombi with or without recanalization, fibrous occlusions of arteries or arterioles, and focal cortical atrophy [6].

37. **Which clinical or laboratory findings can predict that an antiphospholipid syndrome patient will run a serious clinical course?**

Presence of arterial thrombosis and highly positive direct Coombs test.

38. **What is the clinical presentation of catastrophic antiphospholipid syndrome (cAPS)?**

Infection usually precedes the cAPS. cAPS is a very infrequent medical condition. It affects only 1% of the antiphospholipid syndrome patient population. The clinical highlights of cAPS are simultaneous multiple organ (e.g., brain, kidneys, lungs) involvement, high titers of circulating antiphospholipid antibodies, and histopathologic confirmation of multiple – in different body sites – vessel occlusions.

39. **How common is asymptomatic aseptic bone necrosis in antiphospholipid syndrome, and which patient population is more prone to develop it?**

Antiphospholipid syndrome patients who had never received steroids and were asymptomatic for aseptic bone necrosis have been evaluated with magnetic resonance imaging (MRI), and aseptic bone necrosis (Fig. 4.15) was found in one out of five patients tested. Younger antiphospholipid syndrome patients and those with clinically apparent livedo reticularis tend to develop aseptic

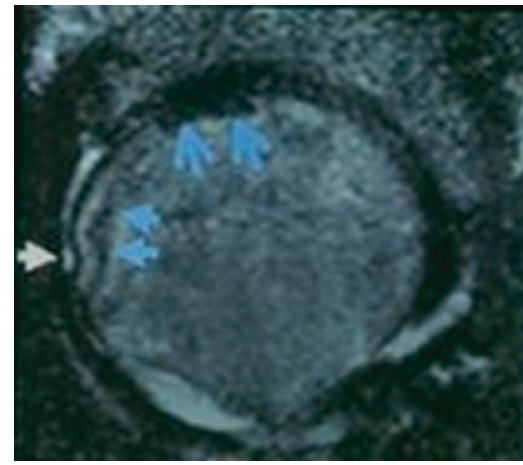

Fig. 4.15 Avascular femoral head necrosis in a 39-year-old female patient with primary antiphospholipid syndrome. Magnetic resonance of the femoral head reveals an early low-intensity band in the subchondral zone of the femoral head (the band sign, blue arrows)

bone necrosis more often than older patients and patients without livedo reticularis [7].

40. **An antiphospholipid syndrome patient develops an arterial thrombosis. Which is the commonest vascular area of recurrence when this patient will have another thrombotic episode?**

Usually arterial thrombosis is followed by arterial thrombosis and vein thrombosis by vein thrombosis.

41. **Which is the pregnancy morbidity in antiphospholipid syndrome?**

Antiphospholipid syndrome-related pregnancy morbidity includes:

- Fetal loss – either as miscarriage, intrauterine fetal death, or stillbirth
- Obstetric complications, such as intrauterine growth restriction, uteroplacental insufficiency, preeclampsia, and preterm birth delivery

42. **Which antiphospholipid syndrome patients demonstrate an increased risk for cognitive dysfunction?**

Cognitive dysfunction (mainly complex attention and verbal fluency) are often found in patients with antiphospholipid syndrome, regardless of any history of central nervous system involvement. Livedo reticularis and the presence of white matter lesions on brain magnetic resonance imaging are associated with an increased risk for cognitive dysfunction in patients with antiphospholipid syndrome [8].

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Inflammatory Muscle Disease

5

Abstract

The main types of inflammatory muscle disease (IMD) are dermatomyositis (DM), polymyositis (PM), necrotizing autoimmune myositis (NAM), and sporadic inclusion body myositis (sIBM). Major clinical and laboratory manifestations are proximal muscle weakness, skin manifestations (Gottron's sign, heliotropic rash, mechanic's hands, and calcinosis cutis), lung involvement, elevated muscle enzymes, and myositis-specific autoantibodies. The latter can be biomarkers for certain disease features: (a) anti-PMScl for interstitial lung disease (ILD), inflammatory arthritis, Raynaud's phenomenon (RP), and mechanic's hands; (b) anti-U1snRNP for myositis in the context of mixed connective tissue disease (MCTD); (c) anti-Ku for overlap myositis with other autoimmune systemic diseases; (d) anti-Ro52 for mechanic's hands and malignancy when it co-occurs with anti-Jo1 antibodies; (e) antibodies to aminoacyl-tRNA synthetases (anti-Jo1) for mechanic's hands, arthritis, ILD, and RP; (f) anti-SRP (signal recognition particle), for severe muscle and heart involvement; (g) anti-HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) for statin use-related necrotizing myopathy; (h) anti-MDA5 (melanoma differentiation-associated gene 5) for amyopathic myositis with ILD; and (i) anti-cN1A (cytosolic 5'nucleotidase 1A) for sIBM. Paraneoplastic myositis is characterized by autoantibodies to TIF-1 (transcriptional intermediary factor 1) antigen. In terms of histopathology, DM is characterized by prominent perivascular and perifascicular inflammation, PM by endomysial inflammation, and sIBM by a combination of inflammation and degeneration of muscle fibers with internal rimmed vacuoles. NAM is considered a macrophage-mediated inflammatory process. Scattered necrotic muscle fibers surrounded by sparse inflammatory cells (predominantly lymphocytes) is characteristic. Endocrine conditions (Cushing's disease, thyroid dysfunction, and diabetes mellitus) as well as genetic abnormalities (mitochondrial myopathies) induce muscle diseases which have to be distinguished from IMDs.

H.M. Moutsopoulos et al., *Rheumatology in Questions*, https://doi.org/10.1007/978-3-319-71604-6_5

1. **Which are the main types of inflammatory muscle disease?**

   The main types of inflammatory muscle disease are dermatomyositis (DM), polymyositis (PM), necrotizing autoimmune myositis (NAM), and sporadic inclusion body myositis (sIBM).

2. **Which are the major clinical and laboratory manifestations of dermatomyositis?**
   - Proximal muscle weakness: occurs insidiously and is more prominent in the shoulder and pelvic girdle muscles. In more severe disease, pharyngeal and esophageal muscles may also be involved.
   - Characteristic skin manifestations:
   – Gottron's sign (Fig. 5.1): red-to-violaceous papules over the dorsal surface of the metacarpophalangeal and interphalangeal joints. It can also occur on the extensor surfaces of the knees and elbows.
   – Heliotrope rash (Fig. 5.2): purple-red rash occurring around the eyelids, forehead, and nasolabial folds.
   – V-sign rash: violaceous rash occurring on the anterior chest wall and the neck.
   – Shawl sign: redness occurring over the shoulders.
   – Mechanic's hands: hyperkeratotic papules along with fissured and cracked palmar and finger-pad skin.
   – Calcinosis cutis: deposition of insoluble calcium salts in the cutaneous and subcutaneous tissue (Fig. 5.3a, b). It is more commonly seen in the juvenile form of DM.
   – Extramuscular manifestations: constitutional symptoms, arthralgias/arthritis, interstitial lung disease, electrocardiographic abnormalities, myocarditis, and Raynaud's phenomenon.
   - Laboratory abnormalities:
   – Elevated serum muscle enzymes: creatine phosphokinase, aspartate and alanine aminotransferase, and lactate dehydrogenase.
   – Acute-phase reactants may be elevated or within normal levels.
   – Presence of myositis-associated and myositis-specific autoantibodies.

3. **Which are the myositis-associated and myositis-specific autoantibodies and with what particular clinical manifestations do they correlate?**

   Autoantibodies have been identified in over 50% of patients with inflammatory myopathies, and they are divided into myositis-associated autoantibodies and myositis-specific autoantibodies. They are important biomarkers, aiding in diagnosis, predicting additional clinical complications

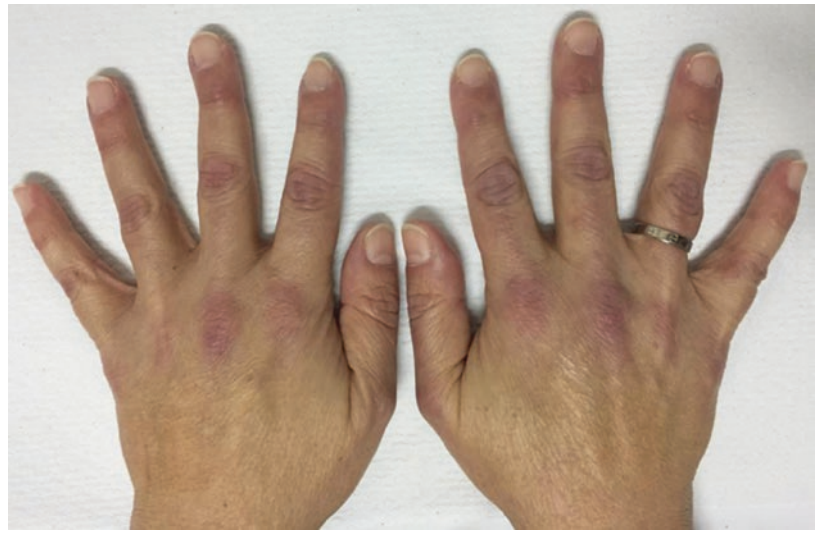

Fig. 5.1 Gottron's sign: faint red-violaceous papules over the metacarpophalangeal joints and the interphalangeal joints in a 45-year-old woman with dermatomyositis

and response to treatment, and helping classify patients into more homogeneous groups.

- **Myositis-associated autoantibodies to:**
  - **PMScl**: a 75 kD protein found in polymyositis (PM)-scleroderma (Scl) overlap. Correlating clinical manifestations: increased risk of interstitial lung disease (ILD), inflammatory arthritis, mechanics hands, and Raynaud's phenomenon.
  - **U1snRNP** (U1 small nuclear ribonucleoprotein particle): found in patients with myositis and mixed connective tissue disease overlap.
  - **Ku**: (composed of 70 and 80 kD subunits, has high affinity for DNA ends) found in 9–19% of myositis patients with overlap syndromes including systemic lupus erythematosus, scleroderma, and mixed and undifferentiated connective tissue disease. These patients present with increased frequency of arthralgias, Raynaud's phenomenon, musculoskeletal manifestations, and ILD.
  - **Ro52**: found in 56–72% of anti-Jo-1-positive patients. Patients with both anti-Jo-1 and anti-Ro-52 autoantibodies have an increased risk for mechanics hands, more severe ILD and malignancy. They have a poorer outcome compared to patients with anti-Jo-1 alone.
- **Myositis-specific autoantibodies to:**
  - **ASA** (aminoacyl-tRNA synthetases): correlating clinical manifestations – mechanics hands, arthritis, and Raynaud's phenomenon.
  - **SRP** (signal recognition particle): patients with this autoantibody reactivity typically present highly elevated creatine phosphokinase (CK), severe weakness and muscle

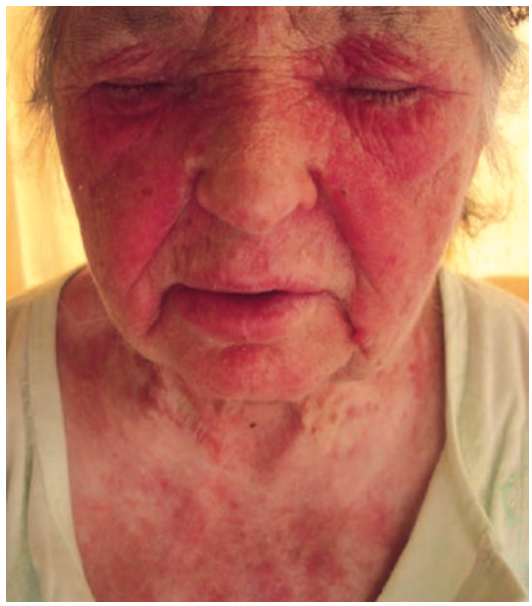

Fig. 5.2 Heliotrope rash: purple-red rash occurring around the eyelids and nasolabial folds as well as erythro-violaceous rash on the "V" of the chest in a 74-year-old female with dermatomyositis

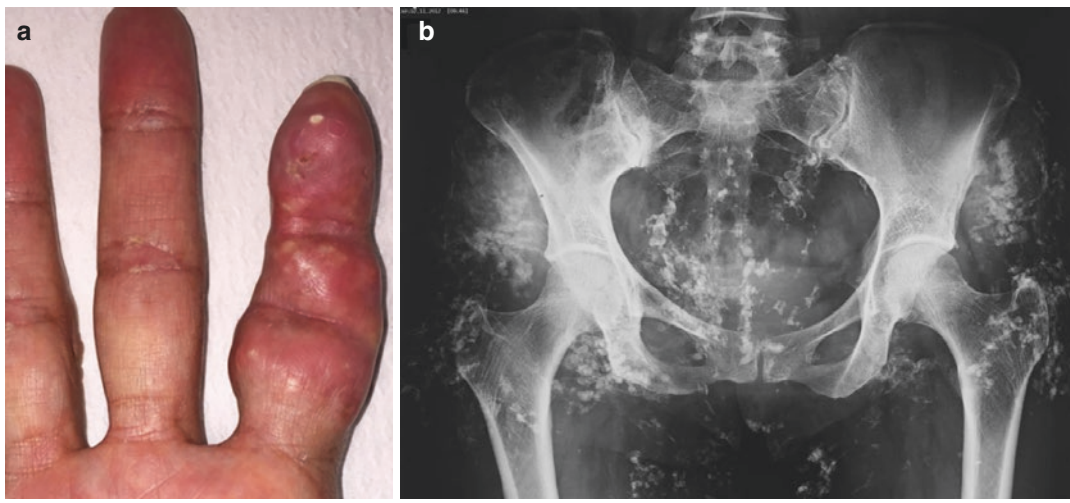

Fig. 5.3 Calcinosis cutis: hard calcified subcutaneous nodules have developed in various areas (knees, elbows, gluteal areas, and fingers) in a 56-year-old female patient with long-standing, ineffectively treated dermatomyositis. (**a**) Extensive subcutaneous calcifications are evident on the index finger, (**b**) on pelvis X-ray, of the same patient, extensive calcinosis of the gluteal and hip areas is apparent

pain, dysphagia, and cardiac involvement and have a poor response to treatment. Muscle histology can reveal signs of necrotizing autoimmune myopathy [1].
- **HMGCR** (3-hydroxy-3-methylglutaryl-coenzyme A reductase): these patients have highly elevated CK and significant necrotizing myopathy which correlates with statin use [1].
- **Mi-2** (nucleosome-remodeling deacetylase complex): it is significantly associated with skin rash.
- **SAE** (small ubiquitin-like modifier activating enzyme): myositis in this subgroup of patients can be amyopathic at onset; nevertheless skin rash is typically present.
- **MDA5** (melanoma differentiation-associated gene 5): patients with this autoantibody typically present with amyopathic myositis and rapidly progressive ILD.
- **NXP2** (nuclear matrix protein 2): this autoantibody reactivity is significantly associated with skin rash, malignancy in adults, and calcinosis in juveniles.
- **TIF1** (transcriptional intermediary factor 1): it is strongly associated with underlying malignancy.
- **cN1A** (cytosolic 5′-nucleotidase 1A): it is associated with sporadic inclusion body myositis [2, 3].

4. **Which are the nail findings in patients with dermatomyositis?**
   - Periungual erythema
   - Nail bed telangiectasias

5. **Which are the major clinical findings of patients with anti-synthetase myositis?**

   The anti-synthetase syndrome is seen in myositis patients who present DM/PM and/or scleroderma-like manifestations. It is characterized by the presence of antibodies directed against aminoacyl-tRNA synthetases. The most common antibody of this group is anti-Jo1 (against histidyl transferase), present in 15–30% of PM and in 10% of DM patients. The anti-synthetase syndrome is characterized by myositis, interstitial lung disease (40–90%), Raynaud's phenomenon (60%), mechanic's hands (70%), and symmetric nonerosive small joint arthritis (60%). Some patients have anti-Ro/SSA (Ro52) antibodies. These patients have worse arthritis, and their myositis is more resistant to therapy. Anti-synthetase syndrome patients show extremely rarely association with malignancy.

6. **Which are the symptoms and clinical signs of patients with sporadic inclusion body myositis?**

   Patients with sporadic inclusion body myositis (sIBM) are usually males over 50 years of age with insidious onset of proximal and later distal muscle weakness. Muscle atrophy is very prominent, especially in the thigh/pelvic muscles and the brachial/antebrachial muscles. sIBM patients present typically with a difficulty in shaking hands and frequently suffer from recurrent falls. Besides myopathy they can also have mild peripheral neuropathy with decreased deep tendon reflexes. sIBM is rarely associated with underlying malignancy and rarely exhibits lung, joint, or heart involvement.

7. **What is the clinical picture of amyopathic myositis (myositis sine myositis)?**

   The patients of this subcategory of DM present with skin rashes characteristic of DM, yet without muscle weakness. Some patients develop rapidly progressive ILD. A small percentage of this patient population, particularly of Asian origin, may have in their sera anti-melanoma differentiation-associated gene 5 (MDA5) autoantibodies.

8. **Which are the muscle manifestations which can develop in patients receiving statins? Which ones are transient and which persist and oblige the physician to discontinue statin therapy?**

   Muscle aches, fatigue, and symmetrical proximal muscle weakness can be attributed to unwanted effects of statin therapy if they develop 2 weeks after initiation of statins and disappear 2 weeks after statin discontinuation. The majority

of muscle complains in patients on statin therapy are self-limited and disappear without sequelae after their discontinuation. In a small portion of patients on statins, necrotizing myositis can develop which persists after discontinuation of statins and should be treated as idiopathic necrotizing myositis. In this patient subgroup autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the pharmacologic target of statins, can be detected.

9. **In which patient age group myositis can be a paraneoplastic phenomenon?**

   It is seen in myositis patients over the age of 50 years with severe cutaneous and muscle manifestations as well as circulating antibodies to TIF-1 antigen. These individuals should be evaluated for underlying cancer. Squamous cell carcinoma, adenocarcinoma, and hematologic/lymphoid malignancies should be excluded.

10. **Which are the major muscle histopathologic findings in patients with dermatomyositis, polymyositis, sporadic inclusion body myositis, and necrotizing autoimmune myositis?**

    Dermatomyositis: it is a complement-mediated vasculopathy of the muscle small vessels. The characteristic histological finding is perifascicular atrophy of muscle fibers with increased endomysial connective tissue and inflammatory infiltrates. Overexpression of type I interferon α/β by plasmacytoid dendritic cells, increased MHC-I antigens, and immunoglobulin gene transcripts can be also observed (Fig. 5.4a).

    Polymyositis: it is a cell-mediated cytotoxic immune response, where CD8 (+) cytotoxic T cells and macrophages clonally expand and infiltrate the endomysium. The surrounded and invaded muscle cells express MHC class I molecules (Fig. 5.4b).

    Sporadic inclusion body myositis: atrophic and hypertrophic muscle fibers with internal rimmed vacuoles are the typical histopathologic findings (Fig. 5.4c).

    Necrotizing autoimmune myositis: it is thought to be a macrophage-mediated immune response. Overexpression of MHC-I molecules in necrotic and regenerating muscle fibers, surrounded by T lymphocytes, are the major histopathologic findings (Fig. 5.4d) [4].

11. **Which are the typical histopathologic muscle findings of patients with mitochondrial myopathy?**

    The presence of ragged red fibers. This ragged appearance of fibers sometimes can be seen in muscle specimen stained with hematoxylin and eosin. These fibers are typically recognized with modified Gomori-trichrome staining. This stain shows a red peripheral rim or granular red of the sarcoplasm. The red staining is the result of the increased amount of phospholipids in the membranes of proliferated mitochondria (Fig. 5.4e).

12. **Which endocrine conditions can present with myopathy?**

    Cushing's disease, thyroid dysfunction (hypothyroidism, myxedema, thyrotoxic myopathy), parathyroid dysfunction (multiple endocrine neoplasia), pituitary dysfunction, and islands of Langerhans dysfunction (ischemic infarction of the femoral muscles in diabetic myopathy).

13. **Which drugs induce myopathies?**
    - Corticosteroids (mainly fluorinated preparations)
    - Combination of drugs such as fibrates and statins or colchicine and cyclosporine-A

14. **On what grounds a physician should think that the patient has drug-induced myopathy?**
    - Lack of muscular complains prior to the initiation of therapy
    - Lack of another cause accounting for the myopathy
    - Complete or incomplete resolution of symptoms and signs after discontinuation of the medication

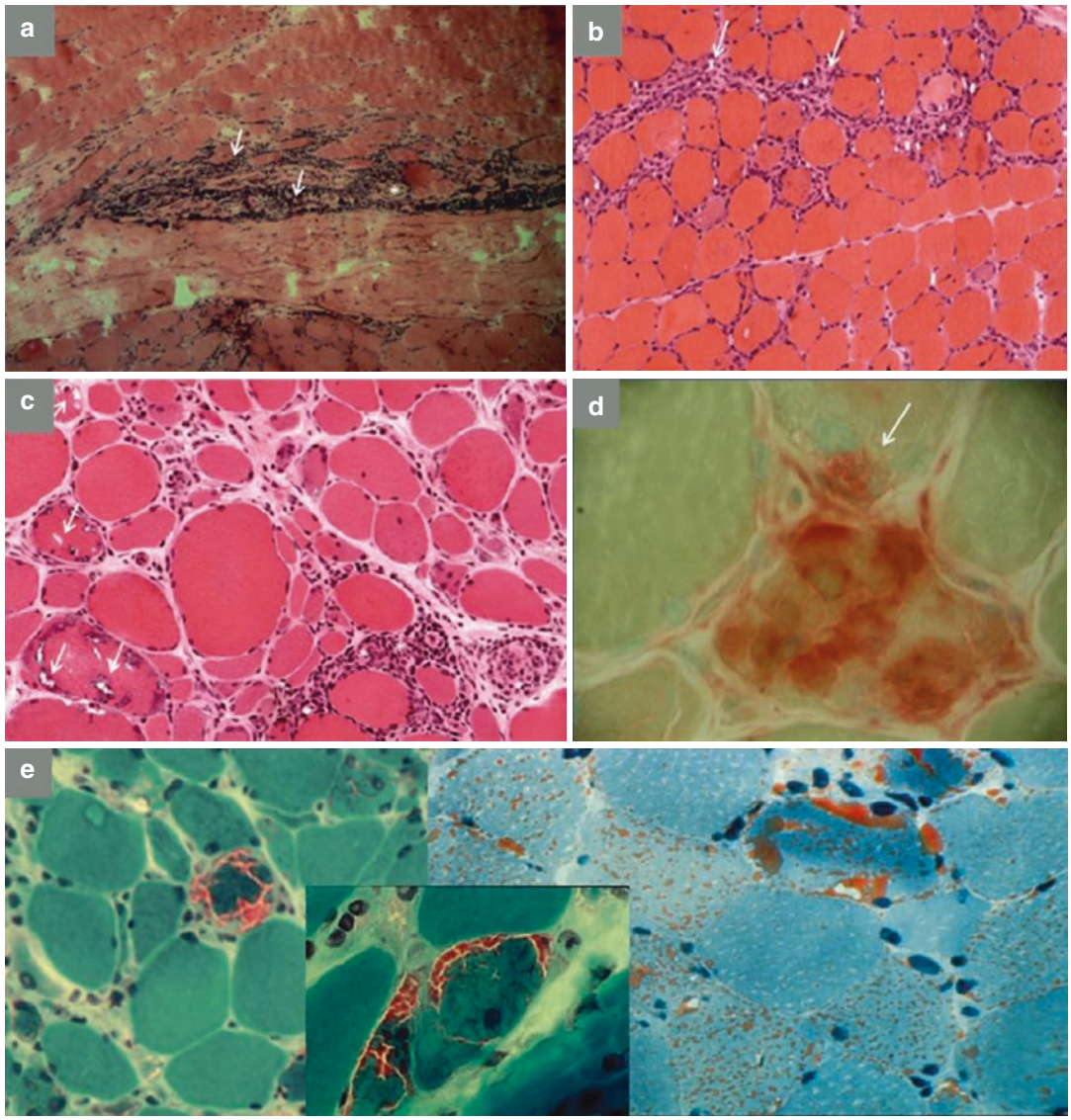

Fig. 5.4 Muscle histopathology: (**a**) Dermatomyositis: inflammation is most prominent perivascularly (asterisk) and perifascicularly (arrows). (**b**) Polymyositis: endomysial inflammation (arrows), (**c**) Sporadic inclusion body myositis: a combination of inflammatory and degenerative process. T cells invading healthy-appearing muscle fibers (asterisks) and vacuoles (in fibers not invaded by T cells, arrows). (**d**) Necrotizing autoimmune myositis: see necrotic fibers invaded by macrophages identified in red with alkaline phosphatase staining. (**e**) Mitochondrial myopathy: left – cross section of muscle biopsy stained with trichrome shows "ragged-red" fibers characterized by red stains in the periphery of the fibers due to accumulations of mitochondria. At high magnification, one such fiber also shows the cracks (ragged) parenchyma. Right: mitochondrial dysfunction indicative of defects in oxidative phosphorylation is accompanied by accumulation of fat visualized with oil red O stain (*Figures courtesy of Professor Marinos C. Dalakas, MD, FAAN*)

15. **Which corticosteroid preparations mainly induce glucocorticoid-induced myopathy?**

    Steroid-induced myopathy is mostly associated with increased doses of fluorinated glucocorticoid preparations, which lead to type IIb muscle fiber atrophy.

16. **When should immunosuppressive agents be considered for a dermatomyositis patient?**

    If the patient has:

    - A poor response or is refractory to corticosteroid therapy or presents glucocorticoid-related side effects

- A rapidly progressively disease
- Severe internal organ involvement

17. **What is the clinical picture of McArdle's syndrome?**

McArdle's syndrome is a type V glycogen storage disease. It is caused by myophosphorylase deficiency. It starts in childhood, but the diagnosis is usually set in adulthood. It presents with muscle pain and painful cramps upon exercise which obligate the patient to rest. Upon strenuous exercise myoglobinuria can develop. The characteristic clinical sign observed in these patients is the second wind phenomenon. This phenomenon is characterized by the patient's better tolerance for aerobic exercise such as walking and cycling after resting for approximately 10 min.

18. **Which are the muscle histopathologic findings in patients with McArdle's syndrome?**

Muscle fibers of patients with McArdle's syndrome are characterized by subsarcolemmal storage of normal glycogen and by absent histochemical stain for phosphorylase reaction. In contrast, intramuscular vessels stain histochemically for phosphorylase.

19. **What is the clinical picture and which are the causes of camptocormia?**

Camptocormia is an acquired disease of body posture, presenting with forward bending of the thoracolumbar spine. The individual's forward bending of the body worsens when he/she walks or stands, while the posture is corrected when lying on supine position. Many neurological, muscular, and spine disorders may account for the development of camptocormia. Among them Parkinson's disease is the main etiology. Other causes include:

Myopathy (inclusion body myositis)
Alzheimer's disease
Motor neuron disease
Myasthenia gravis
Severe osteoporosis with multiple vertebral fractures
Spinal trauma/arthritis
Psychiatric syndromes
Paraneoplastic disorders [5]

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Sjögren's Syndrome, IgG_4-Related Disorders

6

Abstract

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disorder affecting predominantly middle-aged females. SS clinical manifestations can be related to glandular dysfunction (keratoconjunctivitis sicca, oral dryness, bronchitis sicca, parotid gland enlargement) and extra-glandular/systemic involvement. The latter is either due to peri-epithelial infiltrates in parenchymal organs (small airway disease, interstitial nephritis, biliary cirrhosis) or due to immune complex deposition (palpable purpura, peripheral neuropathy, glomerulonephritis, systemic vasculitis). In the majority of patients, SS runs an indolent benign course. In a small yet not negligible number of cases (5–10%), SS is complicated by lymphoid neoplasia. Sicca manifestations, increased fatigability, arthralgias/myalgias, nonerosive arthritis, Raynaud's phenomenon (RP), and signs of renal tubular acidosis may be initial manifestations of SS. After excluding other causes of sicca symptomatology, patients should be assessed for lacrimal and salivary gland function (ocular staining with lissamine green or rose bengal, Schirmer's test and unstimulated saliva secretion, respectively), and a biopsy of labial minor salivary glands should be performed to evaluate the presence of lymphocytic infiltrates around salivary gland epithelium. SS patients presenting salivary gland enlargement, Raynaud's phenomenon, lymphadenopathy, anti-Ro/SSA or anti-La/SSB autoantibodies, rheumatoid factor positivity, monoclonality, and low serum C4 levels should be monitored closely, since these clinical, laboratory, and immunologic parameters have been shown to be independent predictors for non-Hodgkin's lymphoma development.

IgG4-related disease (IgG4-RD) has recently emerged as a new clinical entity. It comprises numerous conditions previously thought to be unrelated, such as sclerosing dacryoadenitis/orbital pseudotumor, sialadenitis, autoimmune pancreatitis, retroperitoneal fibrosis/periaortitis, sclerosing cholangitis, Riedel thyroiditis, hypophysitis, and prostatitis. IgG4-RDs are clinically characterized by tumor-like lesions in affected organs. Histopathologically, they typically present lymphoplasmacytic infiltrates

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with increased IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis, and tissue eosinophilia, while serum IgG4 concentration is usually increased. Typically IgG4RD symptoms respond promptly to steroids.

1. **Which age group is primarily affected from Sjögren's syndrome?**

   Females in the fourth and fifth decade of life are usually affected.

2. **Which are glandular and extra-glandular disease manifestations that present early before the full clinical picture of Sjögren's syndrome develops? How long does it take from the initial manifestations to full-blown disease?**

   The initial manifestations of Sjögren's syndrome are usually nonspecific and include arthralgias, arthritis, fatigability, Raynaud's phenomenon, dry eyes and/or mouth, bronchitis sicca and infrequently parotid gland enlargement, purpura, and signs of renal tubular acidosis. Sjögren's syndrome is a slowly progressing disorder; 6–8 years may elapse from the initial manifestations to full-blown disease development. Glomerulonephritis, systemic vasculitis, and lymphoma are manifestations that develop years after Sjögren's syndrome diagnosis.

3. **Compare the arthritis seen in patients with rheumatoid arthritis with that seen in Sjögren's syndrome patients.**

   Arthritis in both disease entities is symmetrical, accompanied by morning stiffness, and can affect primarily the wrists, metacarpophalangeal, and proximal interphalangeal joints. In contrast to rheumatoid arthritis, arthritis in Sjögren's syndrome is milder, usually transient, and does not lead to joint erosive changes. In some Sjögren's syndrome patients, Jaccoud's arthropathy may develop.

4. **Which histopathological findings in a labial minor salivary gland biopsy are characteristic for focal lymphocytic sialadenitis?**

   Labial minor salivary gland biopsy (LMSGB) is one of the objective tests used in order to set the diagnosis of Sjögren's syndrome. Although it is an invasive procedure (Fig. 6.1), it is safe and is associated with few local adverse effects. The key requirements for a correct histological evaluation of a LMSGB include a minimum size of biopsy material of 4 mm^2 containing an adequate number – at least five – salivary gland lobules. A cluster of round cells with at least 50 lymphocytes is called a focus. Focal lymphocytic sialadenitis is diagnosed when in the biopsy specimen multiple, dense aggregates of $\geq$50 lymphocytes in peri-epithelial ductal areas in the majority of sampled glands are evident. This constitutes the characteristic histopathological feature of Sjögren's syndrome (Fig. 6.2). The severity of the histopathologic lesion of the labial minor salivary glands is graded according to the system described by Chisholm and Mason, which counts the number of lymphocytic foci per 4 mm^2 of the salivary tissue under investigation.

5. **What is the cellular composition of the labial minor salivary gland focal round cell infiltrates of patients with Sjögren's syndrome?**

   In mild inflammatory lesions in labial minor salivary gland tissues from Sjögren's syndrome patients, T lymphocytes predominate, while in severe lesions B lymphocytes are more prominent than T lymphocytes.

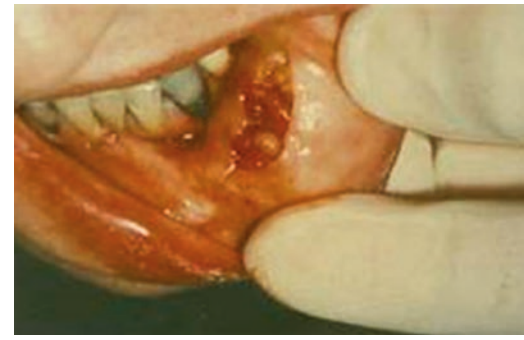

Fig. 6.1 Labial minor salivary gland biopsy: it is obtained by an approximately 1 cm wide incision of the lower lip mucosa

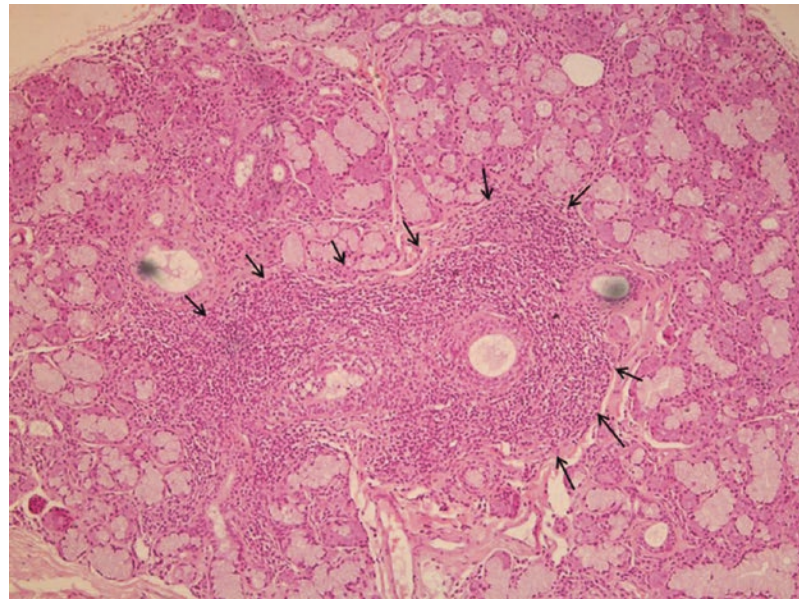

Fig. 6.2 Labial minor salivary gland histopathology: a cluster of round cells (at least 50 lymphocytes), called a focus, is seen (black arrows) in the salivary gland tissue specimen. The focal lymphocytic infiltrates are localized around ducts, and replace functional glandular epithelium

Furthermore, in the severe lesions, increased numbers of macrophages and dendritic cells are present [1].

6. **Which are the major immunohistological findings in the labial minor salivary gland tissues of patients with primary Sjögren's syndrome?**

T helper (Th)-1 cytokines (IL-1, IL-6, and TNF-α) predominate in the lesions, while chemoattractant chemokines are also present. Glandular epithelial cells, which are surrounded by focal lymphocytic infiltrates, become activated since:

- They inappropriately express immunoregulatory molecules like the co-stimulatory molecule B7, intercellular adhesion molecule (ICAM), etc.
- They produce pro-inflammatory cytokines and chemokines.
- The B7 co-stimulatory molecule provides a second signal for the T-lymphocyte activation.
- The glandular epithelial cells release Ro/SSA and La/SSB autoantigens, either through apoptotic blebs or exosomes, and can play the role of antigen-presenting cells.

From all the above findings, it appears that the glandular epithelial cells are able to initiate and fuel the autoimmune reactivity [2].

7. **What clinical/laboratory and histological parameters are required to set the diagnosis of Sjögren's syndrome?**

The parameters required include anti-Ro/SSA as well as anti-La/SSB antibody positivity and focal lymphocytic sialadenitis with a focus score of ≥1 foci/4 mm^2 (each scoring 3); an abnormal ocular staining score (with lissamine green or rose bengal, measured by the van Bijsterveld scale and having a score of ≥4), a Schirmer's test result of ≤5 mm/5 min and an unstimulated salivary flow rate of ≤0.1 mL/min (each scoring 1). Individuals with signs and/or symptoms suggestive of Sjögren's syndrome who have a total score of ≥4 after adding the scores of the above items meet the criteria for primary Sjögren's syndrome [3].

8. **What is keratoconjunctivitis sicca?**

Keratoconjunctivitis sicca (KCS) is a condition commonly referred as "dry eyes" syndrome, where damage of the cornea and/or conjunctival epithelium results in secondary inflammation. The patients complain of burning sensation, feeling of sand or grit in the eyes, eye fatigability, and pressure behind the eyes, symptoms which become worse as the day goes on. It is the result of meibomian gland dysfunction, allergies, Sjögren's syndrome,

vitamin A deficiency, and drugs (antidepressants, antihistamines, and others). The diagnosis of KCS is placed with slit-lamp examination after the conjunctiva and cornea are stained either with lissamine green or rose bengal.

9. **How Schirmer's I test is performed?**

Schirmer's I test measures the lacrimal flow. It is performed by placing a piece of Whatman filter paper under the inferior eyelid, usually without prior application of topical anesthetic, and measuring the amount of wetness over a specified time. Normal wetting is >15 mm in 5 min, whereas <5 mm is a strong indication of diminished tear production. It should be taken into account that lacrimal flow varies according to the time of the day measured, the hydration status of the individual, the phase of the menstrual cycle, and the environmental humidity.

10. **Which are the therapeutic interventions for keratoconjunctivitis sicca of Sjögren's syndrome?**

Artificial tears (preservative-free), stimulation of tear secretion (e.g., pilocarpine hydrochloride 5 mg t.i.d.), tear retention treatment, and local application of immunomodulatory agents with anti-inflammatory activity, like cyclosporine-A, may be used for keratoconjunctivitis sicca in Sjögren's syndrome according to disease severity.

11. **Which are other causes of dry eyes except Sjögren's syndrome?**

- Aging
- Medical conditions, including diabetes mellitus, thyroid disease, and vitamin A deficiency
- Medications: antihistamines, decongestants, hormone replacement therapy, antidepressants, and antihypertensives
- Laser eye surgery, though symptoms of dry eyes related to this procedure are usually temporary
- Lacrimal gland damage from inflammation or radiation
- Sarcoidosis
- Chronic hepatitis C and HIV infections
- Chronic graft-versus-host disease

12. **Which are the main symptoms of a patient with xerostomia?**

- Sticky, dry feeling in the mouth and in the throat
- Difficulty swallowing dry food
- Burning or tingling sensation in the mouth and especially on the tongue (Fig. 6.3)
- Change in taste sensation
- Frequently sipping water
- Frequent dental caries and predisposition to oral candidiasis
- Gastroesophageal reflux symptoms

13. **Which are the diagnostic value and major salivary gland ultrasound and sialography findings in Sjögren's syndrome patients?**

Major salivary (parotid) gland imaging with ultrasound can differentiate inflammatory from neoplastic disease and diffuse from focal suppurative syndromes, it can also identify sialoliths, and demonstrate salivary duct morphology. In the salivary glands, at an early phase of Sjögren's syndrome, sialectasis (punctate 1 mm lesions representing cystic dilatation of the ducts within salivary glands) can be observed during sialography throughout the glandular tissue; the main ducts appear normal, and the intraglandular ducts may be narrowed. In advanced disease states, punctate lesions increase in size and have irregular shape, and cavitary sialectasis throughout the gland can be apparent.

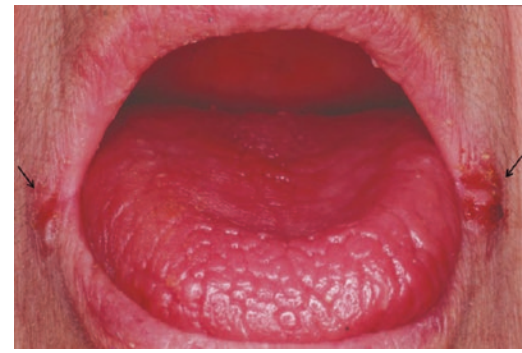

Fig. 6.3 Atrophic tongue papillae: a beefy-red, deeply fissured tongue with atrophic lingual papillae of a 45-year-old female with severe xerostomia. Angular cheilitis is also present (arrows)

14. **Which medical conditions except Sjögren's syndrome can present with major salivary gland enlargement?**

Unilateral:

- Primary salivary gland neoplasms
- Obstruction (stones or plugs), bacterial infection
- Chronic sialadenitis

Bilateral: (Fig. 6.4)

- Viral infection: mumps, cytomegalovirus, influenza, and coxsackie A
- IgG4-related disease
- Granulomatous disease: sarcoidosis, tuberculosis, and leprosy
- Acquired immunodeficiency (HIV)
- Alcoholism, malnutrition, hepatic cirrhosis, and chronic pancreatitis
- Diabetes mellitus
- Hyperlipoproteinemia types IV and V

15. **Which are the clinical and laboratory similarities and differences among sicca syndrome caused from viral infection and Sjögren's syndrome?**

Acquired immunodeficiency (HIV) and hepatitis C (HCV) viruses are epitheliotropic. They can infect the epithelial cells of the exocrine glands (lacrimal, salivary) leading to xerostomia and xerophthalmia. In that sense, viral sicca syndrome does not differ from sicca manifestations seen in patients with Sjögren's syndrome. However viral sicca syndrome affects equally both sexes, while Sjögren's syndrome is predominantly a female disease. Furthermore anti-Ro/SSA and anti-La/SSB reactivities which are found in the sera of two thirds of Sjögren's syndrome patients are not present in the circulation of HIV-/HCV-induced sicca syndrome.

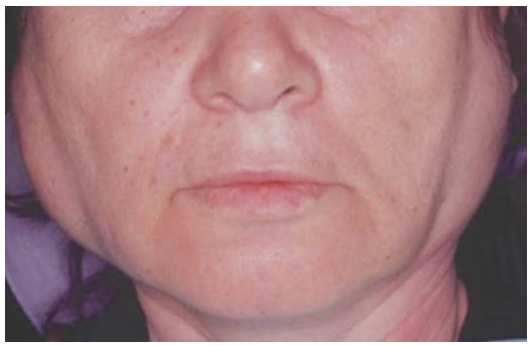

Fig. 6.4 Parotid gland enlargement: a 60-year-old lady with Sjögren's syndrome and persisting enlargement of both parotid glands. In this patient the possibility of lymphoma, sarcoidosis, and IgG4-related-disease should be ruled out

16. **How are the extra-glandular manifestations of Sjögren's syndrome classified?**

- Nonspecific manifestations: fatigability, arthralgias, myalgias, and Raynaud's phenomenon
- Manifestations due to peri-epithelial lymphocytic infiltrates (peri-bronchial, peri-cholangial, perirenal tubular) leading to small-airway disease, biliary chirrhosis and interstitial nephritis respectively
- Manifestations due to immune complex-deposition: raised purpura, peripheral neuritis, glomerulonephritis
- B-lymphocyte lymphoma [4]

17. **Which are the main skin rashes seen in patients with Sjögren's syndrome?**

- Purpura (palpable or flat), red spots primarily on the lower extremities, 1–4 mm diameter (Fig. 6.5)
- Annular erythema consisting of wide erythematous plaques with elevated borders and central pallor located on the face, upper extremities, and back
- Lupus pernio-like lesions of the distal extremities

18. **Which are the types of purpura which can be seen in Sjögren's syndrome patients and provide the pathogenetic mechanism for its development?**

- Palpable purpura which is due to small vessel vasculitis
- Flat (not palpable) purpura which can be the result of hypergammaglobulinemia (increased serum viscosity) and less often of thrombocytopenia

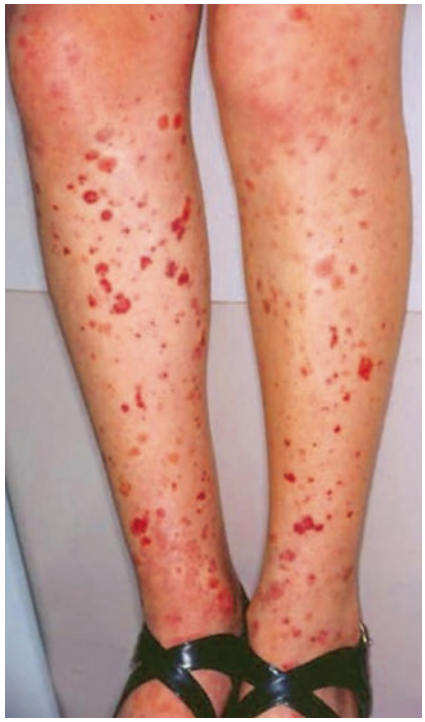

Fig. 6.5 Palpable purpura: of the lower extremities in a 50-year-old female patient with Sjögren's syndrome

19. **What is the commonest type of lymphoma in primary Sjögren's syndrome patients?**

Non-Hodgkin's lymphoma develops in 5–10% of Sjögren's syndrome patients. The majority of lymphomas are marginal zone, low grade, and without B symptoms. Extranodal lymphomas are often identified in the salivary glands.

20. **Which are the clinical, laboratory, and immunologic parameters which can predict future lymphoma development in a Sjögren's syndrome patient?**

Univariate and multivariate analyses have revealed that salivary gland enlargement, Raynaud's phenomenon, lymphadenopathy, anti-Ro/SSA or anti-La/SSB autoantibodies, rheumatoid factor positivity, monoclonal gammopathy, and low serum C4 levels are independent predictors for non-Hodgkin's lymphoma development in patients with Sjögren's syndrome. Presence of all seven factors in a patient with Sjögren's syndrome has a probability to predict future lymphoma development by 100% [5].

21. **Which manifestations of a Sjögren's syndrome patient will direct the physician to evaluate the patient for autoimmune liver disease?**

Elevated liver enzymes and antibodies either against mitochondria or smooth muscle antigens.

22. **Which are the characteristics of Sjögren's syndrome patients with anti-centromere autoantibodies?**

Anti-centromere (ACA) autoantibody-positive Sjögren's patients are predominantly females as are Sjögren's patients without ACA. They present however higher incidence of Raynaud's phenomenon, dysphagia, and lower incidence of antibodies to Ro/SSA and La/SSB autoantigens. After a long follow-up period, a small fraction of these patients can evolve to scleroderma [6].

23. **Which is (according to incidence) the respiratory pathology seen in Sjögren's syndrome patients?**

The most common histopathological diagnoses in patients with primary Sjögren's syndrome and lung involvement are according to their incidence: xerotrachea, bronchitis sicca, bronchiolitis with small airway disease, lymphocytic and nonspecific interstitial pneumonitis, and seldomly primary lymphoma. Pleurisy is more commonly seen in patients with Sjögren's associated with other connective tissue diseases.

24. **Which is the early and which is the late kidney disease in patients with Sjögren's syndrome? What is their clinical presentation?**

Clinically significant renal involvement in Sjögren's patients is infrequent (~5%). Approximately half of the patients with renal involvement develop interstitial nephritis (IN) (Fig. 6.6). IN patients have an onset of Sjögren's syndrome at a younger age, and the renal disease develops early in the dis-

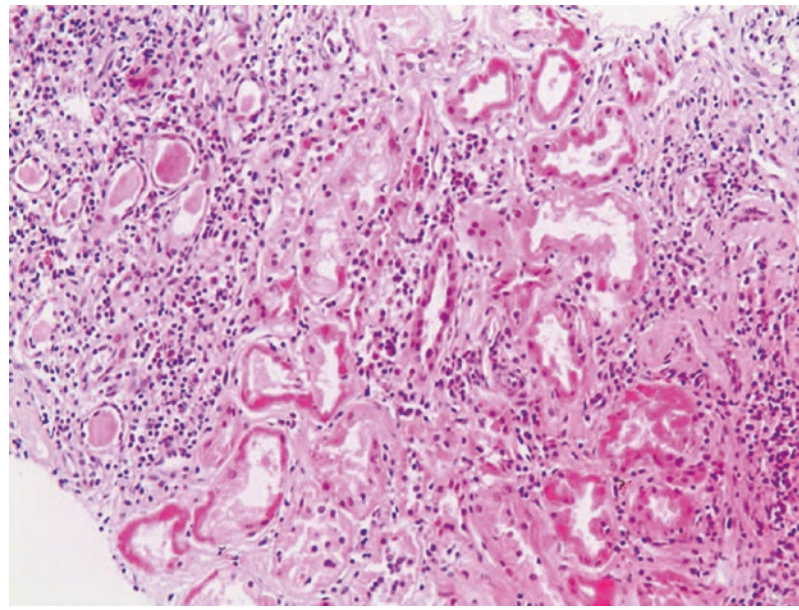

Fig. 6.6 Interstitial nephritis: a 26-year-old lady with Sjögren's syndrome with signs of distal tubular acidosis. Renal biopsy revealed heavy round cell interstitial infiltrates with tubular atrophy

ease course. Manifestations of the distal tubule malfunction prevail and include low blood Ph (acidosis), high urine Ph, hypokalemia, and hyperchloremia. Glomerulonephritis (GMN) develops in the other half of Sjögren's syndrome patients with renal involvement. These patients have longer disease duration, present with hypertension, hematuria, and mild proteinuria. The majority has circulating monoclonal cryoglobulins type II with rheumatoid factor activity and low serum complement C4 levels.

25. **Which are the long-term sequelae of Sjögren's syndrome patients with renal disease?**

After a 10-year follow-up, equal percentage of interstitial nephritis- and glomerulonephritis-Sjögren's syndrome patients develop chronic renal disease and 20% of those require hemodialysis. Overall, the 5-year survival of Sjögren's syndrome patients with renal involvement is reduced compared to survival of patients without renal disease. Major causes of death of Sjögren's syndrome patients with renal involvement include lymphoma, cerebrovascular accidents, cardiovascular events, and infection. Sjögren's syndrome patients with glomerulonephritis have higher risk to develop lymphoma, and their survival is poor compared to Sjögren's patients with interstitial nephritis [7].

26. **Which are the main peripheral nervous system syndromes observed in Sjögren's syndrome patients?**

Trigeminal neuropathy is not uncommon in Sjögren's syndrome patients as is carpal tunnel syndrome. Peripheral neuropathy is seen in Sjögren's syndrome patients with extra-glandular manifestations and is usually axonal. Sensory neuropathy and sensorimotor neuropathy are seen with the same frequency. Small fiber and autonomic neuropathy can also affect Sjögren's syndrome patients.

27. **Which are the clinical, laboratory, and immunogenetic similarities and differences of patients with Sjögren's syndrome alone, patients with rheumatoid arthritis and Sjögren's syndrome, and patients with systemic lupus erythematosus and Sjögren's syndrome?**

Sjögren's syndrome in rheumatoid arthritis patients develops many years after the diagnosis of rheumatoid arthritis, while Sjögren's syndrome in systemic lupus ery-

thematosus patients can precede the systemic lupus erythematosus diagnosis or the two entities can appear at the same time. Clinically, parotid gland enlargement (transient or persistent) occurs more often in patients with Sjögren's syndrome alone called primary Sjögren's syndrome as well as in patients with Sjögren's syndrome/systemic lupus erythematosus. Antibodies to Ro/SSA and La/SSB autoantigens appear in the circulation of patients with primary Sjögren's syndrome and Sjögren's syndrome/systemic lupus erythematosus, while their presence in the sera of patients with rheumatoid arthritis and Sjögren's syndrome can be found very infrequently.

In primary Sjögren's syndrome and Sjögren's syndrome/systemic lupus erythematosus patients, there is an association with the HLA-DR3 alloantigen, while in Sjögren's syndrome/rheumatoid arthritis patients, there is an association with the HLA-DR4 alloantigen.

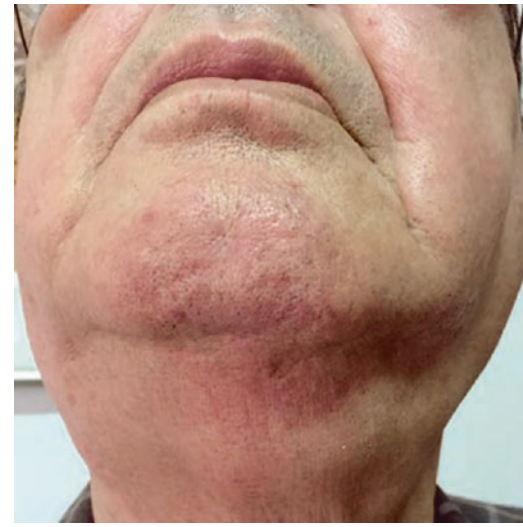

Fig. 6.7 Sclerosing sialadenitis (Mikulicz's disease): enlargement of submandibular and parotid glands bilaterally is presented in a 60-year-old man who fulfilled diagnostic criteria of IgG4-related sialadenitis (*Reproduced from Fragoulis GE et al. 2017*)

28. **Which are the common clinical, serologic, histologic features and therapeutic responses that patients with IgG4-related diseases (IgG4RD) share?**

Clinical: tumor-like lesions in affected organs (Fig. 6.7).

Histological: dense lymphoplasmacellular inflammatory infiltrates containing more than 30–50 IgG4+ plasmacytes per high-power field or a IgG4+/IgG+ ratio greater than 40, a peculiar pattern of fibrosis (known as storiform fibrosis), a tendency to affect veins by vascular inflammation that leads to obliterative phlebitis, and a mild to moderate tissue eosinophilia.

Serologic: serum IgG4 concentration >135 mg/dL and elevated serum IgG2 and IgE levels

Therapeutic response: prompt response to glucocorticoids

29. **Which IgG4RD patients have the highest probability of having elevated serum IgG4 levels?**

Patients older than 65 years of age with active disease, greater number of involved organs, lower levels of complement proteins, higher absolute number of peripheral blood eosinophils, and higher serum IgE levels [8]

30. **Which are the similarities and differences of sclerosing sialadenitis (Mikulicz's disease) and Sjögren's syndrome?**

Similarities: glandular enlargement, sicca symptoms, arthralgias, hypergammaglobulinemia, hypocomplementemia, and presence of ANA.

Differences: sclerosing sialadenitis affects more often men, while Sjögren's syndrome is mostly a disease of females. Anti-Ro/SSA and anti-La/SSB autoantibodies are infrequently found in the sera of patients with sclerosing sialadenitis, the numbers of IgG4+ plasma cells in the salivary gland infiltrates of patients with sclerosing sialadenitis are increased, and sclerosing sialadenitis patients can benefit from corticosteroid therapy [9].

31. **Which clinical entities (besides Mikulicz's disease) have been classified under the umbrella of IgG4-related diseases?**

– Sclerosing dacryoadenitis/orbital pseudotumor (Fig. 6.8a, b)
– Autoimmune pancreatitis

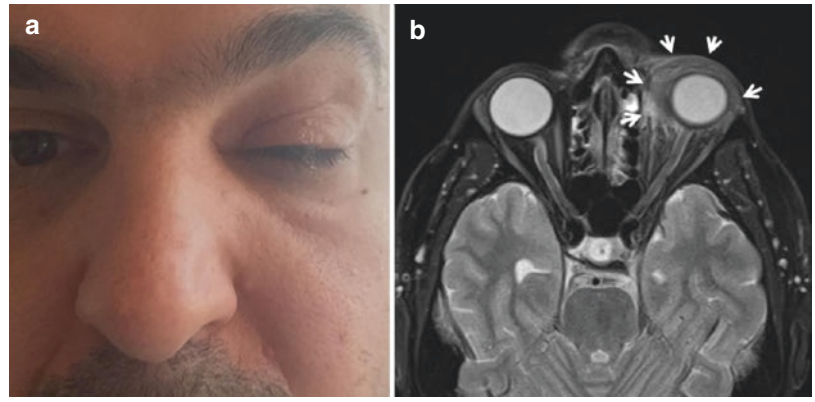

Fig. 6.8 Orbital mass: in a 41-year-old man who fulfilled diagnostic criteria of IgG4-related disease. (**a**) Magnetic resonance imaging showed diffuse soft tissue swelling surrounding the left orbit, exhibiting hypointensity on T2-weighted images (**b**, arrows) (*Reproduced from Zampeli E et al. 2016*)

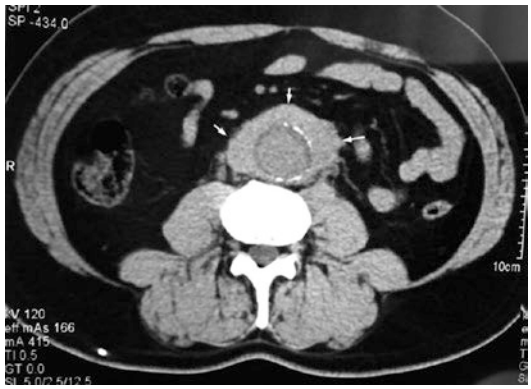

Fig. 6.9 Periaortitis: abdominal CT scanning revealing a soft tissue mass surrounding the aorta (arrows) in a 60-year-old man fulfilling the diagnostic criteria of IgG4-related disease

- Retroperitoneal fibrosis/periaortitis (Fig. 6.9)
- Sclerosing cholangitis
- Riedel thyroiditis
- Hypophysitis, prostatitis, orchitis

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Systemic Sclerosis

7

Abstract

Systemic sclerosis (SSc) is an autoimmune systemic disease characterized by autoimmune reactivity (autoreactive B and T cells), which induces endothelial cell and fibroblast activation as well as overproduction of collagen leading to diffuse vascular pathology and widespread collagen accumulation. The vascular pathology is expressed by Raynaud's phenomenon (RP), telangiectasias, ischemic digital ulcers, and pulmonary arterial hypertension (PAH). SSc can have three distinct clinical presentations: (a) limited cutaneous systemic sclerosis characterized by skin thickening on the face, neck, and distal aspects of the extremities, long-standing RP, esophageal hypomotility, anti-centromere antibodies, and a tendency for developing PAH; (b) diffuse cutaneous systemic sclerosis characterized by extensive and rapidly progressive skin thickening, acute development of RP and arthritis, presence of anti-topoisomerase I and anti-RNA polymerase III antibodies, a higher risk for interstitial lung disease, and scleroderma renal crisis development; and (c) systemic sclerosis sine scleroderma which refers to patients who develop internal organ involvement without skin involvement. Scleroderma can also present as a localized disease type which involves only the skin, and then it is termed morphea (single or multiple painless, discolored patches of the skin) or linear scleroderma (bands of skin thickening affecting a unilateral limb or the scalp and face, which may extend deeper into fascia, muscle, and bone and cause tissue atrophy). Diffuse fasciitis with eosinophilia, scleredema, and scleromyxedema are some of the scleroderma mimickers, and differential diagnosis can be challenging especially early in the disease course.

1. **Which are the main clinical characteristics of localized scleroderma?**

In localized scleroderma, skin changes consist of cutaneous fibrosis without involvement of internal organs. The two types of localized scleroderma are:

- *Morphea*: single or multiple painless, discolored patches of the skin (Fig. 7.1a). Typically, the skin changes appear on the trunk, can occur on the extremities, but spare the hands and the fingers. Patients with morphea do not suffer from Raynaud's

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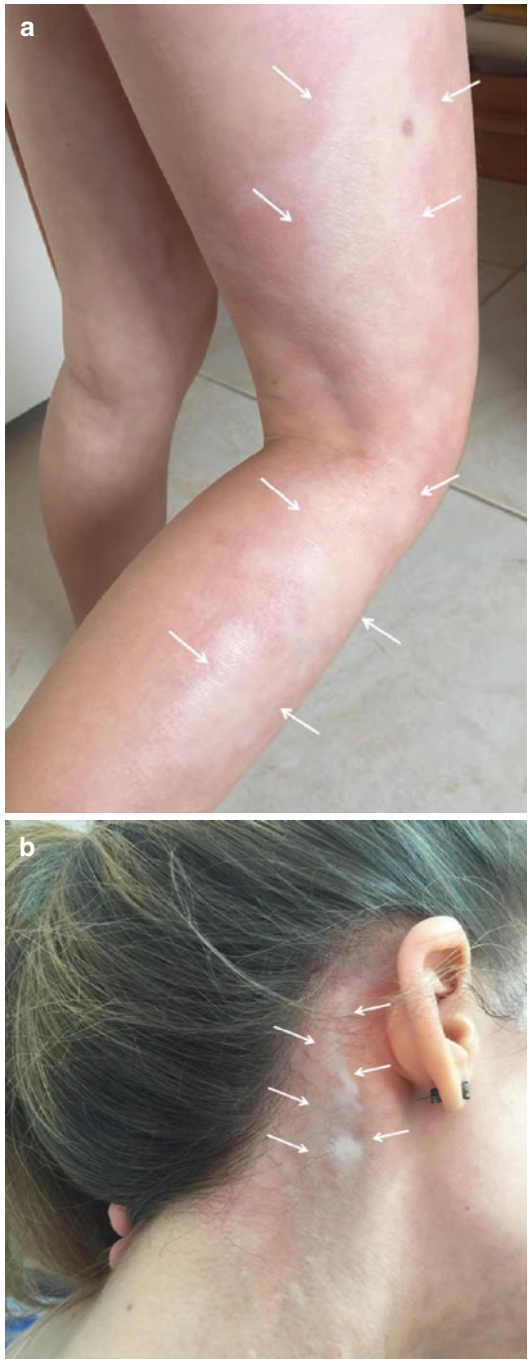

Fig. 7.1 Localized scleroderma (morphea): (**a**) multiple painless, discolored sclerotic skin lesions which become confluent in the lateral aspect of the right thigh in a 24-year-old female patient as well as (**b**) ivory-colored band of thickened skin and atrophic changes in the right retroauricular area (linear localized scleroderma-morphea)

phenomenon, and internal organs of the patients are not affected. The skin lesions can be circumscribed (focal skin and subcutaneous fibrosis), generalized (defined as four or more lesions >3 cm in size that become confluent in two or more anatomical sites), and pan-sclerotic (generalized involvement including the face, trunk, and extremities; these patients are at greater risk for squamous cell carcinoma development).

– *Linear scleroderma* (*linear morphea*): bands of skin thickening affecting a unilateral limb or sometimes the scalp (Fig. 7.1b) and face (*en coup de sabre*). It can extend beyond the skin to fascia, muscle, and bone leading to tissue atrophy. Patients with linear scleroderma do not suffer from Raynaud's phenomenon; arthritis can be a manifestation in a minority (10–15%) of these patients, while internal organs are not affected.

2. **Which are the main clinical characteristics of generalized scleroderma (systemic sclerosis)?**

There are two types of systemic sclerosis: the *limited* and *diffuse*.

(a) *Limited cutaneous systemic sclerosis* (lcSSc): patients with lcSSc have skin thickening restricted to the face, neck, or distal aspects of upper and lower extremities (below the elbows and knees). These patients often have history of long-standing Raynaud's phenomenon and gastroesophageal reflux disease and may develop telangiectasias (Fig. 7.2), skin calcifications (calcinosis), puffy hands and fingers, and sclerodactyly (Fig. 7.3a). In the past, the term CREST (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, and telangiectasia) was used to refer to a subgroup of patients with lcSSc, but nowadays this term has been abandoned, as it describes only a narrow part of the spectrum of clinical manifestations. In patients with lcSSc, the presence of anti-Scl70 (anti-topoisomerase) antibody is associated with high risk for the

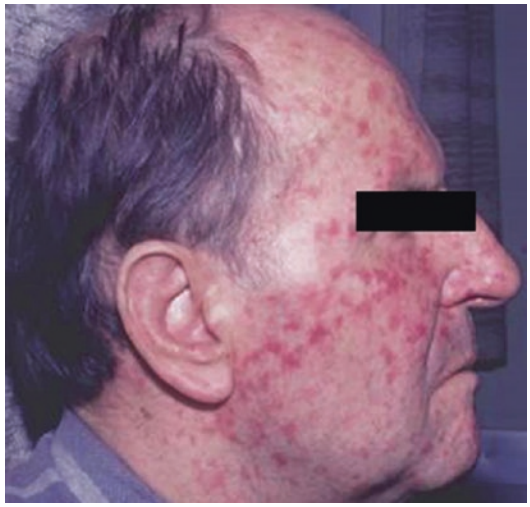

Fig. 7.2 Telangiectasias: multiple small dilated blood vessels close to the surface of the skin in a 70-year-old man with limited scleroderma

development of interstitial lung disease (ILD), and the presence of anti-centromere antibodies is associated with a particularly high risk of pulmonary arterial hypertension (PAH). Renal crisis very rarely affects patients with lcSSc.

(b) *Diffuse cutaneous systemic sclerosis* (*dcSSc*): patients present with skin thickening proximal to the elbows and knees, or trunk. Symptoms including puffy hands, Raynaud's phenomenon, rapidly progressive skin thickening, and arthritis appear relatively acutely. Patients with dcSSc are at higher risk to develop scleroderma renal crisis (even higher if positive for anti-RNA polymerase III antibodies) and progressive ILD (particularly within the first 5 years of disease onset).

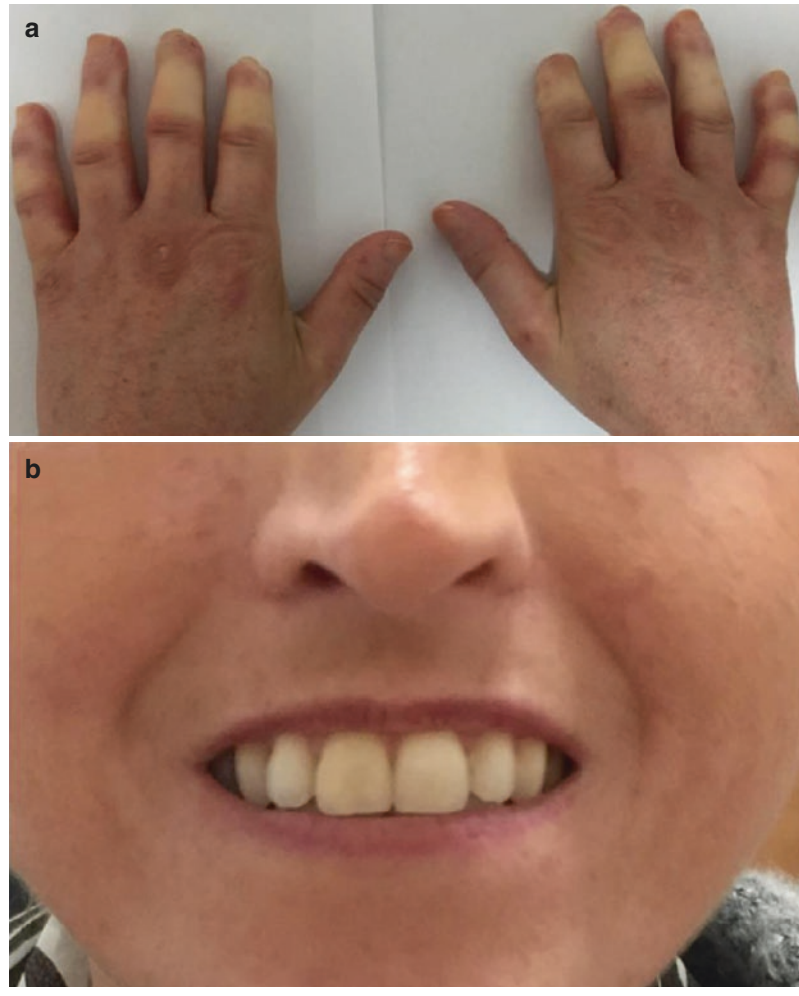

Fig. 7.3 Scleroderma in a 33-year-old lady with systemic sclerosis: thickened skin of the face neck, trunk, and extremities with (**a**) sclerodactyly resulting in claw deformity of the fingers and (**b**) microstomia

(c) *Systemic sclerosis sine scleroderma*: refers to patients with systemic sclerosis manifestations from internal organ, such as esophageal involvement and ILD, along with scleroderma-specific autoantibodies (anti-Scl-70, anti-centromere, anti-RNA polymerase III) without evidence of skin fibrosis.

3. **Which environmental agents have been implicated in the development of scleroderma?**

Exposure to silica, solvents, epoxy resins, silicone breast implants, pesticides, and welding fumes has been implicated in the pathogenesis of scleroderma.

4. **Which are the pathogenetic steps that lead to scleroderma development?**

An environmental agent in a genetically predisposed individual leads to endothelial activation and vascular changes. This pathologic process through the production of cytokines and chemokines activates the immune system (T and B lymphocytes) resulting in chronic inflammation. Immunocytes through cytokines, chemokines, and growth factors cause fibroblast activation and transformation of the endothelial cells into myofibroblasts which in turn produce serious fibroproliferative vascular pathology and accumulation of fibrotic tissue, the pathologic hallmarks of scleroderma.

5. **What is microchimerism? Does it play any role in the pathogenesis of autoimmune diseases?**

Fetal cells, including stem cells, cross the placenta during normal pregnancy and enter maternal blood. They reside in maternal tissues during and after pregnancy and remain for decades in the bone marrow and other organs. This small number of fetal cells, being genetically distinct, constitutes an allogeneic cell population within the host, the mother in this case. This is called microchimerism. Although persistent fetal cells were first implicated in autoimmune disease, and particularly in the pathogenesis of systemic sclerosis, subsequent studies have shown that microchimeric cells can be found in healthy as well as in tissues from individuals with non-autoimmune disease [1].

6. **Which are the oral manifestations of scleroderma?**

- Microstomia (tightening of the face skin around the mouth resulting in reduction in the size of the oral aperture) (Fig. 7.3b)
- Xerostomia
- Loosening of periodontal tooth ligament and tooth mobility
- Accelerated tooth decay
- Shortening of the frenulum linguae
- Temporomandibular joint disease
- Telangiectasias of the mucosal lining of the lips
- Mandible resorption

7. **In which body areas of patients with scleroderma telangiectasias can be seen?**

Telangiectasias in scleroderma patients can occur on the face (Fig. 7.2), neck, anterior chest wall, hands, mucous membranes (inner lining of the lips), tongue, and mucosa of gastrointestinal tract, particularly in the antrum or the last part of the stomach giving the appearance of "watermelon" (streaky long arches).

8. **Which are the symptoms and findings of large intestine involvement in patients with scleroderma?**

According to different series, the large intestine is involved in 10–50% of scleroderma patients. Involvement of the large bowel frequently affects the anorectal area and can be manifested as loss of rectal sphincter tone resulting in fecal incontinence. This is most likely due to a neuropathy (arteriolar changes of the vasa nervorum) and not to sphincter atrophy/fibrosis. In the colon, atrophy and thinning of the muscular wall can lead to formation of wide mouth diverticula. Scleroderma patients have poor gastrointestinal tract motility with abdominal distension causing

pain and malabsorption. The proposed sequence of events leading to malabsorption in scleroderma patients is diminished peristalsis leading to stasis, which results in colonic bacterial overgrowth and finally to diarrhea.

9. **Which scleroderma patients are particularly at high risk for developing interstitial lung disease and what is the most common interstitial lung disease pattern seen in scleroderma?**

Clinically significant interstitial lung disease (ILD) is most often identified within the first 3 years of disease onset. Patients at highest risk for clinically significant ILD are those with:

- Diffuse scleroderma (dcSSc).
- Positive anti-Scl70 antibody (irrespective of skin involvement).
- Positive ANA (nucleolar pattern) and negative anti-Scl70.
- The most common ILD patterns seen in scleroderma patients are fibrotic nonspecific interstitial pneumonia (F-NSIP) (Fig. 7.4) seen in 75% of cases, followed by usual interstitial pneumonia (UIP) (Fig. 7.5) in 25% of cases.

10. **Which clinical and laboratory manifestations are indicative of scleroderma renal crisis?**

Scleroderma renal crisis is the abrupt onset of arterial hypertension (>150/90 mmHg; however, 10% are normotensive and have a worse prognosis), hypertensive retinopathy, and rapid deterioration of renal function. Pericardial effusion and myocardial involvement can be present. Abnormal laboratory tests include elevated serum creatinine levels, consumptive thrombocytopenia, microangiopathic hemolysis (schistocytes), mild proteinuria, and elevated renin levels.

11. **Which scleroderma patients are more at risk to develop scleroderma renal crisis?**

Those scleroderma patients with:

- Clinical features of dcSSc
- Short disease duration (<4 years)

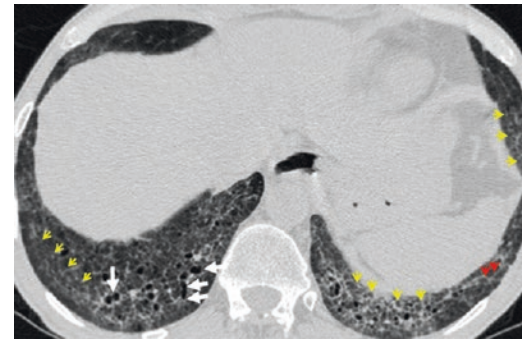

Fig. 7.4 Nonspecific interstitial pneumonia in a 57-year-old male patient with diffuse systemic sclerosis. Chest computed tomography (CT) scan shows predominantly ground-glass opacities (yellow arrows), irregular reticular opacities (red arrows) with or without traction bronchiectasis (white arrows), minimal honeycomb changes, and subpleural sparing, which are some of the radiographic characteristics that differentiate nonspecific from usual interstitial pneumonia (*Figure courtesy of Christos Kampolis, MD*)

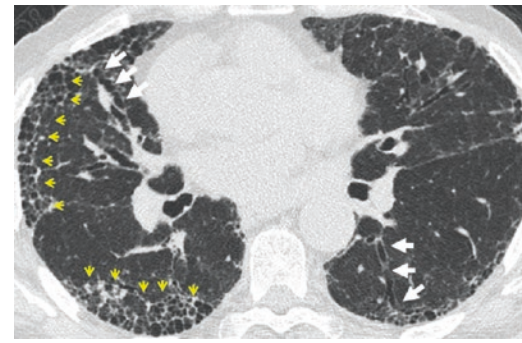

Fig. 7.5 Usual interstitial pneumonia in a 46-year-old female patient with diffuse systemic sclerosis. Chest computed tomography (CT) scan in usual interstitial pneumonia shows a pattern characterized by reticular septal thickening and honeycombing (yellow arrows) with or without traction bronchiectasis (white arrows) with a predominantly subpleural-basal distribution (*Figure courtesy of Christos Kampolis, MD*)

- Rapid skin thickening
- Tendon friction rubs
- New-onset microangiopathic hemolytic anemia
- New cardiac events (pericarditis, myocarditis, congestive heart failure)
- High doses of corticosteroids
- Cyclosporine-A use
- Anti-RNA polymerase III antibody positivity

12. **Which are the renal histopathologic findings in patients with scleroderma renal crisis?**

The primary renal histopathologic changes are localized in the small arcuate and interlobular arteries and the glomeruli. The characteristic finding is intimal proliferation and thickening that leads to narrowing and obliteration of the vascular lumen, with concentric "onion skin-like" hypertrophy. These histopathologic findings are similar to systemic sclerosis-associated vascular lesions found in other organs. Scleroderma renal crisis is a thrombotic microangiopathy similar to malignant nephrosclerosis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and antiphospholipid syndrome.

13. **Which scleroderma patients are prone to develop pulmonary arterial hypertension (PAH)?**

Those scleroderma patients with:

- Clinical features of lcSSc
- Duration of Raynaud's phenomenon more than 8 years
- Anti-centromere antibody positivity
- Anti-nucleolar antibodies
- Extensive telangiectasias
- Diffusing capacity of the lungs for carbon monoxide (DLCO) <60% in the absence of extensive interstitial lung disease
- Forced vital capacity (FVC%)/DLCO% ratio > 1.6

14. **Is it possible for a patient with localized scleroderma (morphea or linear scleroderma) to evolve to systemic sclerosis?**

The possibility that a patient with localized scleroderma evolves to systemic sclerosis is very low (<1%), and it has been described very infrequently in morphea patients that have positive anti-centromere antibodies (ACA) (2% of morphea patients).

15. **Which organ in addition to the skin can be affected in limited scleroderma?**

Other organs that can be affected in limited scleroderma besides the skin (skin thickening, telangiectasia, calcinosis, Raynaud's) include the joints (arthralgias-arthritis), the esophagus (esophageal dysmotility), and the lungs (pulmonary arterial hypertension, pulmonary fibrosis).

16. **Which are the early electrocardiographic findings in patients with scleroderma cardiomyopathy?**

The heart is one of the major organs which can be involved in systemic sclerosis. Cardiac involvement can be manifested as myocardial disease, conduction system abnormalities, arrhythmias, or pericardial disease. The most frequent abnormalities on the resting electrocardiogram of scleroderma patients are left anterior fascicular block (16%) and first-degree atrioventricular heart block (8%). Supraventricular arrhythmias are considered to be more common in scleroderma patients, occurring in approximately two thirds of the cases, and much more frequent than ventricular tachyarrhythmias.

17. **Which are the magnetic resonance imaging (MRI) findings in patients with scleroderma cardiomyopathy?**

Cardiac MRI can detect heart pathologies in up to 75% of affected scleroderma patients, including:

- Increased intensity signal of the myocardium (T2-weighted images)
- Thinning of the left ventricle (LV)
- Pericardial effusion
- Reduced LV and right ventricle (RV) ejection fractions
- LV diastolic dysfunction and kinetic abnormalities
- Myocardial delayed contrast enhancement (Fig. 7.6a–c)

In addition, cardiac MRI can be used to differentiate structural from functional pathologies, such as myocardial inflammation and fibrosis (the extent of fibrosis and viable tissue is properly measured after contrast enhancement). The method gives an opportunity for quantitative assessment of myocardial perfusion and the effect of vasodilators [2].

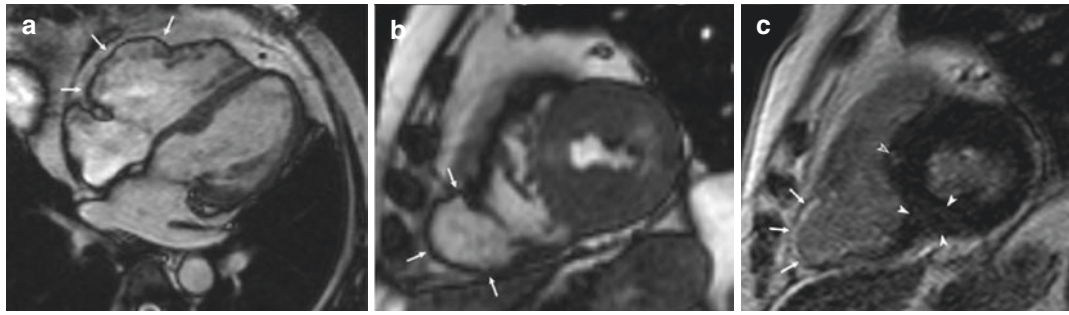

Fig. 7.6 Myocardial involvement in a 60-year-old female with systemic sclerosis. Cardiac magnetic resonance imaging (MRI) revealed thinning of the right ventricular (RV) myocardium with aneurysm formation (**a**, **b**, arrows) in the subtricuspid area. An abnormal linear enhancement (**c**, arrows) of the aneurysmal myocardium, as well as a patchy subtle enhancement (**c**, arrowheads) of the lower RV insertion point, and a somewhat more intense focal enhancement (**c**, open arrowhead) at the anteroseptal medial segment of the left ventricular myocardium are seen (*Figure courtesy of Sotiris C. Plastiras, MD*)

18. **What is calcinosis cutis?**

Calcinosis cutis refers to cutaneous deposits of basic calcium phosphate that typically occur in the hands (especially over proximal interphalangeal joints and fingertips), periarticular areas, and over bony prominences (especially the extensor surface of the elbows and the knees) but can occur virtually anywhere on the body. The deposits of calcium are firm and irregular and can become inflamed, infected, or ulcerated and discharge a chalky white material.

19. **What are possible therapeutic options of calcinosis cutis?**

Calcinosis cutis is extremely difficult to be treated. Therapies that have been used include low-dose (1 mg/day) warfarin (inhibits the vitamin K-dependent γ-carboxyglutamic acid matrix protein, found to be high in areas of calcinosis), colchicine (suppresses local inflammation in calcinosis lesions), topical sodium thiosulfate, and aluminum hydroxide, administration of diltiazem (doses up 360 mg/day) and probenecid (500 mg b.i.d), and high doses of bisphosphonates (e.g., alendronate 10 mg/day). All however have limited success. Preliminary studies have shown that intravenous immunoglobulins (2 g/kg) in a 4-day protocol once a month seem to have a beneficial effect after the third monthly dose.

20. **What are the clinical differences between scleroderma and diffuse fasciitis with eosinophilia?**

The presentation of diffuse fasciitis with eosinophilia can be similar to scleroderma. It is of unknown cause, yet it has been reported to develop after strenuous exercise in 50% of the cases and mostly during spring and autumn. In contrast to systemic sclerosis, it does not involve the skin and subcutaneous tissues of the face or the hands and feet of the affected individuals. Raynaud's phenomenon, fingertip ulcerations, and telangiectasias are not present. Internal organ involvement (esophagus, lungs, kidneys) is exceedingly rare [3].

21. **What is the clinical picture of diffuse fasciitis with eosinophilia?**

It may have a rapid onset with generalized manifestations like low-grade fever, muscle aches, cramps, and fatigability. Initially pitting edema, usually on both arms and legs simultaneously, becomes apparent, and typically the face, hands, and feet are spared. Carpal tunnel syndrome can be an early symptom in many patients. As the disease progresses, the skin becomes

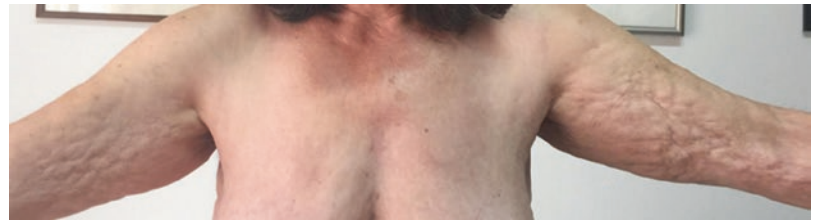

Fig. 7.7 Diffuse fasciitis with eosinophilia: a hard lumpy dimpling of the skin (*peau d' orange*) and subcutaneous tissue of the brachial areas of the arms in a 51-year-old woman, following unusual exercise

stiff, having a woody texture and an "orange peel" appearance (peau d' orange) (Fig. 7.7). At later stages, the fascia is involved and flexion contractures as well as muscle atrophy, yet without muscle weakness, can occur.

22. **Which are the laboratory and histopathologic differences among scleroderma and diffuse fasciitis with eosinophilia?**

The major laboratory finding in the initial phase of diffuse fasciitis with eosinophilia is peripheral eosinophilia (85%), while hypergammaglobulinemia and increased erythrocyte sedimentation rate are present in all phases of diffuse fasciitis with eosinophilia. A small number of patients may show a transient positivity of rheumatoid factor and antinuclear autoantibodies.

Histologically the diagnosis of diffuse fasciitis with eosinophilia is confirmed by a deep wedge en bloc full-thickness biopsy of the involved area. The most typical histological finding is thickening of the deep fascia due to inflammation, edema, and fibrosis. The inflammatory cells are predominantly lymphocytes, histiocytes, and plasma cells with scattered clusters of eosinophils. The dermis is not thickened and does not show condensation of fibrous tissue. In contrast, in scleroderma, the deep fascia shows no significant abnormality, whereas the dermis appears thickened.

23. **What are the entities scleredema and scleromyxedema?**

Scleredema is a sclerotic skin disease. It is characterized by firm, non-pitting skin edema that begins in the neck and upper back and spreads to the shoulders and trunk. The face and extremities are less commonly involved, while the hands and feet are typically spared. Scleredema generally occurs in association with poorly controlled diabetes mellitus, following streptococcal infection or in association with a paraproteinemia (usually IgG or IgA). Skin biopsy shows normal epidermis but thickened dermis with deposition of excessive collagen and mucin between collagen bundles.

Scleromyxedema is characterized by multiple flesh-colored papules of 2–3 mm in diameter on the face, posterior auricular area, glabella, neck, upper trunk, distal forearms, and hands but sparing the palms. Over 80% of individuals have an IgG mini-monoclonal protein (usually IgGλ), while 10% develop multiple myeloma. Systemic involvement has been reported with the occurrence of dysphagia, myopathies, and cardiopulmonary involvement. Skin biopsy shows normal epidermis, mucin deposition in the dermis, fibroblast proliferation, and fibrosis [4].

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Vasculitides and Related Diseases

8

Abstract

The term "vasculitis" stands for a spectrum of diseases characterized by an inflammatory injury of the vascular wall which may affect arteries and veins; it may lead to necrosis or to granulomatous inflammation of the vascular wall, occlusion of the vascular lumen, and ischemic injury of the affected tissues. Depending on the size of vessels affected, vasculitides are categorized into large-vessel vasculitis – affecting the aorta and its direct branches – such as giant cell arteritis (GCA) and Takayasu arteritis (TA); medium-vessel vasculitis, such as polyarteritis nodosa (PAN) and Kawasaki disease (KD); as well as small-vessel vasculitis. The small-vessel vasculitides comprise the ANCA-associated vasculitides (AAV), which are associated with the presence of circulating antineutrophil cytoplasmic antibodies (ANCA), and the ones without autoantibodies. The AAV are granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss syndrome). Other non-ANCA-associated small-vessel vasculitides are typically characterized by either the presence of immune complex deposition (cryoglobulinemic and IgA vasculitis/Henoch-Schönlein purpura) or are the result of a neoplasia (paraneoplastic phenomenon).

GCA is diagnosed by temporal artery biopsy, while for TA, gadolinium-enhanced magnetic resonance angiography (MRA) and positron emission tomography associated with computed tomography (PET/CT) is used both for diagnosis and assessment of disease activity. Medium- and small-sized vasculitides should be diagnosed by biopsy of affected tissues. Microaneurysms seen with conventional angiography in the tripod of Haller support the diagnosis of PAN.

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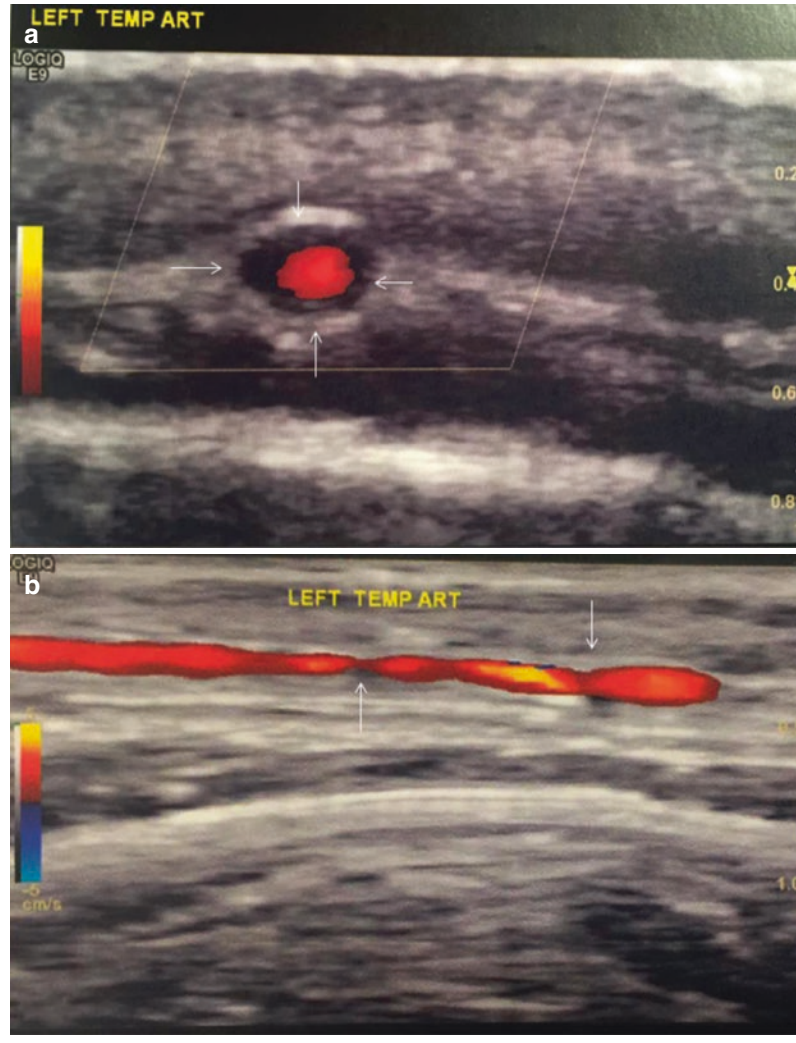

Fig. 8.1 Temporal arteritis-temporal artery ultrasound findings: (**a**) a hypoechogenic ring area is apparent around the lumen of the temporal artery (*halo sign*), and (**b**) segmental artery stenosis is seen on sagittal sections in a 72-year-old man whose temporal artery biopsy confirmed the diagnosis of temporal arteritis

1. **Which are the clinical and histological characteristics of giant cell arteritis?**

Giant cell arteritis (GCA) occurs primarily in patients over 50 years of age (female:male = 2–3:1) and affects mostly the extracranial branches of carotid arteries. Clinically detectable involvement of the aorta and its branches occurs in 15% of the cases. Symptoms of GCA include low-grade fever, polymyalgia rheumatica (PMR)-related symptoms, anorexia, new headache, scalp tenderness, jaw claudication, and weight loss. Enlarged/difficult to compress/pulseless temporal arteries, visual symptoms (diplopia, amaurosis fugax, unilateral loss of vision), and limb claudication are additional disease findings. Rare manifestations include hypertension, cough, tongue pain/ulcers, mononeuritis multiplex (affects the shoulder producing sudden weakness and pain mimicking a C5 radiculopathy), and large artery disease (aorta and major branches). Diagnosis of GCA can be assisted by Doppler ultrasound of temporal arteries (Fig. 8.1a, b), yet temporal artery biopsy remains the gold standard for GCA diagnosis. Histologically, inflammation of the arterial wall is evident, especially at arterial bifurcations, with fragmentation and disruption of the internal elastic lamina being a classic finding. Multinucleated giant cells are found in 50% of the cases [1].

2. **How often the coronary and renal arteries are involved in giant cell arteritis?**

   There have been isolated case reports indicating involvement of coronary arteries in patients with giant cell arteritis (GCA). However, a recent systematic review and meta-analysis did not show any statistically significant increased risk for coronary artery involvement in GCA [2].

3. **Which are the clinical and histologic characteristics of Takayasu arteritis?**

   Takayasu arteritis (TA) occurs most commonly in young women (female: male = 8:1), of young age (median age of 25 years; in 15% it occurs after the age of 40). TA affects primarily the aorta and its branches and more commonly the aortic arch and the abdominal aorta. Initial manifestations can be nonspecific, including constitutional symptoms such as low-grade fever, fatigue, arthralgias, anorexia, and weight loss. Later on typical manifestations and findings include claudication of upper extremities, bruits on large-vessel auscultation, decreased or even absent pulses (therefore also called "pulseless disease"), and asymmetric blood pressure in the extremities. Pulmonary and coronary artery involvement is less frequent. TA diagnosis is based on angiography. Nowadays computer tomography angiography, gadolinium-enhanced magnetic resonance angiography (MRA) (Fig. 8.2), and positron emission tomography (PET) can be valuable noninvasive diagnostic tools. Thickening of the arterial wall and narrowing of the arterial lumen with subsequent aneurysmal dilatations are characteristic TA imaging findings.

   The histologic appearance of TA is a focal panarteritis that can be very similar to giant cell arteritis (GCA). Like GCA, focal "skip lesions" are common, and lesions can be active, chronic, or healed. Mononuclear cell infiltrates (CD4 and CD8 lymphocytes, plasma cells, and macrophages) in the outer parts of the media and adventitia are prominent, in contrast to GCA where inflammatory infiltrates concentrate around the inner half of the media.

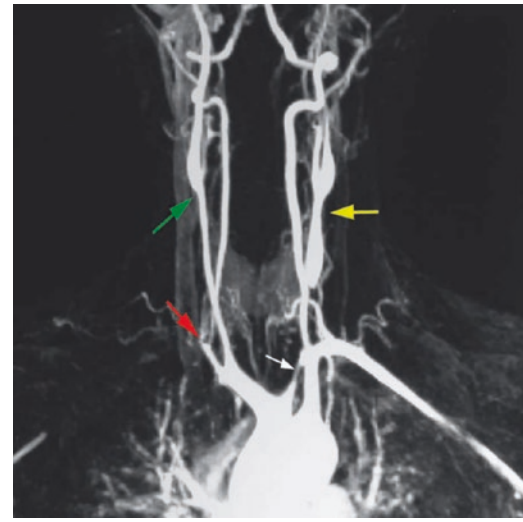

Fig. 8.2 Takayasu arteritis: magnetic resonance angiography of the major aortic arch branches revealing complete obstruction of the right subclavian artery (red arrow) obstruction and post-stenotic dilatation of the right common carotid artery (green arrow), severe stenosis of the left subclavian artery (white arrow), and stenosis of the left common carotid artery with post-stenotic dilatation in a 30-year-old female diagnosed with Takayasu arteritis

4. **Which are the clinical and laboratory features of polymyalgia rheumatica?**

   Polymyalgia rheumatica (PMR) is an inflammatory syndrome affecting older individuals (>50 years of age) and women more often than men (2:1). PMR is about two to three times more common than giant cell arteritis (GCA). Cardinal features include abrupt onset of pain and stiffness, especially in the neck and shoulder/pelvic girdles, that can be so severe that patients may be unable to lift their arms to comb their hair, rise from a chair, or even get out of bed without assistance.

   Morning stiffness, elevated acute-phase reactants (ESR, CRP), as well as absence of rheumatoid factor and anti-cyclic citrullinated autoantibodies are found in patients with PMR. These features are accompanied by constitutional symptoms, including low-grade fever and weight loss, in more than 50% of patients and are particularly common in patients aged 70 years or older. A remarkable response to corticosteroid administration is not diagnostic, yet poor or unsustained

response to this therapy may indicate another diagnosis, including GCA, cancer-related muscle pain, fibromyalgia, chronic infection, or endocrinopathy (such as hypothyroidism). At times patients with PMR may present with peripheral arthritis (knees, wrists, sternoclavicular joints) which is non-erosive and asymmetrical. In all cases of PMR, concurrence of GCA should be considered, as GCA may occur in 30% of patients with PMR and PMR may be the initial symptom in 20–40% of patients with GCA.

5. **What other diseases should be considered before setting the diagnosis of polymyalgia rheumatica?**

The diagnosis of polymyalgia rheumatica is a clinical one and is made after excluding other possible disease entities, such as:

- Occult infection
- Giant cell arteritis
- Malignancy
- Rheumatoid arthritis
- Polymyositis
- Fibromyalgia

6. **Which are the main clinical and laboratory characteristics of patients with microscopic polyangiitis?**

Microscopic polyarteritis (MPA) is one of the ANCA-associated vasculitides affecting small vessels (capillaries, arterioles, or venules). Its main clinical characteristics are:

Nonspecific constitutional symptoms, such as fever, malaise, myalgias, and weight loss, are common.

Kidney involvement is typical, and rapidly progressive glomerulonephritis (GMN) (focal segmental necrotizing, pauci-immune) is detected in more than 80% of MPA patients.

Mononeuritis multiplex occurs in almost 60% of MPA patients.

Cutaneous vasculitis (palpable purpura, ulcers, vesiculobullous lesions).

Migratory arthralgias or arthritis, which is pauciarticular or polyarticular, yet nondestructive.

Lung involvement is not uncommon, and it can manifest with symptoms ranging from pulmonary effusions and infiltrates to diffuse alveolar hemorrhage with hemoptysis and even pulmonary fibrosis. Pulmonary fibrosis in a patient with MPA can be an early manifestation and connotes poor prognosis [3].

Gastrointestinal tract involvement with mesenteric vasculitis.

Laboratory characteristics of MPA are:

- Mild to moderate leukocytosis and thrombocytosis.
- Elevated acute-phase reactants (ESR and CRP).
- Positive rheumatoid factor in 40–50% of MPA patients.
- Microscopic hematuria and proteinuria.
- Perinuclear antineutrophil cytoplasmic antibodies (pANCAs) directed against myeloperoxidase (MPO) are detected in the serum of the majority of MPA patients and support the diagnosis; yet a few MPA patients may have cytoplasmic antineutrophil cytoplasmic antibodies (cANCAs), directed against proteinase 3 (PR3).

7. **Which are the main clinical and laboratory characteristics of patients with eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)?**

Eosinophilic granulomatosis with polyangiitis (EGPA) is an ANCA-associated granulomatous vasculitis affecting small- and medium-sized vessels. Its main clinical characteristics are:

- The majority of patients have a history of allergic manifestations such as allergic rhinitis, nasal polyposis, and adult-onset asthma.
- It affects the lungs, the heart, the peripheral nerves, the skin, and the gastrointestinal tract and is associated with peripheral blood and tissue eosinophilia.
- Lung involvement presents with patchy transient pulmonary infiltrates without cavitation.
- Heart involvement can manifest as pericarditis, pericardial effusion, valvular heart disease, cardiomyopathy, acute myocardial infarction, myocarditis, and acute heart failure.

- Although uncommon, cardiac involvement represents a major cause of morbidity and mortality.
- Mononeuritis multiplex and asymmetric sensorimotor polyneuropathy (glove/stocking distribution) are frequent (65–75%) manifestations.
- Subcutaneous nodules, petechiae, palpable purpura, and ulcers due to skin infarction are manifestations of skin involvement.
- Eosinophilic gastroenteritis with abdominal pain and bloody diarrhea occurs in some EGPA patients.
- Kidney involvement is uncommon, and acute kidney injury may be caused by eosinophil-mediated interstitial nephritis.

Laboratory characteristics of EGPA are:

- Peripheral blood eosinophilia (often >3000/mm^3).
- Elevated acute-phase proteins (CRP/ESR) and serum IgE levels.
- ANCAs directed against myeloperoxidase (MPO) (30–40%).
- Patients who are MPO positive tend to have higher prevalence of arthritis and glomerulonephritis than those who are MPO negative.

8. **Which hypereosinophilic conditions should be considered in the differential diagnosis of eosinophilic granulomatosis with polyangiitis?**
   - Strongyloidiasis: infection from the nematode *Strongyloides stercoralis*
   - Löffler syndrome
   - Chronic eosinophilic pneumonia
   - Eosinophilic gastroenteritis
   - Hypereosinophilic syndrome
   - Eosinophilic fasciitis
   - IgG4-related disease
   - Eosinophilic leukemia [4]

9. **Which are the main clinical and laboratory characteristics of granulomatosis with polyangiitis (formerly Wegner's granulomatosis)?**

Granulomatosis with polyangiitis (GPA) is a systemic ANCA-associated vasculitis affecting small- to medium-sized vessels (both arterial and venous). Its main clinical characteristics are:

- GPA presents usually in a subacute way. Chronic sinusitis and inflammation of the nasal mucosa and purulent/hemorrhagic nasal discharge, nasal mucosa crusts, and/or ulcerations are common initial manifestations.
- Patients are frequently *Staphylococcus aureus* carriers, which can lead to GPA relapses.
- Oral manifestations include typically painful ulcers on the lateral sides of the tongue (Fig. 8.3) and gum inflammation giving the appearance of "strawberry gums."
- Acute suppurative otitis media or chronic serous otitis media as well as mixed-type conductive and sensorineural hearing loss.
- Scleritis, episcleritis, retinal artery occlusion, and orbital pseudotumors.
- Chronic inflammation of the laryngeal and tracheal mucosa can lead to hoarseness and subglottic stenosis.
- Lung involvement is the presenting symptom in 50% of GPA patients, while more than 80% will present clinical evidence of lower respiratory tract involvement during their disease course.
- Pulmonary capillaritis may lead to alveolar hemorrhage.
- Pulmonary fibrosis may result from healing of acute or chronic inflammation.
- Kidney involvement is very frequent (80% of GPA patients). It can manifest as micro-

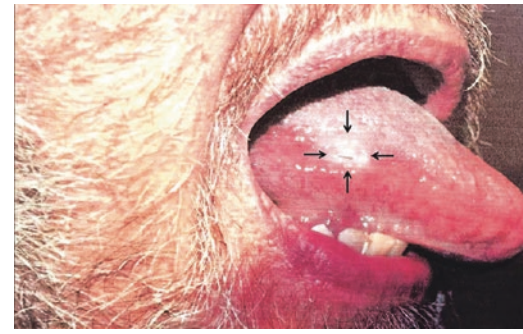

Fig. 8.3 Deep painful tongue ulcer: in a 62-year-old male with granulomatous polyangiitis (Wegener's granulomatosis)

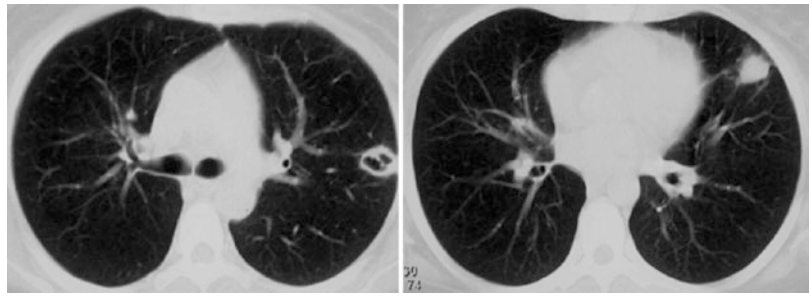

Fig. 8.4 Granulomatous polyangiitis (Wegener's granulomatosis) lung lesions: chest computerized tomography (CT) showing bilateral round opacities with and without cavitation in a 36-year-old male patient with granulomatous polyangiitis (*Figure courtesy of Christos Kampolis, MD*)

scopic hematuria, proteinuria, cellular casts, and variable degree of renal function compromise. The histopathologic renal lesion is pauci-immune focal segmental necrotizing glomerulonephritis.
- Deep vein thrombosis can occur in GPA patients as a result of venous circulation involvement.
- Skin manifestations include a wide range of cutaneous vasculitis signs: palpable purpura, subcutaneous nodules, papules, ulcers, and vesicles.
- Peripheral and central nervous system involvement in the form of mononeuritis multiplex, meningeal inflammation, and central nervous system vasculitis.

Laboratory characteristics of GPA are:
- Anemia and elevated acute-phase reactants (ESR, CRP) are common.
- Microscopic hematuria and proteinuria occur with renal involvement.
- Rheumatoid factor may be positive in 30–40%.
- Cytoplasmic ANCAs directed against proteinase 3 (PR3) are found in 90%.

10. **Which are the common lung computerized tomography (CT) findings in patients with granulomatosis with polyangiitis?**

Cavitating pulmonary nodules and masses (usually 2–4 cm, rarely up to 10 cm) are present in 50% of cases. The lesions tend to be multiple, bilateral, and well defined (Fig. 8.4). Airspace disease may include the following: (1) bilateral and diffuse disease caused by pulmonary hemorrhage, (2) scattered parenchymal disease with eventual coalescence of lesions, or (3) localized disease with ill-defined margins and air bronchograms or central cavitation. In the last case, the lesions may be surrounded by a halo of ground-glass opacity, which presumably occurs secondary to hemorrhage. Interstitial abnormalities are often present. These include interlobular septal thickening, parenchymal bands, and bronchial wall thickening. Pleural thickening, pleural effusion, and lymphadenopathy may be present.

11. **Which drugs have been implicated in drug-induced ANCA-associated vasculitis?**

Propylthiouracil, minocycline, clozapine, levamisole, allopurinol, hydralazine, montelukast, and anti-tumor necrosis factor agents have been reported to be possibly implicated in drug-induced ANCA vasculitis. Constitutional symptoms, skin vasculitis, and arthralgias are common manifestations, while lung and kidney involvement occurs less frequently. Timely withdrawal of the offending drug usually leads to recovery, while late withdrawal of the drug and more advanced disease may require administration of immunosuppressive therapy. In these patients multiple antigens can be responsible for ANCA positivity.

12. **Which are the main clinical and laboratory characteristics of patients with polyarteritis nodosa?**

Polyarteritis nodosa (PAN) is a necrotizing inflammation of medium-sized arteries and muscular arterioles. The main clinical features suggestive of PAN are:

Anorexia, weight loss, myalgias, and low-grade fever.

Skin lesions: livedo reticularis, palpable purpura, nodules, papules, ulcers, and digital ischemia/gangrene.

Peripheral neuropathy, most frequently mononeuritis multiplex.

Testicular pain.

Mesenteric vasculitis presenting with abdominal pain/intestinal angina.

Hypertension due to renal artery involvement.

Glomerulonephritis, lung involvement, and ANCA positivity are not PAN manifestations.

Laboratory findings are nonspecific and include:

- Elevated acute-phase proteins (CRP, serum complement).
- Leukocytosis, normochromic anemia, or thrombocytosis.
- Presence of hepatitis B or C viral infection in around 30% of patients.
- Elevated creatinine levels and mild proteinuria.
- Elevated levels of liver enzymes.
- Hypergammaglobulinemia (in 30% of patients with PAN).
- To confirm the diagnosis of PAN, biopsy of an accessible affected tissue and/or visceral angiography should be performed.

13. **Which are the angiographic and histopathology findings of polyarteritis nodosa?**

The typical angiographic findings in PAN are microaneurysms (small saccular aneurysms), occlusions, abrupt vessel cutoffs, irregularities of the vessel lumen, and stenosis of the small and medium vessels of the viscera. To confirm the diagnosis of PAN, biopsy of an accessible affected tissue should be performed. Skin, nerve, or muscle biopsies are preferred since they yield high diagnostic value with the lowest morbidity. The characteristic pathologic picture shows focal transmural necrotizing inflammation of small- and medium-sized arteries, disrupting the normal architecture of the vessel wall and leading to aneurysmal dilatations. The inflammatory process is pleomorphic with predominance of round (lymphocytes/macrophages) cells. The elastic lamina is disrupted and the vessel wall is destroyed. Proliferation of fibrous tissues and endothelial cells can lead to vessel lumen occlusion

14. **What is cutaneous polyarteritis nodosa?**

Cutaneous PAN is a distinct subset of the systemic disease, where skin is the sole organ affected. Patients present with firm, painful subcutaneous nodules, which may ulcerate, most often found on the legs and feet. A deep skin biopsy, including subcutaneous tissue, is necessary for the accurate diagnosis of cutaneous PAN. Necrotizing inflammation of small- to medium-sized arterioles of the deep dermis and/or hypodermis with or without fibrinoid necrosis is the characteristic histopathologic finding (Fig. 8.5). Cutaneous PAN runs a chronic but relatively benign course.

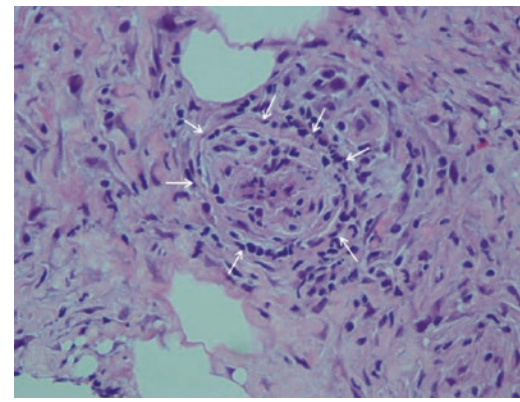

Fig. 8.5 Cutaneous polyarteritis nodosa: deep skin biopsy (HE × 200) revealing focal fibrinoid necrosis, a mixed inflammatory infiltrate, as well as occlusion of the arteriole's lumen in the medium-sized arterioles of hypodermis in a 56-year-old female patient with recurrent painful, indurated subcutaneous nodules on the lower extremities

15. **Which conditions can present as pulmonary-renal syndrome?**

Pulmonary-renal syndrome is defined as the combination of alveolar hemorrhage and glomerulonephritis. It can be caused by a variety of diseases, such as:

- Primary systemic vasculitis (especially microscopic polyangiitis and granulomatosis with polyangiitis)
- Goodpasture syndrome (associated with autoantibodies against type IV collagen, the major component of alveolar and glomerular basement membranes)
- Systemic lupus erythematosus
- Antiphospholipid syndrome

16. **What is middle line lethal granuloma? Which autoimmune condition resembles it?**

It is a natural killer/T-cell non-Hodgkin's lymphoma causing destruction of the nasal septum, the hard palate, the nasopharynx, and the orbit. It can resemble the clinical picture of granulomatosis with polyangiitis (Wegener's granulomatosis) when the latter affects the upper airways.

17. **Which are the major and minor criteria for the diagnosis of Behçet's syndrome?**

- Major criterion: recurrent oral ulceration (Fig. 8.6)
- Minor diagnostic criteria:

Recurrent genital ulceration

Ocular lesions: anterior/posterior uveitis or cells in vitreous on slit-lamp examination or retinal vasculitis observed by ophthalmologist

Skin lesions: erythema nodosum (Fig. 8.7), superficial thrombophlebitis, pseudofolliculitis or papulo-pustular lesions, or acneiform nodules in post-adolescent patients

Positive pathergy test (Fig. 8.8)

For the diagnosis of Behçet's syndrome, one major and two minor criteria are required.

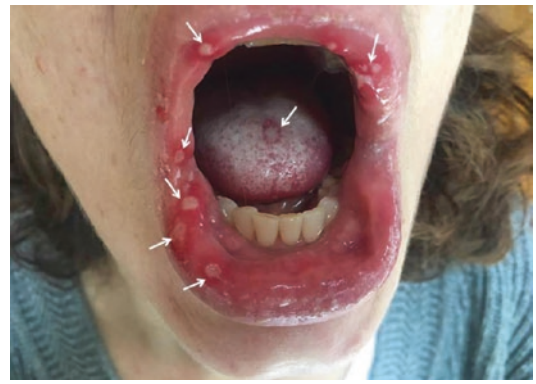

Fig. 8.6 Painful aphthous oral ulcers: in a 52-year-old woman with Behçet's syndrome

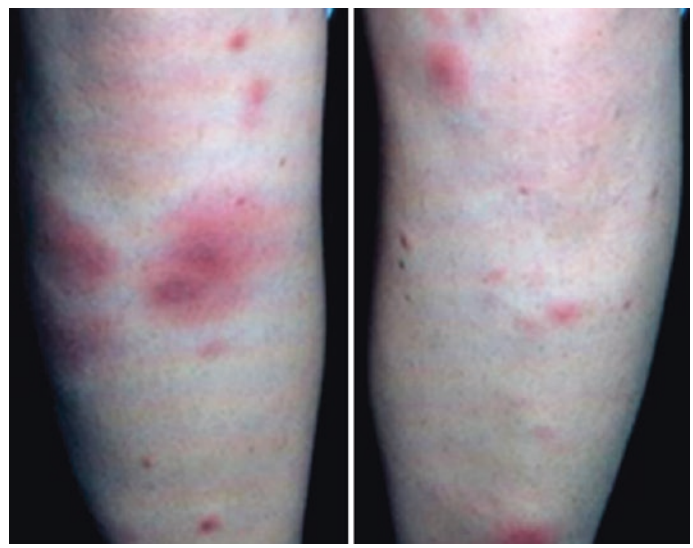

Fig. 8.7 Erythema nodosum: in a 29-year-old male patient with Behçet's syndrome

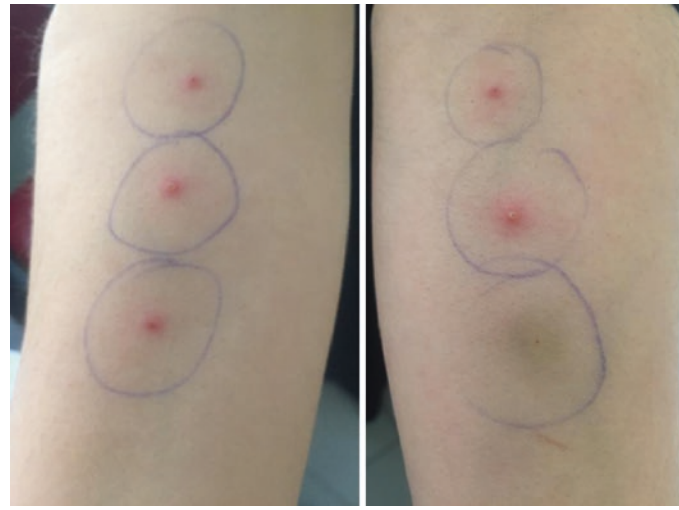

Fig. 8.8 Pathergy test: in a young male with Behçet's syndrome. Pustule formation could be seen in 5/6 needle insertion sites on the antecubital area (*Figure courtesy of Professor Emire Seyahi, MD*)

18. **What is pathergy test? In which patient population is it more often positive?**

Pathergy is skin hyper-reactivity to any cutaneous injection or needle stick. Pathergy test is the development of a ≥2 mm erythema 24–48 h after a 20 or 21 gauge needle prick subcutaneously to a depth of 5 mm. This reaction is believed to be pathognomonic of Behçet's disease. The mechanism of pathergy is thought to be related to increased neutrophil chemotaxis. The rate of a positive reaction varies in different populations, being more common in Japan and Turkey.

19. **In which autoinflammatory diseases pulmonary artery aneurysms can manifest?**

Behçet's disease (Fig. 8.9) and Takayasu arteritis.

20. **Which are the commonest clinical manifestations of Cogan syndrome?**

Cogan syndrome is a rare inflammatory disorder presenting with:

- Interstitial keratitis (non-syphilitic): manifests as an acute onset of unilateral or bilateral redness, pain, photophobia, and increased lacrimation. Uveitis, choroiditis, and retinal artery occlusion can occur with or without concomitant keratitis. Episcleritis/scleritis and uveitis are not uncommon in these patients.
- Vestibulo-auditory dysfunction: is usually acute in onset and manifests with episodes of tinnitus, vertigo, and sensorineural (Ménière-like) hearing loss which might be initially fluctuating but progressively leads to deafness in more than 50% of cases. Unilateral involvement is typical.

21. **Which are the systemic manifestations of Cogan syndrome?**

The most common systemic manifestations in patients with Cogan syndrome are:

- Musculoskeletal complaints: arthralgias, myalgias, and inflammatory arthritis.
- Constitutional symptoms: mostly in systemic disease.
- Gastrointestinal involvement: abdominal pain, bleeding, and hepatomegaly.
- Cardiac involvement: pericarditis and aortic insufficiency.
- Neurologic manifestations: headache, peripheral neuropathy, mononeuritis multiplex, and meningitis.
- Skin: nodules and rash.
- Lymphadenopathy and splenomegaly.
- Systemic vasculitis: occurs in 10–15% of cases, usually affecting large- more often than medium-sized vessels. Large-vessel vasculitis predominantly affects the aorta and its major branches resembling Takayasu arteritis.

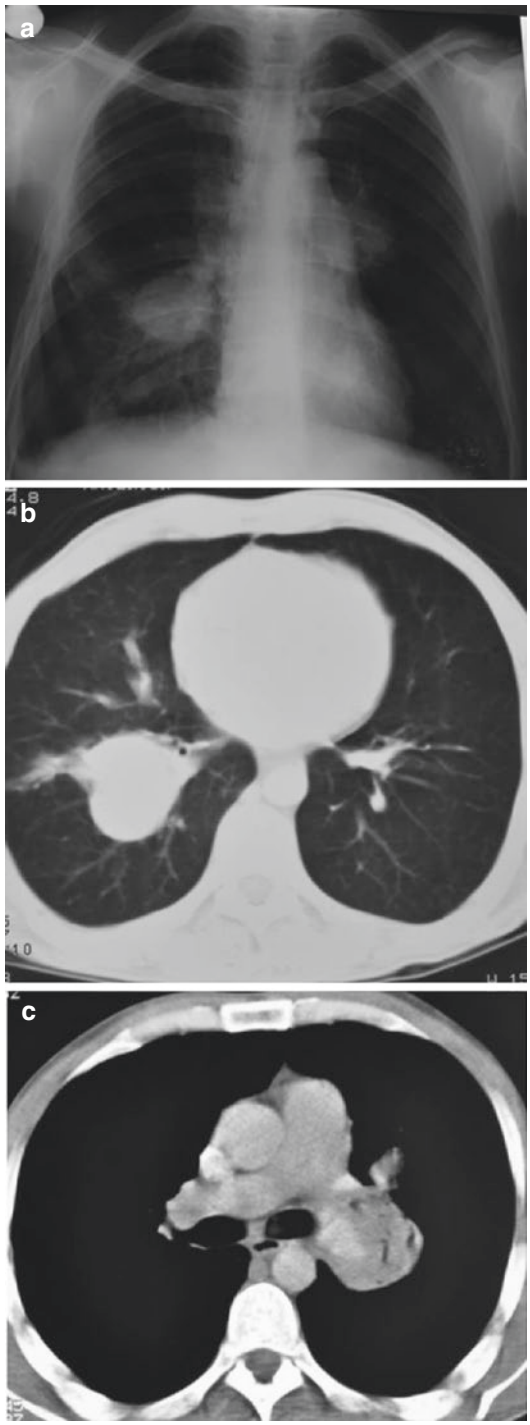

Fig. 8.9 Pulmonary artery aneurysms: (**a**) chest plain radiography and (**b**, **c**) computed tomography (CT) scans of a young male patient with Behçet's syndrome: multiple aneurysms completely thrombosed can be observed. Aneurysms are located on the right descendant artery (5 cm), distal portion of the left main artery (5 cm), and on the left descendant artery (1.5 cm) (*Figure courtesy of Professor Emire Seyahi, MD*)

22. **Which are the poor prognostic factors in patients with cryoglobulinemic purpura?**

Male sex, age over 60 years old, type II cryoglobulinemia, renal and gastrointestinal tract involvement, as well as chronic hepatitis C infection.

23. **Which are the clinical and histopathologic findings of IgA vasculitis (formerly called Henoch-Schönlein purpura)?**

This type of small-vessel vasculitis is more common than granulomatous polyangiitis. It is usually triggered either by an infection or a medication. It occurs more frequently in children than in adults. In adults it presents with palpable purpura (Fig. 8.10a), arthritis of the lower extremities large joints, while gastrointestinal and kidney involvement is seen in two thirds of the patients. In the majority of patients, it is self-limited. Direct immunofluorescence of the skin biopsy specimens reveals selective IgA deposition on the vessel wall of the dermis (Fig. 8.10b).

24. **What is Moya-Moya disease and which are its prominent clinical manifestations?**

Moya-Moya disease is a rare cerebrovasculopathy characterized by progressive stenosis of the circle of Willis arteries (internal carotid, anterior, and middle cerebral arteries) and their branches. The term Moya-Moya (Japanese for "puff of smoke") refers to the appearance on angiography of abnormal vascular collateral networks that develop adjacent to the stenotic vessels. The steno-occlusive areas are usually bilateral.

The disease can present as transient ischemic attack or stroke in children, while adults usually present hemorrhagic stroke [5].

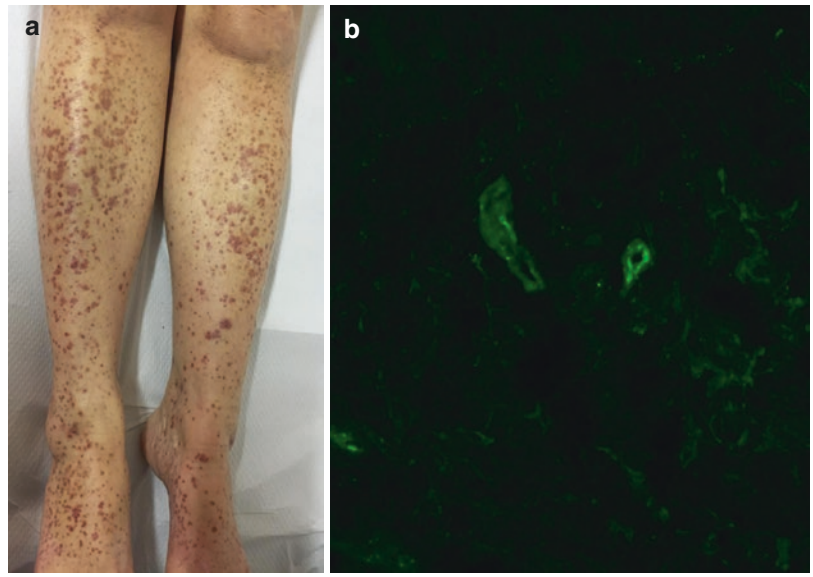

Fig. 8.10 IgA vasculitis (Henoch-Schönlein) : (**a**) palpable purpura on the lower extremities, at sites coalescing to ecchymoses, in a 55-year-old lady. Skin biopsy of the lesions revealed leukocytoclastic vasculitis and (**b**) direct immunofluorescence showed selective IgA deposition on the vessel wall of the dermis

25. **What is Sweet's syndrome?**

Sweet's syndrome is also known as acute febrile neutrophilic dermatosis and it can present as a vasculitis mimic. Its characteristic manifestations are acute presentation of raised painful papules on the extremities, face, neck, and trunk, accompanied by fever and polyarthritis in 20% of cases. Neutrophilic leukocytosis is common, and skin biopsy reveals dense dermal neutrophilic infiltrates without evidence of vasculitis. It is associated with underlying malignancy in 10–15% of patients (mostly with acute myelogenous leukemia). Other conditions associated with acute neutrophilic dermatosis are sun exposure, upper respiratory tract infection, inflammatory bowel disease, rheumatoid arthritis, lupus erythematosus, relapsing polychondritis, pregnancy, and drugs (oral contraceptives, trimethoprim-sulfamethoxazole, and minocycline).

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Autoinflammatory Syndromes

9

Abstract

Autoinflammatory syndromes constitute a group of genetic disorders, in which gene mutations coding for significant inhibitory inflammatory molecules have been identified. These disorders can manifest with inflammatory signs and symptoms of one or many organs without an apparent exogenous or endogenous insult. The mutated genes responsible for the main clinical syndromes are the MEFV gene on chromosome 16 in patients with Mediterranean fever; the type I TNF-α receptor (TNFRSF1A) gene on chromosome 12 in patients with TNF-α receptor-associated periodic syndrome (TRAPS); the mevalonate kinase (MVK) gene on chromosome 12 in patients with hyperimmunoglobulin D syndrome (HIDS); the CIAS1 gene on chromosome 1 in patients with cryopyrin-associated periodic syndrome (CAPS); the PSTPIP1 gene on chromosome 15q in patients with pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome; the IL1RN gene, which encodes interleukin-1 receptor antagonist, in patients with deficiency of the interleukin-1 receptor antagonist (DIRA) and the TMEM173 gene, encoding the stimulator of interferon genes (STING) in patients with STING-associated vasculopathy with onset in infancy (SAVI), a recently described autoinflammatory syndrome. The age onset of the different syndromes is variable. The clinical picture of these syndromes usually manifests with recurrent fevers, skin rashes, mucosal lesions, thoracic or abdominal pains (due to serositis), arthritis, and elevated acute-phase proteins. Cornerstone therapy of these disorders includes colchicine and anti-interleukin-1 receptor antagonist.

H.M. Moutsopoulos et al., *Rheumatology in Questions*, https://doi.org/10.1007/978-3-319-71604-6_9

1. **What is the role of the inflammasome in the pathogenesis of familial autoinflammatory syndromes?**

NALP3 is also known as cryopyrin, and it is encoded by the NLRP3 gene, located on chromosome 1. This protein is primarily found on neutrophils and monocytes and serves as an intracellular sensor of pathogens and danger signals. NALP3 consists of a pyrin domain (PYD), a nucleotide-binding oligomerization domain (NOD, also called NACHT), and a leucine-rich repeat (LRR) domain. Upon stimulation, NLRP3 interacts with adaptor proteins (ASC and cardinal), forming a multiprotein complex known as NLRP3 inflammasome. A cascade of interactions between the different protein parts of this complex leads to activation of procaspase 1 to caspase 1. Caspase 1, in turn, activates pro-IL-1β to be released as the pro-inflammatory cytokine IL-1β. Genetic mutations of any of these protein parts can contribute to the development of familial autoinflammatory syndromes [1].

2. **Which are the main familial autoinflammatory syndromes?**

The main periodic fever syndromes are:

- Familial Mediterranean fever (FMF)
- TNF-α receptor-associated periodic syndrome (TRAPS)
- Hyper immunoglobulin D Syndrome (HIDS) also known as Mevalonate Kinase Deficiency (MKD)

The main cryopyrinopathies (cryopyrin-associated periodic syndromes, CAPS) are:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) (also called Chronic Infantile Neurologic Cutaneous Articular, or CINCA, Syndrome)

The main pyogenic disorders are:

- Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome
- Deficiency of IL-1 receptor antagonist (DIRA) syndrome familial autoinflammatory [2]

3. **Which are the major characteristics of familial Mediterranean fever (FMF)?**

FMF is associated with mutations in MEFV gene on short arm of chromosome 16 that encodes the pyrin protein. It is inherited in an autosomal recessive way. FMF can present in two distinct ways: either as recurrent episodes of inflammation (patients, if untreated, can develop amyloidosis (AA) and subsequent renal failure) or it can present with AA amyloidosis (especially renal) as the first manifestation, without previous history of inflammatory episodes. FMF affects mainly children (<20 years) of Eastern Mediterranean ancestry (Armenian, Jewish, Arabian, and Turkish origin). Episodes of inflammation present with recurrent episodes of fever lasting 12–72 h, generalized peritonitis, unilateral pleurisy, nondestructive large joint monoarthritis (hip, knee, ankle, wrist) with absence of erythema and warmth (typically nonresponding to prednisone), and an erysipelas-like rash. Recurrence of attacks is usually every 2–4 weeks. Attacks respond to colchicine therapy.

4. **Which are the major characteristics of TNF-α receptor autoinflammatory periodic syndrome (TRAPS)?**

TRAPS is due to mutations (mostly single-nucleotide missense) in the gene of type I TNF-α receptor (TNFRSF1A) on the short arm of chromosome 12. It is inherited in an autosomal dominant way. It can manifest in children as well as in middle-aged adults. Presents with high spiking fever of varying duration (yet always more than 5 days of duration); thigh myalgias that can become migratory, migratory erythematous patches, or urticarial plaques over the areas of myalgias; ocular inflammation (conjunctivitis, periorbital edema); peritonitis; pleurisy; and arthralgias (rarely synovitis), all responding to glucocorticoids. These patients do not respond to colchicine. The attacks reoccur two to six times per year.

5. **Which are the major characteristics of hyperimmunoglobulin D syndrome (HIDS)?**

HIDS is due to a mutation of the mevalonate kinase (MVK) gene on chromosome 12 that encodes the MVK enzyme. It is inherited in an autosomal recessive way. The symptomatology starts in infancy (younger than 1 year old). Presents with fever (lasting 1–10 days) which is associated with cervical adenopathy, abdominal pain and vomiting, splenomegaly, skin rash with erythematous macules (including face, palms, and soles), genital ulcers, large joint arthritis, headache, myalgias, constantly elevated IgD levels, and during flares increased urinary mevalonic acid.

6. **Which are the major characteristics of cryopyrin-associated periodic syndromes (CAPS)?**

CAPS are due to mutations in CIAS1 gene found on long arm of chromosome 1, which encodes for cryopyrin (NALP3). They are inherited in an autosomal dominant way or are due to sporadic mutations.

(a) Familial cold autoinflammatory syndrome (FCAS): is the mildest form of CAPS. Symptoms develop within the first year of life and get less severe with aging. Fever, chills, rash (Fig. 9.1), arthralgias, and conjunctivitis, within 1–3 h after cold exposure, are typical.

(b) Muckle-Wells syndrome: starts in adolescence, and the episodes can be triggered by fatigue, hunger, or cold exposure. Attacks last 24–48 h and are characterized by fever, chills, abdominal pain, myalgia, urticarial rash, and conjunctivitis. Late onset of sensorineural hearing loss is common and renal AA amyloidosis can occur.

(c) Chronic infantile neurologic, cutaneous, and articular syndrome (CINCA)/neonatal-onset multisystem inflammatory disease (NOMID): it is the most severe form of CAPS. It is characterized by the triad of chronic aseptic meningitis, neonatal-onset skin lesions, and arthropathy. Prognosis is poor with 20% mortality in childhood.

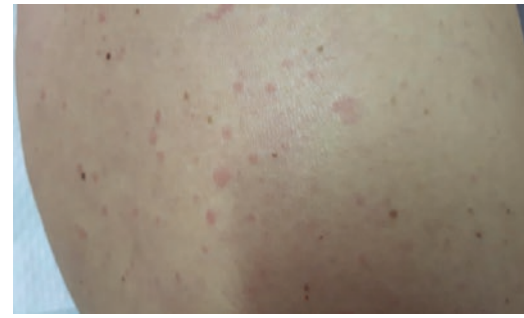

Fig. 9.1 Urticaria-like rash: in a 65-year-old woman with cryopyrin-associated periodic syndrome (CAPS) triggered by exposure to cold (*Figure courtesy of Professor Fotini N.Skopouli, MD*)

7. **Which are the diagnostic criteria for cryopyrin-associated periodic syndromes (CAPS)?**

A recent study identified seven parameters which were significantly associated with CAPS diagnosis (sensitivity 81%, specificity 94%). It was suggested that in order to establish CAPS diagnosis, elevated acute-phase proteins (C-reactive protein/serum amyloid A protein) plus two or more of the following CAPS typical signs/symptoms, urticarial-like rash, episodes triggered from cold, sensorineural hearing loss, musculoskeletal symptoms, chronic aseptic meningitis, and skeletal abnormalities, are needed. The criteria place the diagnosis of CAPS in both children and adults [3].

8. **Which are the major characteristics of pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome?**

PAPA syndrome is inherited in an autosomal dominant way. It is due to a mutation in the proline serine threonine phosphatase-interacting protein 1 (PSTPIP1) gene on chromosome 15q. Clinical features of PAPA syndrome include early-onset, painful flares of recurrent sterile arthritis involving a prominent neutrophilic infiltrate along with skin ulcerations, frank pyoderma gangrenosum, or severe cystic acne. Symptoms persist into adulthood, leading to severe joint destruction.

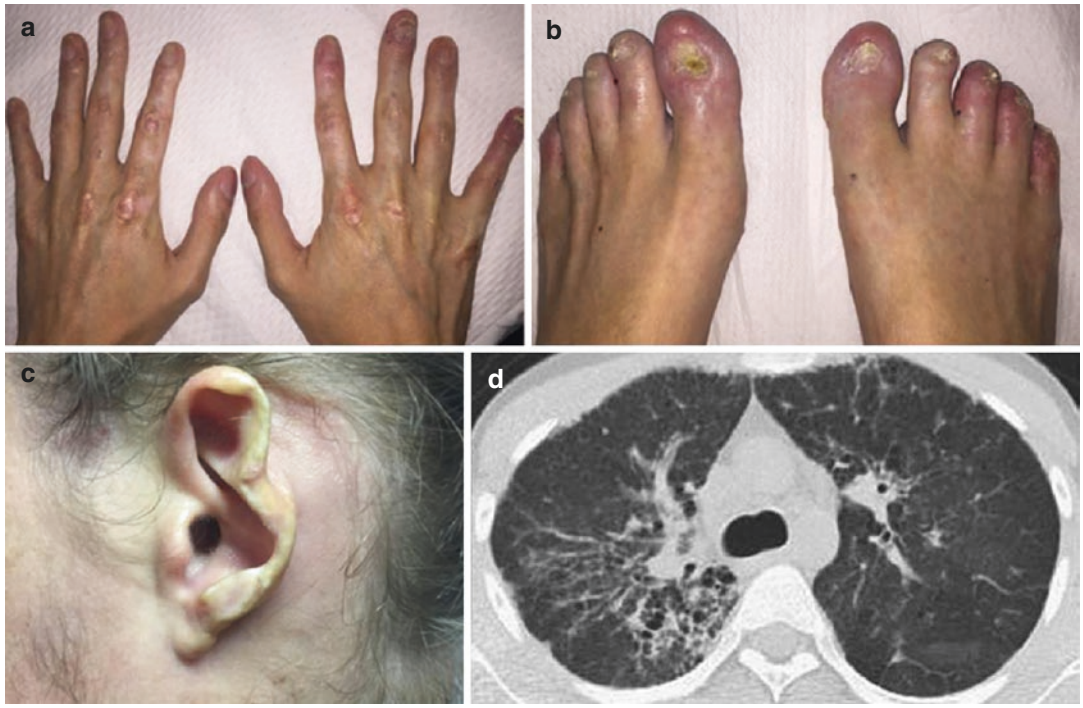

Fig. 9.2 STING-associated vasculopathy with onset in infancy (SAVI): recurrent vasculitic skin lesions of the fingers, the toes, the ears, and the nose, unresponsive to immunosuppression, which led to resorption of distal phalanges, nail dystrophy (**a**, **b**), scarred ears (**c**), and interstitial lung disease with areas of honeycombing, reticular opacities, and patchy ground glass (**d**) in an 18-year-old male in whom genetic analysis revealed a mutation in exon 6 of TMEM173 gene (encoding STING – stimulator of interferon genes) (*Reproduced from Manoussakis MN et al. 2017*)

9. **What is the clinical picture of deficiency of the interleukin-1 receptor antagonist (DIRA) syndrome?**

DIRA is an autosomal recessive autoinflammatory syndrome, which is due to mutations in the gene encoding interleukin (IL)-1 receptor antagonist. This genetic defect has as a result the production of an abnormal non-secretory protein which exposes the cells to a continuous IL-1 activity. The syndrome is clinically expressed with a wide range of symptoms from very serious (i.e., respiratory distress syndrome, cerebral vasculitis) to arthritis, hepatomegaly/splenomegaly, osteomyelitis, and oral ulcers/stomatitis.

10. **What is STING-associated vasculopathy with onset in infancy (SAVI)?**

SAVI is a recently identified autoinflammatory disease caused by sporadic or inherited gain-of-function mutations in TMEM173 gene. This gene encodes for a protein called STING (stimulator of interferon gene), which is involved in the production of beta-interferon (IFN-β). Overproduction of IFN-β causes excessive inflammation which results in tissue damage, leading to the signs and symptoms of SAVI.

The signs and symptoms of SAVI begin in the first few months of life. Recurrent low-grade fever, lymphadenopathy, livedo reticularis, and Raynaud's phenomenon may be the presenting symptoms. Affected infants present extended vasculopathy with areas of severely damaged skin, particularly the face, ears, nose, fingers, and toes. These lesions begin as rashes and can progress to become ulcerated and necrotic. The skin lesions are worse upon exposure to cold and stress and may lead to scarring of the ears, nasal sep-

tum perforation, and absorption of the distal phalanges (Fig. 9.2a–c). The most severe and potentially lethal complication in SAVI patients is rapidly progressive interstitial lung disease (Fig. 9.2d). Options for treating patients with SAVI are currently limited, but the blockade of interferon signaling with a Janus kinase (JAK) inhibitor could offer a therapeutic strategy [4, 5].

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Part III

Rheumatic Disorders and Manifestations in Various Organs, Systems and Disciplines

The Skin, the Eyes, and the Ears in Rheumatic Diseases

10

Abstract

The skin, the eyes, and the ears are sense organs which are very frequently involved in rheumatic diseases. The skin is an easily accessible organ to physical examination and biopsy. Taking into account the morphology, location, distribution, and histological characteristics of cutaneous manifestations in patients with rheumatic disorders, particular skin rashes may aid the diagnosis (e.g., butterfly rash, systemic lupus erythematosus) and/or define disease activity and prognosis (e.g., raised purpura, risk factor for lymphoma development in patients with Sjögren's syndrome).

Ocular manifestations may serve as a guide to proper diagnosis of an autoimmune disorder or indicate necessity for intensified treatment of the underlying rheumatic disease. Keratoconjunctivitis sicca, keratitis, uveitis, scleritis, and retinal vasculitis are often diagnosed in patients with rheumatic diseases. Some ocular symptoms of rheumatic diseases (e.g., amaurosis fugax in giant cell arteritis) or of drugs used to treat the diseases (e.g., antimalarial agents causing maculopathy) are sight-threatening, and they should be recognized promptly to prevent permanent loss of vision.

Ear manifestations of rheumatic diseases can often be the initial symptom of an undiagnosed autoimmune disease. Hearing disturbances may be encountered in systemic lupus erythematosus, relapsing polychondritis, Sjögren's syndrome, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, Cogan syndrome, sarcoidosis, and Behçet's disease. They can manifest as otalgia, otitis, uni- or bilateral sensorineural or conductive hearing loss, as well as audiovestibular deficits.

The questions and answers of this chapter aim (a) to familiarize a rheumatologist and any related subspecialty physician with the vast variety of rashes associated with rheumatic diseases, (b) to depict the different ocular manifestations of autoimmune diseases, and (c) to raise the clinical awareness that hearing disturbances can be the initial manifestation of a rheumatic disease.

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1. **With which autoimmune disorder(s) chronic autoimmune urticaria coexists**?

   Chronic autoimmune urticaria is caused by autoantibody formation against the Fc portion of the immunoglobulin (Ig) E receptor and less frequently by an autoantibody against IgE. These autoantibodies activate blood basophils and cutaneous mast cells which release histamine and other proinflammatory mediators. High percentage of patients with autoimmune thyroid disease has chronic autoimmune urticaria. Female patients with chronic urticaria present a higher incidence of rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, celiac disease, and type I diabetes mellitus [1].

2. **Which skin rashes are suggesting a diagnosis of a clinical entity?**
   - **Heliotrope** (Fig. 5.2) on eyelids and **Gottron's papules** (Fig. 5.1) over the metacarpophalangeal and proximal interphalangeal joints = dermatomyositis
   - **Butterfly rash** = systemic lupus erythematosus (Fig. 4.6)
   - **Lupus pernio** = sarcoidosis (Fig. 10.1)
   - **Erythema migrans** = Lyme disease (Fig. 10.2)
   - **Salmon-rash** = adult-onset Still's disease (Fig. 10.3)

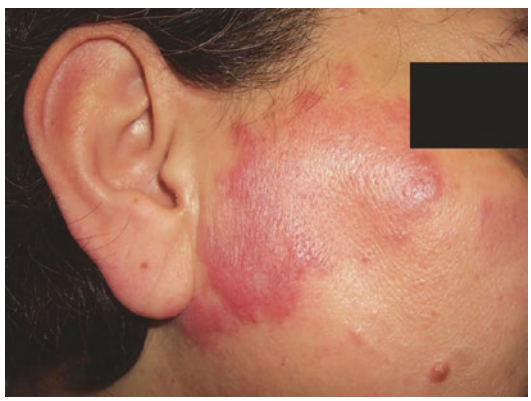

Fig. 10.1 Lupus pernio: a red-purple, swollen, shiny plaque on the cheek in a 30-year-old female with sarcoidosis

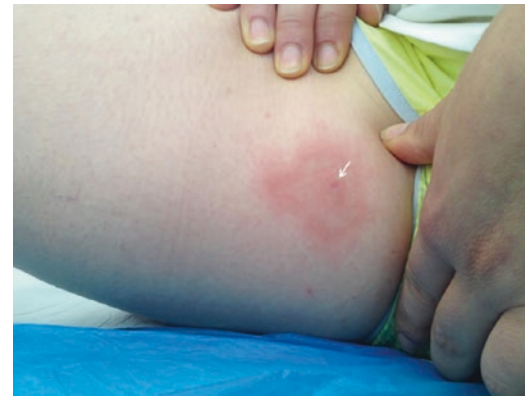

Fig. 10.2 Erythema migrans: a painless round skin rash, 5 cm in diameter, on the right inner thigh with a central spot (tick bite, arrow) ringed by an expanding red rash (like a bull's eye) in a 39-year-old female patient with IgM antibodies to *Borrelia burgdorferi. Figure courtesy of Professor Alexandros A. Drosos, MD*

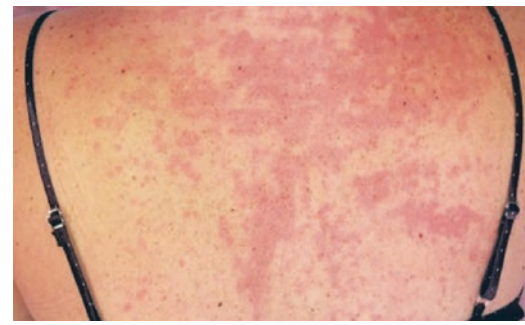

Fig. 10.3 Salmon-like rash: in a 31-year-old female patient with adult-onset Still's disease

   - **Annular-psoriasiform rash** on the trunk and upper extremities = subacute cutaneous lupus erythematosus (Fig. 4.8)
   - **Erythema marginatum** = rheumatic fever

3. **What is the cause of livedo reticularis?**

   Livedo reticularis (Fig. 4.5), a mottled reticular vascular pattern, seems to occur more in women than in men and usually in the third decade of life. It has many causes. Spasm of the blood vessels or an abnormality of the local circulation and disturbances of hormonal and autonomic regulatory mechanisms may account for its pathogenesis. More specifically livedo

reticularis can be seen either without any underlying cause (idiopathic) or in patients with:

- Hypercoagulable states: antiphospholipid syndrome, coagulopathies related to proteins C and S or antithrombin III deficiencies
- Hyperviscosity states: cryoglobulinemias (type I), paraproteinemias/multiple myeloma
- Vessel wall pathology: medium-sized vasculitis (i.e., polyarteritis nodosa, granulomatosis with polyangiitis), calciphylaxis (deposition of calcium within the vessel walls usually in chronic renal failure)
- Autoimmune diseases: systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, dermatomyositis
- Embolic diseases: cholesterol emboli, atrial myxoma
- Infections: syphilis, tuberculosis, mycoplasma, brucellosis, streptococcemia, hepatitis
- Neurologic diseases: reflex and sympathetic dystrophy, Sneddon's syndrome [2]

4. **What are the causes of erythema nodosum? Name them according to their incidence.**

Idiopathic (60–70%), streptococcal pharyngitis, drugs (penicillin, oral contraceptives, sulfonamides), infectious diseases (tuberculosis, leprosy, syphilis, yersinia, Epstein-Barr virus infection, cat-scratch disease), inflammatory bowel disease, Behçet's disease, sarcoidosis, systemic lupus erythematosus, malignancy (lymphoma, carcinoid, pancreatic cancer) [3].

5. **What is the pancreatitis, panniculitis, and polyarthritis (PPP) syndrome?**

PPP syndrome is a combination of extrapancreatic manifestations occurring in some patients with pancreatitis. The pathogenesis is unknown; nevertheless it is postulated to be due to augmented secretion of pancreatic enzymes in the circulation leading to systemic fat necrosis especially in subcutaneous fat tissue (panniculitis) as well as bones and joints (polyarthritis). Clinical manifestations include pancreatitis (most commonly due to pancreas carcinoma, usually with mild abdominal symptoms), arthritis (usually ankles and knees) with noninflammatory and creamy synovial fluid (lipid droplets that give the creamy appearance stain with Sudan black), red and tender nodules on the extremities (lobular panniculitis with fat necrosis), eosinophilia, febrile pleuropericarditis, and osteolytic bone lesions. Amylase, lipase, and trypsin are elevated in the serum [4].

6. **Chronic recurrent hidradenitis is considered an autoinflammatory disorder. What is the therapy nowadays?**

Chronic recurrent hidradenitis (hidradenitis suppurativa) is an inflammatory skin disease affecting the apocrine glands of the skin mainly in the areas of the axillae and the groins and under the breasts. It is characterized by painful groups of small skin abscesses which can persist for years, are difficult to heal, and often lead to sinus tracts and scar formation. Flares are triggered by sweating, stress, warm/humid environment, and hormonal changes. Genetic predisposition has been identified and autoimmune reactivity plays a significant role. For mild cases, topical clindamycin (1% solution or gel twice daily for 12 weeks) has proven effective. Tetracycline (500 mg p.o. twice daily for 4 months) is used in more widespread disease, and if the patient fails to respond, combination of tetracycline and rifampicin (600 mg p.o. daily for 10 weeks) should be initiated. In patients who are unresponsive or intolerant to oral antibiotics, adalimumab (40 mg subcutaneously weekly) should be considered as the next therapeutic modality. Infliximab should be considered as a second-line option treatment, only after failure of adalimumab and surgical intervention should be applied for particular cases. In addition to pharmaceutical treatment, all patients should be advised to lose weight and discontinue tobacco smoking [5].

7. **Can you tell from the location of the rash on the dorsum of the hands which patient has dermatomyositis and which systemic lupus erythematosus?**

Erythematous lesions on the dorsum of the hands and fingers affecting the skin between the finger joints are a rash seen in systemic lupus erythematosus patients, while erythematous rash over the metacarpophalangeal and proximal interphalangeal joints is a characteristic rash for dermatomyositis (Gottron's papules).

8. **What is lupus pernio? What is its etiology?**

Lupus pernio is truly a misnomer. It is a particularly disfiguring skin manifestation of sarcoidosis and not a skin manifestation of lupus. It is characterized by erupting violaceous plaques and nodules (Fig. 10.1) of the nose/nostrils, malar areas, and nasolabial folds, around the eyes, in the scalp, and along the hairline.

9. **Which pathologic conditions present with flat and which with raised purpura? Provide the pathogenic mechanisms.**

Purpura is caused by extravasation of blood into the skin or mucous membranes producing red-purple lesions. It can be palpable/raised or non-palpable/flat and typically non-blanching upon pressure. Flat purpura can be subdivided into petechiae (small lesions <3 mm) and ecchymoses (larger lesions >3 mm). It occurs either when the hydrostatic pressure inside the capillaries is increased as in the case of hypergammaglobulinemia (Waldenström's hypergammaglobulinemic purpura), because of decreased or altered platelet formation, destruction, or function, or when the integrity of vessels is disrupted as in the case of vitamin C deficiency. In contrast, palpable purpura is a sign of cutaneous vasculitis. The major causes of small-vessel vasculitis leading to palpable purpura are cryoglobulinemic purpura, IgA vasculitis, and leukocytoclastic vasculitis.

10. **Which conditions can present with the clinical picture resembling livedoid vasculopathy (atrophie blanche)?**

Livedoid vasculopathy (LV) is a vasculopathy of middle-aged women, presenting as an occlusive disorder of the capillary microcirculation leading to cutaneous ischemia and infarction (Fig. 10.4a). It can be idiopathic or secondary. The literature on LV presents a confusing picture of its causes, pathogenesis, and treatment. Differential diagnosis should include cutaneous small-vessel vasculitis (leukocytoclastic vasculitis), cutaneous polyarteritis nodosa, antiphospholipid syndrome, chronic venous stasis, pyoderma gangrenosum, factitious dermatitis, pseudo-Kaposi sarcoma and malignant atrophic papulosis, inherited or acquired thrombophilias, chronic myelogenous leukemia, cryoglobulinemia, and heavy-chain disease [6].

11. **Which are the cutaneous histopathologic lesions of livedoid vasculopathy?**

Histology of livedoid vasculopathy (Fig. 10.4b) typically reveals occlusion by fibrin thrombi of capillary vessels in the upper and middle dermis as well as fibrinoid degeneration of the vessel walls in the sense of a vasculopathy. In contrast to primary vasculitis, only a slight or no perivascular inflammatory infiltrate is found initially, and later the secondary inflammation is less prominent. Hyalinization of the dermis and capillary walls characterizes livedoid vasculopathy [6].

12. **What is the pathogenetic mechanism of relapsing polychondritis?**

The main hypothesis on the pathophysiology on relapsing polychondritis (RP) is an autoimmune reaction initially directed against the cartilage, later on spreading to non-cartilaginous tissues. Autoantibodies against cartilage and collagen (mostly type II) have been found in patients with RP, yet

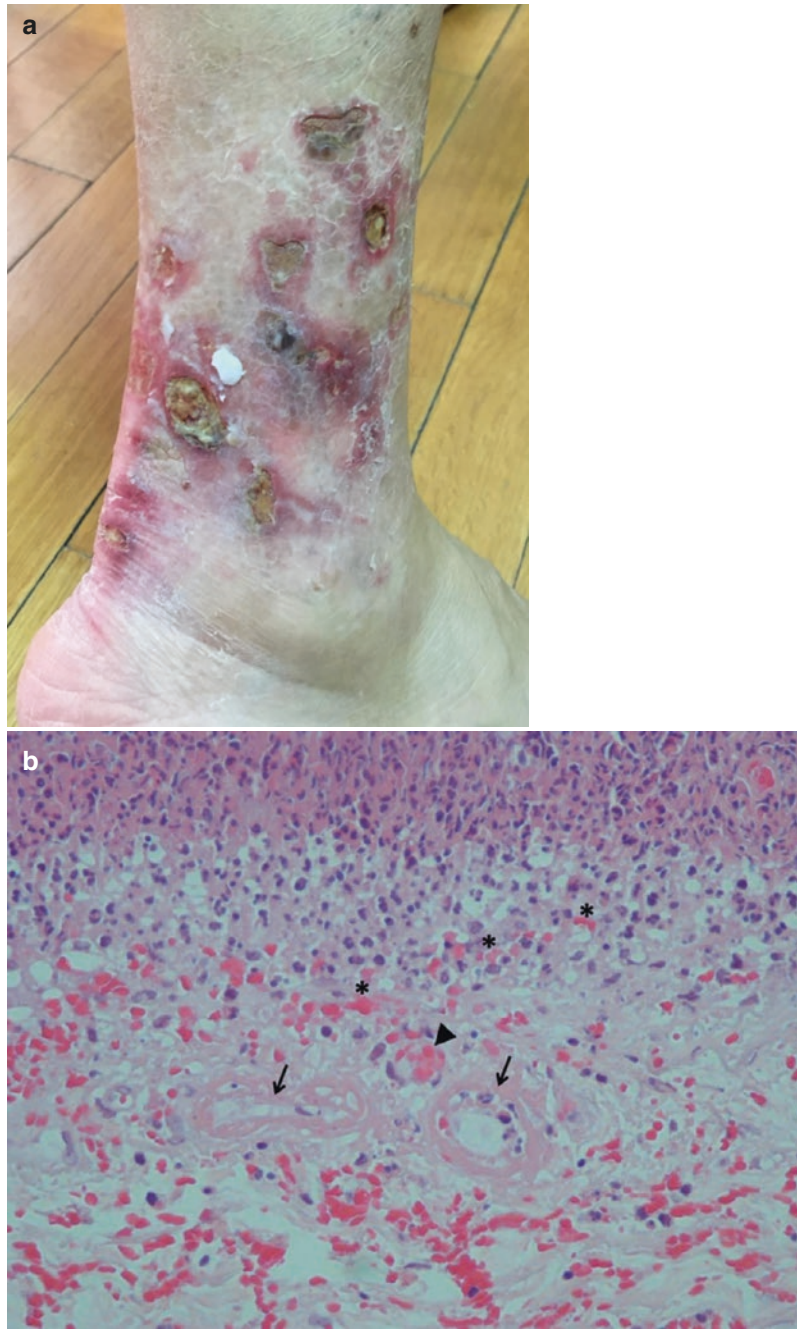

Fig. 10.4 Livedoid vasculopathy: (**a**) multiple, painful, deep, well-demarcated ulcers on a livedoid base, surrounded by atrophic white-ivory skin in the lower legs in a 55-year-old. (**b**) Skin biopsy of the ulcers (HE × 400) showed in the mid-dermis segmental thickening of vessel wall containing fibrin material (black arrows), vessel occlusion with hyaline microthrombi (arrowhead), and extravasated erythrocytes (asterisks) without features of inflammation (*Reproduced from Zampeli E et al. 2017*)

their diagnostic value is extremely poor, since they are found in a limited number of RP patients and can also be found in patients with other autoimmune diseases.

13. **Which are the clinical manifestations of relapsing polychondritis?**

Relapsing polychondritis (RP) is an infrequent autoimmune systemic disease manifesting with relapsing inflammation of cartilaginous tissues which can result in their deformity. The typical clinical presentation of RP is a combination of chondritis (auricular, nasal, laryngeal, tracheal, and cartilaginous bronchi) – which is necessary for the diagnosis – with inflammation of other proteoglycan-rich tissues such as the eyes, heart valves, blood vessels externa or inner ears. The most common and suggestive feature of the disease is chondritis of the pinna of the ear (Fig. 10.5), which presents in up to 90% of patients during the disease course. Chondritis can be acute, subacute, or chronic and unilateral or bilateral. In the acute presentation, the pinna of the ear (helix, antihelix, tragus, antitragus, and external auditory canal) is inflamed, swollen, painful, and red. Typically, the inflammation spares the ear lobe, which does not contain cartilage. The external auditory canal may be obstructed by the inflammatory infiltrate or collapsed, leading to conductive hearing loss and/or recurrent otitis externa. The inflammation may involve surrounding retroauricular soft tissues and could be sometimes associated with lymphadenopathy. Patients cannot press their ear on the telephone handset or the pillow. The inflammation lasts for a couple of days to a few weeks and often resolves spontaneously. Complications include loss of the auricular cartilage resulting in a floppy distorted pinna, giving the appearance of a "cauliflower ear." On the other hand, the pinna can also become thickened with calcification and deformity of the cartilaginous structure. Constitutional symptoms, including fatigue, weight loss, and unexplained prolonged fever, may be the presenting symptoms of RP.

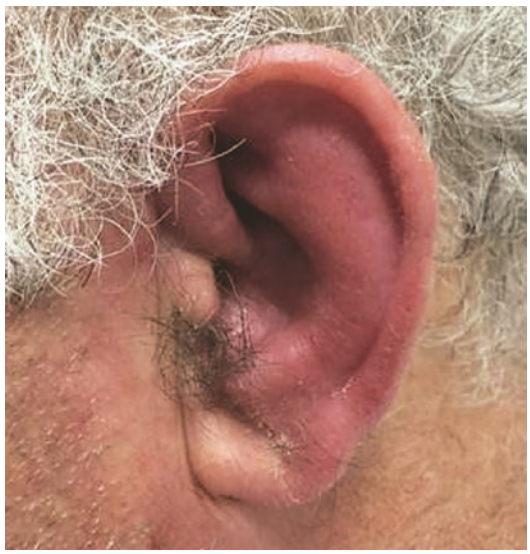

Fig. 10.5 Relapsing polychondritis: bouts of recurrent erythematous swelling of the ear pinna accompanied by hoarseness of voice and scleritis in a 65-year-old male with relapsing polychondritis

14. **Which autoimmune or autoinflammatory conditions affect the sclera and produce episcleritis or scleritis?**

Episcleritis: rheumatoid arthritis, inflammatory bowel disease, ANCA-associated vasculitis

Scleritis: rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's granulomatosis), relapsing polychondritis, systemic lupus erythematosus, inflammatory bowel disease, seronegative spondyloarthritis

15. **Which are the fundoscopic findings in a patient with Ehlers-Danlos?**

Angioid streaks, retinal detachment, carotid-cavernous sinus fistula, lens subluxation, keratoconus, and macular degeneration.

16. **In which medical conditions angioid streaks are seen in the funduscopic examination?**

Angioid streaks are fine, irregular lines deep to the retina arranged in a radiating

fashion resulting from pathological breaks in Bruch's membrane. Angioid streaks may be idiopathic or associated with underlying systemic illnesses, such as: *pseudoxanthoma elasticum*, Paget's disease, sickle cell disease, and Ehlers-Danlos syndrome.

17. **In which connective tissue disorders hypopyon can be seen?**

    Hypopyon is the presence of inflammatory cell exudate in the anterior eye chamber. Hypopyon is commonly seen in HLA-B27-positive patients who develop acute anterior uveitis. It is also seen in 20% of patients with Bechet's disease and is a poor prognostic sign, because it is frequently associated with retinal involvement.

18. **Describe the ophthalmological manifestations induced from rheumatic disorders or from their therapeutic agents.**

    The most common ocular manifestations of rheumatic diseases include keratoconjunctivitis sicca, anterior uveitis, epi- and/or scleritis, diffuse vitritis, papillitis, and retinal vasculitis. Cystoid macular edema and epiretinal membrane are common causes of visual impairment. Another cause of sudden vision loss is involvement of the ophthalmic artery in giant cell arteritis, and it can be the sole presenting clinical manifestation. The most serious ophthalmologic complications of the inherited connective tissue disorders are cataract or lens subluxation. The most significant ophthalmologic complication from drug side effects used in the therapy of rheumatic disorders is maculopathy induced by antimalarial agents and cataract by corticosteroids.

19. **Which rheumatic diseases can be associated with uveitis?**
    - Spondyloarthropathies: most commonly associated with unilateral anterior uveitis of acute onset
    - Psoriatic arthritis and inflammatory bowel disease-related inflammatory arthritis: most commonly associated with bilateral posterior uveitis of subacute onset
    - Juvenile idiopathic arthritis: most commonly associated with bilateral anterior uveitis of subacute onset
    - Sarcoidosis: bilateral and in 90% chronic
    - Behçet's disease: most commonly associated with panuveitis of acute onset
    - Systemic lupus erythematosus and Sjögren's syndrome: most commonly associated with mild anterior uveitis

20. **In which autoimmune disorders the inner ear can be affected?**
    - Systemic lupus erythematosus
    - Sjögren's syndrome
    - Rheumatoid arthritis
    - Seronegative spondyloarthritis
    - Inflammatory bowel diseases
    - Cogan syndrome
    - Systemic vasculitis (ANCA-associated, polyarteritis nodosa)
    - Behçet's disease
    - Antiphospholipid syndrome [7]
    - Relapsing polychondritis

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Rheumatic Disorders Associated with Metabolic, Endocrine, and Hematological Diseases

11

Abstract

The interconnection of metabolic/endocrine disorders and autoimmune/rheumatic diseases is multifaceted. Metabolic and endocrine diseases can be autoimmune in nature (e.g., type I diabetes mellitus, Graves' disease, Hashimoto's thyroiditis). On the other hand, many metabolic/endocrine disorders present with musculoskeletal manifestations that can mimic a rheumatic disease. Patients with hyperlipidemias and the metabolic syndrome can present with gout, migratory arthritis, Achilles tendinitis, and rotator cuff syndrome. Hyperuricemia, gout, and calcium pyrophosphate crystal deposition disease (pseudogout) can be found in patients with primary hyperparathyroidism. A well-documented association between diabetes mellitus and several rheumatic syndromes exists, with severity of the former determining the extent of rheumatic manifestations. Carpal tunnel syndrome, trigger fingers, Dupuytren's contractures, diabetic cheiroarthropathy, diffuse idiopathic skeletal hyperostosis, shoulder bursitis, and neuropathic arthropathy are some of the musculoskeletal manifestations associated with diabetes. In patients with hyperthyroidism, rheumatic manifestations include osteoporosis, painless proximal muscle weakness, thyroid acropathy, and adhesive shoulder capsulitis. In patients with thyroiditis, rheumatic manifestations (osteoarthritis, fibromyalgia, Raynaud's phenomenon, sicca symptoms, and arthritis) frequently occur even in the absence of overt thyroid dysfunction. On the other hand, patients with systemic autoimmune diseases such as rheumatoid arthritis, polymyalgia rheumatica, Sjögren's syndrome, systemic lupus erythematosus, and scleroderma present an increased prevalence of thyroid autoimmune disease. Finally, corticosteroids, which are commonly used in the treatment of various autoimmune disorders, can be an iatrogenic cause of endocrine disorders, such as diabetes mellitus, steroid myopathy, and Cushing's disease.

Hemochromatosis, hemophilia, sickle cell disease, thalassemia, leukemia, lymphoma, myelodysplastic syndromes, multiple myeloma, and cryoglobulinemia may all present with a great variety of autoimmune and rheumatic manifestations.

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1. **Which are the risk factors associated with increased serum uric acid and gout**?
   - Genetic predisposition (family history)
   - Gender and age (more common in men than in women, more common in adults than in children)
   - Obesity
   - Increased alcohol consumption
   - Purine-rich diet (anchovies, sardines, scallops, herring, liver, kidneys, asparagus, mushrooms, dried beans, and peas)
   - Renal insufficiency
   - Medications (diuretics, salicylate-containing drugs, cyclosporine-A, niacin, and levodopa)

2. **Which conditions predispose to acute gout attacks?**

   Trauma, binge alcohol drinking, consumption of food containing high amounts of purines, intense- stressful life events.

3. **Which rheumatic manifestations have been associated with hyperparathyroidism?**

   Rheumatic manifestations are rarely seen in patients with hyperparathyroidism. Hyperuricemia, gout, and calcium pyrophosphate crystal deposition disease (CPPD, pseudogout) have been described to be associated with primary hyperparathyroidism. Pseudogout, a result of calcium pyrophosphate crystal deposition in the cartilaginous tissues of the joints, has been reported after successful parathyroid surgery, though the mechanism of this association is unclear. In severe long-standing primary hyperparathyroidism osteitis fibrosa cystica is the characteristic sequelae. The excessive amount of circulating parathyroid hormone leads to increased osteoclast activity which in turn produces bone resorption. The bones are weakened as their calcified supporting structures are replaced with fibrous tissue. Radiolucent cystic-like lesions composed of fibrous tissue and decomposing blood, known as brown tumors, may form. Diffuse osteopenia is common and the bones have a moth-eaten appearance. The softened bones break easily and thus release calcium from the bone into the circulation. Excess calcium in the blood leads to kidney stone formation and nonspecific manifestations such as anorexia and weight loss.

   Nevertheless, nowadays overt rheumatic manifestations associated with hyperparathyroidism are mainly of historical meaning and not part of the clinical spectrum of contemporary disease.

4. **Which is the easiest and cheap test to diagnose pseudogout?**

   Synovial fluid aspiration and detection of calcium pyrophosphate crystals. In 30% of patients, knee X-ray can reveal chondrocalcinosis (Fig. 11.1).

5. **Which is the birefringence difference among urate sodium and calcium pyrophosphate crystals?**

   Monosodium urate crystals are typically needle-shaped and negatively bire-

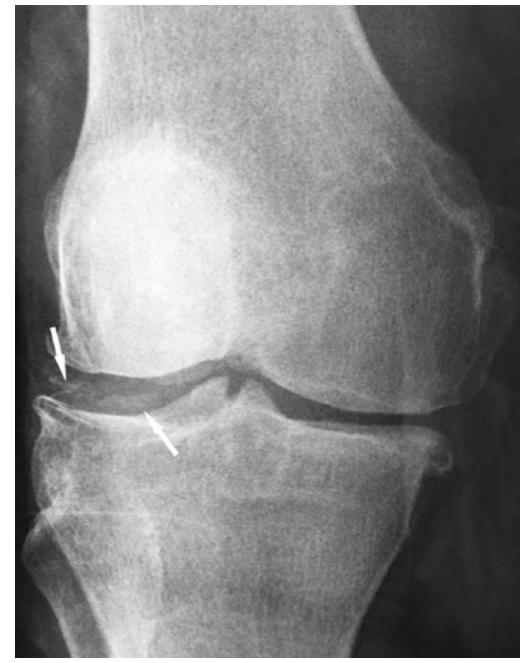

Fig. 11.1 Pseudogout (calcium pyrophosphate dihydrate crystal deposition disease): knee X-ray showing degenerative changes and chondrocalcinosis in a 60-year-old man with pseudogout

fringent. On polarized microscopy, they appear yellow. Calcium pyrophosphate crystals are bright rhomboid-shaped crystals with weakly positive birefringence. They appear blue when viewed under polarized light.

6. **Which are the commonly affected joints from gout and which from pseudogout?**

Gout: commonly affected joints are the first metatarsophalangeal joints (Fig. 11.2), the midfoot, ankle, heel, and the knee. In chronically untreated patients, the following joints can be also affected: the elbow, wrist, and finger joints.

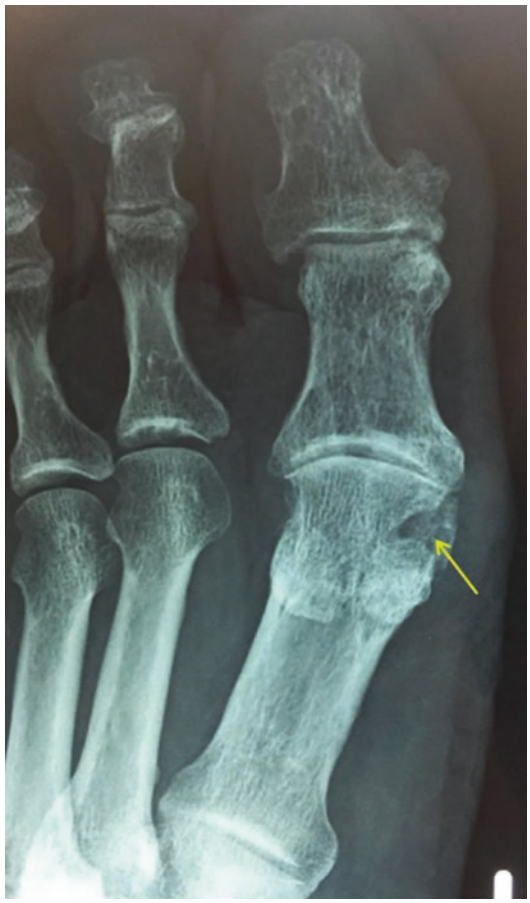

Fig. 11.2 Gout: foot X-ray showing a major erosive, punched-out lesion on the first metatarsal bone (arrow) in a 56-year-old male with recurrent gout attacks (podagra)

Pseudogout: commonly affected joints are the knees (Fig. 11.1), wrists, and less often the hips, shoulders, elbows, finger joints, toes, and ankles.

7. **In which medical conditions cholesterol crystals can be seen in the synovial fluid?**

Cholesterol crystals in synovial fluids can coexist with other crystals like monosodium urate or pyrophosphate. Defective synovial fluid drainage, local destruction, increased permeability of synovial membrane, and intraarticular bleeding are possible etiologies for their presence.

8. **Which are the musculoskeletal manifestations seen in diabetic patients?**
   - Flexor tenosynovitis of the hands (trigger fingers) is quite frequently seen in diabetic patients.
   - Dupuytren's contractures occur in around 15% of diabetics.
   - Carpal tunnel syndrome is seen in 20% of diabetics.
   - Diabetic stiff hand syndrome (limited joint mobility syndrome, diabetic cheiroarthropathy).
   - Diffuse idiopathic skeletal hyperostosis (DISH) is seen in one out of ten diabetic patients.
   - Shoulder bursitis, usually bilateral, is more common in females with insulin-dependent diabetes.
   - Neuropathic arthropathy (Charcot joint) occurs in 1% of diabetics (both type I and type II) and is equally frequent in males and females. These patients have usually long-standing, poorly controlled diabetes complicated by diabetic peripheral neuropathy. It affects the feet, ankles, and knees.

9. **Which are the musculoskeletal manifestations of hyperthyroidism?**
   - Osteoporosis (most common musculoskeletal manifestation).
   - Thyroid acropathy is a rare complication of Graves' disease. It usually occurs after the patient becomes euthyroid and presents

with soft tissue swelling of the hands, digital clubbing, and periostitis particularly of the metacarpal and phalangeal bones. X-rays can reveal periosteal reaction along the shafts of these bones. Patients with Graves' disease complicated with acropathy usually present additionally with ophthalmopathy and pretibial myxedema.
- Painless proximal muscle weakness.
- Adhesive capsulitis of the shoulders [1, 2].

10. **Which musculoskeletal manifestations are associated with hyperlipidemias?**
    - Gout
    - Tendon xanthomas
    - Achilles tendinitis
    - Transient Achilles tendon pain
    - Oligoarthritis and migratory polyarthritis
    - Osteoarthritis
    - Rotator cuff syndrome
    - Epicondylitis
    - Meniscal tears

11. **Which musculoskeletal manifestations are seen in patients with acromegaly?**

    Acromegaly results from the oversecretion of growth hormone and subsequent secretion of insulin-like growth factor 1. Both are produced from a pituitary tumor.

    In patients with acromegaly, arthropathy is a common manifestation. It can be an early disease manifestation, affecting peripheral as well as axial joints (cervical and lumbosacral spine). The peripheral joints affected in acromegalic patients are the hips, shoulders, knees, hands, and elbows. Radiographic changes, in the early phase of the disease, show squaring of the enlarged terminal phalanges, widening of the joint space, and periarticular soft tissue hypertrophy. In the later phases, radiographic changes include narrowing of the joint space, osteophyte formation, calcification, and enlargement of the vertebral bodies. Other musculoskeletal manifestations of acromegaly include carpal tunnel syndrome, proximal myopathy, fibromyalgia, and Raynaud's phenomenon.

12. **What are the causes and symptoms of osteomalacia?**

    Osteomalacia is due to impaired bone metabolism and is caused either from insufficient calcium absorption from the intestines or from vitamin D deficiency or resistance to vitamin D action and increased loss of phosphate from the kidneys. In adults the disorder starts insidiously with pain in the lumbar area as well as in the thighs, and later the aches and pains spread to arms and ribs. Proximal muscle pain and weakness is another manifestation. Characteristic are the "waddling" gait of these patients and the development of spontaneous bone fractures.

13. **Which medical conditions may lead to osteomalacia?**
    - Malnutrition and malabsorption
    - Proximal renal tubular acidosis/chronic renal failure
    - Anticonvulsant medications
    - Hypophosphatemia

14. **Which are the differences between osteomalacia and osteoporosis?**
    - Serum calcium is decreased in osteomalacia and normal in osteoporosis.
    - Serum phosphate is decreased in osteomalacia and normal in osteoporosis.
    - Serum alkaline phosphatase is elevated in osteomalacia and normal in osteoporosis.
    - Parathormone levels are elevated in osteomalacia and normal in osteoporosis.
    - Bone softening in osteomalacia and decreased bone mass in osteoporosis.

15. **What is hypertrophic osteoarthropathy?**

    Hypertrophic osteoarthropathy (HOA) is characterized by clubbing of the digits, noninflammatory arthritis, and periostitis of tubular bones. It is classified into:
    - Primary HOA (pachydermoperiostosis): autosomal dominant inheritance, appears in childhood, affects mostly males, and is characterized by digital clubbing, pachyderma, coarse facial features, and hyperhidrosis.

– Secondary HOA: is associated with intrathoracic malignant neoplasms in 90% of cases. It can also occur secondary to other malignancies (hepatic, gastrointestinal), chronic infections, Graves' disease, inflammatory bowel disease, and cirrhosis.

Platelet and endothelial cell activation with subsequent release of vascular endothelial growth factor and platelet-derived growth factor seem to play a role in the etiopathogenesis of HOA.

16. **Which hematologic conditions can present rheumatic manifestations?**
    – Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency): X-linked coagulation disorders which in males can manifest with arthropathy due to recurrent hemarthroses that lead to accumulation of hemosiderin in the joints, resulting in synovial proliferative response, chronic joint inflammation, and finally cartilage degradation.
    – Sickle cell anemia: patients may demonstrate polyarthralgias (caused by juxtaarticular/periarticular bone microinfarcts), noninflammatory arthritis of large joints, and osteonecrosis. In children with sickle cell anemia, dactylitis, also known as "hand-foot syndrome," can be the first manifestation of the disease. Dactylitis is often self-limited (mean duration of 2 weeks), yet relapsing episodes of pain and edema on the dorsum of the hand, feet or both simultaneously, often accompanied by increased local temperature and erythema can occur. They rarely cause permanent joint sequelae. Initially there is no evidence of joint lesions, but later chronic synovitis can develop.
    – Patients with thalassemia can manifest osteoporosis, pathological bone fractures, and epiphyseal deformities.
    – Hemochromatosis
    – Paraproteinemias (multiple myeloma, Waldenström's macroglobulinemia, and amyloidosis) can present with either rheumatoid arthritis or asymmetric oligoarthritis.

17. **Which are the articular manifestations of hemochromatosis?**

Hemochromatosis is an iron metabolism disorder characterized by excessive deposition of hemosiderin in different organs which can cause them damage and organ malfunction. It is due to a mutation in the hepcidin gene that controls the amount of iron which the body should absorb from food. Usually it begins in men at the ages of 50–60 years and in women after 60 years of age. Arthropathy is not an uncommon manifestation in hemochromatosis patients. It presents with chronic indolent pain, joint stiffness and bony enlargement but without significant signs of inflammation. Small and large joints can be affected symmetrically. A predilection of the disease is the second and third metacarpophalangeal joints. It becomes obvious when the fingers are extended and form the sign of victory "V." Acute arthritis from calcium pyrophosphate crystals can occur in hemochromatosis patients since they deposit in the cartilaginous parts of joints. Other organs which can be damaged in patients with hemochromatosis are the liver (cirrhosis), the pancreas (diabetes mellitus), the heart (congestive heart failure), the reproductive system (erectile dysfunction, menopause), and the skin (bronze or gray appearance).

18. **Which are the autoimmune manifestations in patients with myelodysplastic syndromes?**

Autoimmune disorders or manifestations occur in 10–15% of patients with MDS. Those include:
    – Leukocytoclastic vasculitis
    – Systemic vasculitis
    – Relapsing polychondritis
    – Noninfectious pulmonary infiltrates (interstitial lung disease and bronchiolitis obliterans with organizing pneumonia)
    – Symmetric polyarticular synovitis

- Autoimmune cholangitis
- Hashimoto's thyroiditis
- Erythema nodosum
- Livedo reticularis
- Peripheral neuropathy
- Polymyalgia rheumatica

Common laboratory findings in this patient group include hypergammaglobulinemia, positive ANA, and elevated acute-phase proteins (increased C-reactive protein).

Patients with myelodysplasia expressing interferon regulatory factor-1 (IRF-1, a transcription factor involved in interferon signaling) have an increased incidence of autoimmune manifestations [3].

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Bone, Cartilage, and Soft Tissue Disorders

12

Abstract

In most rheumatic diseases, the homeostasis of bone formation and degradation is disrupted through different mechanisms driven by inflammatory mediators, biomechanical factors, and genetic abnormalities. Osteoarthritis is one of the leading causes of disability in adults worldwide. It is a degenerative disease of the joints secondary to many predisposing factors, most notably age, joint injury, altered mechanical stress, and obesity. All these processes cause a local chronic inflammatory response resulting in the progressive joint failure characteristic of OA. Osteoporosis is the result of cumulative bone loss during aging. Nevertheless, a wide variety of diseases, medications, and lifestyles can cause or contribute to the development of osteoporosis. In addition, the immune system participates in the regulation of bone homeostasis through production of cytokines and inflammatory mediators with subsequent activation of cartilage-degrading proteinases. Paget's disease is a chronic skeletal disorder, caused by enhanced bone resorption followed by abnormal bone formation, in which a potential cross talk between the bone and the immune system takes place.

Hereditary connective tissue diseases (e.g., Marfan's syndrome, Ehlers-Danlos syndromes, osteogenesis imperfecta) are a heterogeneous group of disorders that result from genetic defects that alter the quantity or structure of extracellular matrix proteins. These disorders can present with various clinical manifestations involving the musculoskeletal, cardiovascular, respiratory, and ocular systems.

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1. **What is known to date for the pathogenesis of osteoarthritis?**

   Osteoarthritis (OA) is a particularly common degenerative joint disease; it is characterized by loss of cartilage, remodeling of subchondral bone, and formation of osteophytes. These changes in the joint structure lead to compromised movement, stiffness, and chronic joint pain. Main risk factors for OA include age, obesity, anatomical variations, and joint injury, which are responsible for affecting the mechanical loading on the joint and trigger an imbalance between cartilage matrix synthesis and degradation, in favor of degradation. Collagen and aggrecan (matrix proteoglycan) are the main structural components of the cartilage extracellular matrix (ECM). Increased production of matrix metalloproteinases and aggrecanases by chondrocytes has a well-documented role in degradation of ECM and progression of OA. Although OA is regarded as a noninflammatory disease, in contrast to rheumatoid arthritis, recent studies suggest that in certain patients, OA is an inflammatory disease. In the synovial membranes of these patients, various immune cells have been identified, such as macrophages, T cells, B cells, plasma cells, mast cells, natural killer cells, dendritic cells, and granulocytes [1].

2. **Which are the risk factors for the development of osteoarthritis (OA)?**
   - Age.
   - Family history.
   - Obesity.
   - Sex; females are more prone to develop OA.
   - Trauma and repetitive joint stress.
   - Anatomic joint abnormalities (hip dysplasia or congenital hip dislocation).
   - Other medical conditions (e.g., hemophilia, Paget's disease, gout).

3. **Which joints can be more commonly affected from osteoarthritis?**

   Knees, hips, lower back (lumbar spine), cervical spine, proximal (Bouchard's nodes) and distal (Heberden's nodes) interphalangeal joints of the fingers, the first carpometacarpal joint, and the first metatarsophalangeal joint.

4. **Which are the characteristic radiographic findings in an osteoarthritic joint?**
   - Asymmetric joint space narrowing
   - Sclerotic changes at joint margins
   - Osteophytes
   - Subchondral cysts
   - Subluxation

5. **Which individuals are primarily affected from shoulder periarthritis? What are the causes and what is the evidence-based therapy?**

   Shoulder periarthritis refers to the inflammation of the structures (tendons, bursae, and muscles) around the shoulder. It is observed in middle-aged individuals and can be the result of trauma, strain, or inflammation of other organs. It manifests with shoulder pain and limitation of joint motion. Calcific shoulder periarthritis is more commonly seen in patients with long-standing diabetes mellitus. The goal of therapy for shoulder periarthritis is to relieve pain and to preserve the shoulder's range of motion. Intra-articular corticosteroid injections, especially in the early disease stages, may help decrease pain and improve shoulder mobility. In chronic untreated cases, adhesive capsulitis develops. In such cases, shoulder manipulation, under general anesthesia, is indicated in order to loosen the tightened periarticular tissues.

6. **What are the causes of Milwaukee shoulder? What is its clinical presentation and radiographic findings and how is it treated?**

   Milwaukee shoulder is an unusual crystal (hydroxyapatite) deposition disease which affects women of the late fifth and sixth decades of life. The hydroxyapatite crystals are deposited periarticularly or intra-articularly. The intra-articular crystals initiate an acute inflammatory response leading to release of collagenases, elastases, proteases, and interleukin-1. The joint function is

compromised and joint anatomy destruction follows. Rupture of the rotator cuff is not unusual. Shoulder X-rays and magnetic resonance imaging reveal erosions on the humeral head and destruction of the joint capsule and bursae. The diagnosis is placed with aspiration of the synovial fluid, where hydroxyapatite crystals can be found. In the initial disease stages, nonsteroidal anti-inflammatory drugs or intra-articular corticosteroid injections alone or with physiotherapy are prescribed, while in the advanced stages, joint replacement is indicated.

7. **Which tests should be ordered to evaluate back pain in a man over 65 years of age?**
   - X-ray of the lumbar spine and pelvis
   - Hematocrit/hemoglobin, serum alkaline phosphatase
   - Serum calcium and phosphorus
   - Serum protein electrophoresis

8. **Which are the absolute indications for surgical intervention in a patient with herniated intervertebral disc?**

   Absolute indications for surgery in patients with symptomatic disc herniation include disc herniation causing cauda equina symptoms, progressive spinal stenosis or marked muscular weakness, and progressive neurologic deficits despite conservative management.

9. **Are intradiscal steroids indicated in patients with chronic low back pain associated with acute discopathy?**

   A prospective randomized double-blind study revealed that intradiscal steroid injection alleviates symptoms for a brief period of time (1 month) [2].

10. **What is bursitis?**

    Inflammation of the bursae (small, fluid-filled sacs which alleviate the friction between bones and tendons in the joints). Clinically presents with pain and tenderness over the inflamed bursa and with limited movement of nearby joints.

11. **Which are the causes of olecranon bursitis** (Fig. 12.1)**?**
    - Chronic trauma
    - Rheumatoid arthritis
    - Crystal arthritis
    - Chronic renal failure and patients on dialysis

12. **What is the "Popeye" sign?**

    It is a painful deformity in the anterior mid-upper arm, due to bulging of the biceps muscle, which becomes more evident when the elbow is flexed. It is due to rupture of the long head of the biceps tendon. It occurs usually in elderly with degenerative lesions in the shoulders, tendons, and ligaments after strenuous effort, e.g., lifting heavy objects or overuse. Infrequently it can occur in athletes. While in elderly, rupture of biceps tendon is treated conservatively (analgesics and anti-inflammatory agents), in athletes it requires surgical correction.

13. **Which are the causes of popliteal (Baker's) cyst?**
    - Trauma
    - Rheumatoid arthritis
    - Reactive arthritis
    - Systemic lupus erythematosus
    - Knee osteoarthritis
    - Crystal arthritis
    - Infectious arthritis
    - Hemophilia

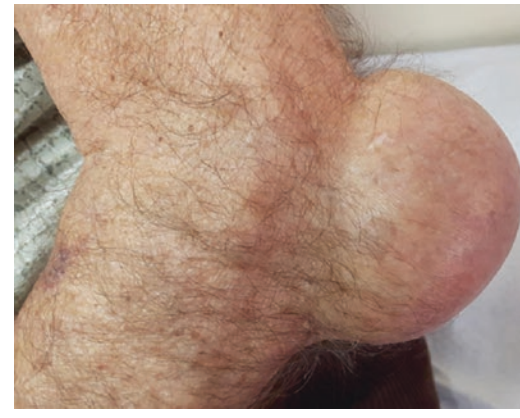

Fig. 12.1 Olecranon bursitis: painful swelling around the elbow containing inflammatory fluid in a 75-year-old man with long standing seropositive rheumatoid arthritis (*Figure courtesy of Professor Fotini N.Skopouli, MD*)

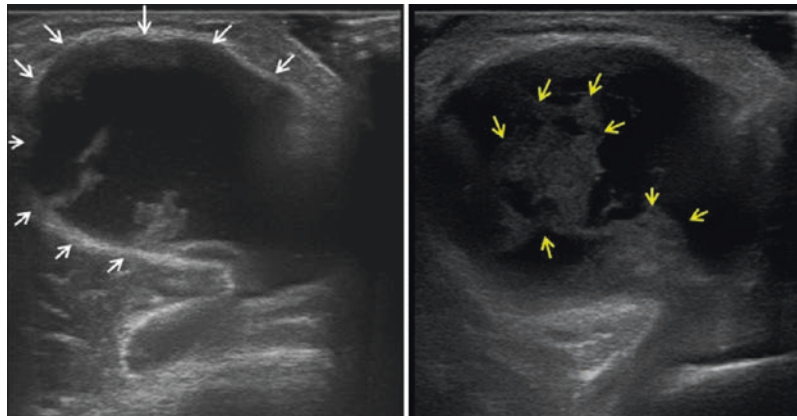

Fig. 12.2 Baker's cyst: knee ultrasound examination of a 62-year-old male. A well-defined fluid-filled cyst (white arrows), extending into the joint space between the semimembranosus tendon and the medial head of gastrocnemius, and synovial hypertrophy (yellow arrows) are apparent (*Figure courtesy of Professor Paraskevi V. Voulgari, MD*)

14. **What is the clinical picture of ruptured Baker's cyst and which easy and cheap method is used to diagnose it?**

Ruptured Baker's cyst sometimes does not produce any symptoms. Often, however, it presents with acute pain behind the knee and calf as well as swelling of the calf. The method to diagnose ruptured Baker's cyst and differentiate it from other conditions which produce similar symptoms (deep vein thrombosis, cellulitis, lymphedema, muscle or tendon tear) is ultrasonography (Fig. 12.2).

15. **Which are the causes of carpal tunnel syndrome (middle nerve entrapment neuropathy)?**

Trauma, diabetes mellitus, thyroid dysfunction, fluid retention from pregnancy or menopause, autoimmune disorders such as rheumatoid arthritis, wrist fractures, and amyloidosis.

16. **Which are the carpal tunnel syndrome symptoms?**

Pain, paresthesia, and sensory loss in the radial side of the palm, the thumb, and the index, middle, as well as ring fingers (distribution of the medial nerve). The pain can radiate up to the elbow, the shoulder, and even the neck. Pain is alleviated relatively when the patient walks.

17. **In which individuals carpal tunnel syndrome is more common?**

In women three times more often than in men, in obese individuals, and in the ages between 30 and 60 years.

18. **Describe a condition in which carpal tunnel syndrome is self-limited.**

Carpal tunnel syndrome occurring in the third trimester of pregnancy goes away after delivery. Wrist splints can relief the symptoms, while local steroid injections are not indicated. Nerve conduction studies should be performed only if symptoms persist after delivery.

19. **What is the clinical picture of osteoporosis?**

Osteoporosis can progress silently over years to a low bone mineral density (BMD) level, thereby reducing bone strength in a way that fragility fractures can occur with minimal impact. Fractures of the spine cause pain that is generally self-limited. Multiple vertebral fractures can lead to loss of height, reduced thoracic expansion capacity, progressive thoracic kyphosis, poor functional status, and ultimately frailty. Frailty itself is a risk factor for fractures, thereby creating a vicious cycle. Hip fractures have a much worse impact and prognosis. They require hospitalization and surgery. Usually the elderly that suffer from a hip fracture have

comorbid conditions that together with prolonged immobilization and rehabilitation required decrease their life expectancy.

20. **Which are the predisposing factors for the development of osteoporosis in men and women?**

In males, besides age, nearly 2/3 of osteoporotic men have an identifiable secondary cause of bone loss, most often alcohol abuse, glucocorticoid use and hypogonadism (including GnRH analog use for prostate cancer), smoking, low body weight, history of chronic lung disease, history of peptic ulcer disease, endocrine disorders (primary hyperparathyroidism, hyperthyroidism, insulin-dependent diabetes mellitus), hematologic disorders (multiple myeloma, lymphoma, leukemia), and gastrointestinal tract disorders (celiac disease, malabsorption, Crohn's disease, chronic liver disease, especially cirrhosis).

Women with the following characteristics, early menopause, low body weight/lean built, low dietary calcium intake, estrogen deficiency, and low levels of vitamin D, have the highest risk of developing osteoporosis. Secondary causes of osteoporosis in women are the same as in men.

21. **What is the fracture risk assessment tool (FRAX)?**

FRAX integrates clinical risk factors (country of origin, age, sex, weight, height, history of previous fracture, hip fracture in the person's mother or father, smoking, glucocorticoid treatment, rheumatoid arthritis and other diseases associated with osteoporosis, alcohol intake of three or more standard drinks/day) and bone mineral density at the femoral neck in order to calculate the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (spine, forearm, hip, or shoulder).

22. **Which psychotropic medications are risk factors for development of osteoporotic fractures?**

Psychotropic medications, including antidepressants, antipsychotics, and benzodiazepines, have been found in a recent study to increase the risk for hip fractures and other major osteoporotic fractures. Furthermore, the study also found that the FRAX tool significantly underestimates fracture risk in patients taking psychiatric medications [3].

23. **Which are the clinical/radiological similarities and differences of osteopetrosis and osteoporosis?**

Osteopetrosis is a very rare inherited bone disease also called "marble or stone" disease, while osteoporosis is the result of interplay between genetic (family history) and environmental factors (smoking, alcohol abuse, lack of exercise, dietary restriction, etc.). In individuals with mild forms of osteopetrosis as well as in osteoporotic individuals, there are no symptoms. Osteopetrosis can be detected in routine X-rays, where the bones appear denser and harder in contrast to osteoporosis where bones appear brittle and less dense. In osteopetrosis elevated serum alkaline phosphatase levels can be found, while in osteoporosis alkaline phosphatase is within normal limits. In severe cases in both disorders, bone fractures can occur. In osteopetrosis narrowing of bone marrow space occurs, leading to anemia and hepatosplenomegaly. Infections can occur due to bone expansion and extramedullary hematopoiesis. Expanded bones can also put pressure on nerves leading to facial paralysis, blindness, and deafness.

24. **How does acute bone necrosis present? Which are commonly affected areas?**

In some patients with bone necrosis, symptoms do not appear until the late stages of the disease process, when collapse of the articular surface occurs. In others pain is an early symptom, which usually occurs upon weight-bearing but can be present at rest and at night due to increased intraosseous pressure. Range of motion is not affected until degenerative changes occur. Commonly affected areas are those with limited blood supply and restricted collateral circulation and include the femoral head, the carpal bones (scaphoid, lunate), the humeral head, the talus, the femoral condyles, the tarsal navicular bone, the proximal tibia, and the metatarsals [4].

25. **Which are the causes of aseptic bone necrosis?**

Corticosteroid administration, alcohol abuse, sickle cell anemia, hemoglobinopathies, hyperlipidemia, hypercoagulable states (thrombophilia, disseminated intravascular coagulopathy), pregnancy, fat emboli, antiphospholipid syndrome, oral contraceptive use, arteriosclerosis/vaso-occlusive disorders, acquired human immunodeficiency syndrome, trauma (fracture of femoral neck), pancreatitis.

26. **What is Charcot arthropathy and which disorders can lead to its development?**

Charcot arthropathy is a progressive destructive process of the musculoskeletal system which leads to joint dislocations, pathologic fractures, and debilitating deformities. Neuropathies induced by diabetes mellitus, syphilis, leprosy, alcoholism, spinal cord injuries, and renal dialysis can be responsible for the development of the disorder.

27. **In which medical conditions shoulder-hand syndrome develops?**

The shoulder-hand syndrome (also known as complex regional pain syndrome, Sudeck's atrophy, algodystrophy) is characterized by pain and swelling in an extremity, trophic skin changes in the same extremity (skin atrophy/hyperpigmentation, hypertrichosis, hyperhidrosis, nail changes), signs and symptoms of vasomotor changes, limited motion in the proximal joints of the affected limb, and neglect-like symptoms of the affected extremity. It occurs most commonly after fractures, peripheral nerve injury, strokes, and myocardial infarctions (especially if associated with prolonged immobilization).

28. **Which joints are affected from sarcoidosis? Describe the characteristic radiological findings.**

The phalanges of the hands and feet are most commonly involved. The metacarpophalangeal joints and wrists are usually spared. Radiological findings include soft tissue swelling, periarticular osteopenia, joint space narrowing, cyst formation, punched-out erosions, sclerosis and periosteal reactions, pathologic fractures, and phalangeal fragmentation. The phalanges in chronic sarcoid bone involvement demonstrate a reticulated trabecular pattern.

29. **Which are the joint/bone findings of Langerhans cell histiocytosis?**

A well-circumscribed punched-out lesion of the skull is characteristic of Langerhans cell histiocytosis (LCH). In the mandible, the loss of supporting bone results in the appearance of "floating teeth." When the metaphysis or diaphysis of long bones is affected, the lesion is associated with endosteal scalloping, giving a budding appearance and extensive thick laminated periosteal reaction. LCH is also one of the causes of complete collapse of a vertebral body, known as vertebra plana. In children with LCH, osseous lesions are similar to those seen in multiple myeloma.

30. **What is the clinical picture of Tietze syndrome?**

Tietze syndrome is a benign inflammatory process of the costal cartilages which is more common in women. It presents with pain, tenderness, as well as swelling of the affected cartilages. It involves a single joint and is rarely bilateral. The pain increases with pressure application as well as with respiratory movements. Generally, it resolves spontaneously in weeks.

31. **Patient with knee monoarthritis with no history of trauma. The aspiration of the synovial fluid of the knee joint yields bloody-appearing synovial fluid. What is your diagnosis?**

The most probable diagnosis in a patient with knee monoarthritis in whom arthrocentesis yields a brown-red synovial fluid is pigmented villonodular synovitis. If the synovial

fluid is hemorrhagic besides trauma, bleeding disorders (hemophilia, coumarin-induced prolonged bleeding time), Charcot joint, sickle cell anemia, scurvy, and tumors should be considered [5].

32. **What is Kienböck's disease?**

Kienböck's disease is the fracture of the lunate bone in the wrist caused by disruption of its blood supply. It is of unknown etiology and presents with painful and swollen wrist with limited range of motion and decreased grip strength. Tenderness directly above the affected bone is a characteristic finding.

33. **What are the Schmorl's nodes?**

It is a common finding of an aging spine. The nodes do not cause any symptoms, and plain profile spinal X-ray reveals a defect at the anterior vertebral body which reflects a protrusion of the intervertebral disc, beneath the ring apophysis of the vertebral body.

34. **Which are the genetics and the clinical picture of Achondroplasia?**

Achondroplasia is a common cause of asymmetric dwarfism. The affected individuals present with a short stature (male adults average height 131 cm, females 123 cm), short proximal limbs, short fingers and toes, large head with prominent forehead and small midface with flattened nasal bridge, spinal kyphosis, and knee with "varus" or "valgus" deformities. It is caused by a sporadic or inherited mutation of the receptor 3 of fibroblast growth factor. This receptor when mutated is constantly active and leads to extremely shortened bones. Achondroplasia can be detected prenatally with ultrasound or DNA test. If the embryo carries two copies of the mutant gene, this leads to stillbirth.

35. **Which are the bone and cartilage findings of alkaptonuria (ochronosis)?**

It is a rare inherited disorder caused by a mutation of the gene responsible for the production of the enzyme homogentisate 1,2-dioxygenase. Individuals who inherit two abnormal gene copies accumulate in their blood and tissues homogentisic acid. Children and young adults are usually asymptomatic, but when their urine is left exposed to open air, it turns to black or inky black color. Accumulation of homogentisic acid in the ears, cartilage, and eyes sclera produces pigmentation, in the bone cartilages leads to osteoarthritis, and in the heart valves of the affected individuals causes regurgitation primarily of mitral and aortic valves. Stones consisting of homogentisic acid can be found in the gallbladder, the kidneys, the prostate, and the major salivary gland. Almost half of the affected individuals suffer from hearing loss. The weight-bearing joints (spine, hips, and knees) are commonly affected, and severe articular pain starts after the age of 30 years. The pain is severe and interferes with the individuals' daily activities. Involvement of the spinal joints limits the ability of the rib cage movement and thus affects lung gas exchange. Bone mineral density is affected leading to osteoporotic bone fractures.

36. **Which are the clinical and radiologic findings of an infected intervertebral disc?**

Infected intervertebral disc (discitis) is the result of a hematogenous spread of a systemic infection which can originate from the skin, the lungs, or the urinary tract. *Staphylococcus aureus* is the most commonly found microorganism, while Gram-negative bacteria (*Escherichia coli*, *Proteus* species) are common in patients with urinary tract infections. *Pseudomonas aeruginosa* or *Klebsiella* species can be the offending microorganisms in intravenous drug abusers. Infrequently discitis can develop postoperatively. Clinically discitis is presenting with fever (however, not unusually the patient can be afebrile), severe back pain and inability to move. The diagnosis can be easily placed with an MRI scan which reveals air changes in the discs sometimes involving the vertebral bone and the epidural area. Biopsy can help the diagnosis but the responsible organism is difficult to be isolated.

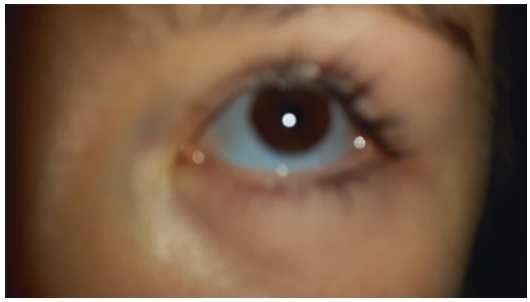

Fig. 12.3 Osteogenesis imperfecta: blue sclera is evident in a 16-year-old young lady with a long history of multiple bone fractures after minimal trauma (*Figure courtesy of Professor Fotini. N. Skopouli, MD*)

37. **Which are the clinical features, usual locations and radiologic characteristics of osteoid osteomas?**

Osteoid osteomas are benign, small (diameter < 1.5 cm) tumors which arise from the osteoblasts. They can be found in any body bone but more frequently are located in the long bones, e.g., the femur or the tibia. Continuous, deep pain, especially at night at the site of the lesion, is the principal symptom of osteoid osteomas. The pain characteristically responds to salicylates. Usually the diagnosis is delayed. Radiographs show a radiolucent area of around 1 cm in diameter, called nidus, with sometimes calcified center. The nidus is surrounded by radiodense cortical hypertrophy.

38. **Which are the prominent manifestations of pseudoxanthoma elasticum (PXE)?**

Skin: small, yellowish papules are evident on the neck, axillae, and groin and inside the surface of elbows and knees. The skin may become lax and redundant.

Retina: on fundoscopic examination, angioid streaks are present. These develop because Bruch's membrane, which separates the blood-vessel-rich layer from the pigmented retina layer, is mineralized creating cracks (angioid streaks) that radiate out from the optic disc. The retinal blood vessels sometimes leak, and the hemorrhages may lead to the loss of central vision.

The gastrointestinal (GI) and cardiovascular systems can also be involved in PXE; the principal GI symptom is gastrointestinal bleeding, usually from the stomach. This occurs in a very small number of patients. Peripheral arteries can be affected and the individual presents with intermittent claudication. In later disease stages coronary artery disease may develop. Joint hypermobility and chronic synovitis can be seen in patients with PXE.

39. **Which proteins are affected from gene mutations and for which hereditary connective tissue disorders are they responsible?**

Hereditary connective tissue diseases (HCTD) are a heterogeneous group of disorders that result from genetic defects that alter the quantity or structure of extracellular matrix (ECM) proteins including collagens, fibrillins, elastin, and non-collagenous matrix proteins. Depending on the ECM protein involved, the tissues most likely to be affected can be predicted, e.g., osteogenesis imperfecta, collagen type I defect; Ehlers-Danlos, collagen type I, III, or V defects/fibronectin defects; and Marfan's syndrome, fibrillin-1 defect.

40. **Which are the major clinical findings of Marfan's syndrome?**

Patients with Marfan's syndrome have a characteristic phenotype: tall stature, long-thin extremities, abnormally low upper/lower body segment ratio, diminished subcutaneous fat, arachnodactyly, pectus excavatum or carinatum, loss of thoracic kyphosis, scoliosis, reduced elbow extension (<170°), and pes planus. Scoliosis is a major problem in Marfan patients which might be rapidly progressive during adolescence requiring surgery. Joint hypermobility leading to arthralgias, spinal pain, and ligament injuries are common manifestations in adult patients with the syndrome. Facial characteristics include a high arched palate, long-narrow face, retrognathia, and enophthalmos.

Ectopia lentis occurs in 50–80% of patients.

Cardiovascular complications: aneurysmal dilatation of the ascending aorta with dissection is the most common cause of death in these patients. Mitral valve prolapse with regurgitation or aortic insufficiency are common. Pulmonary manifestations: cystic disease, spontaneous pneumothorax.

41. **Which are the major clinical findings of osteogenesis imperfecta?**
   - Fragile bones
   - Blue sclera (Fig. 12.3)
   - Short height
   - Loose joints
   - Decreased hearing

42. **What is the clinical picture of Paget's bone disease?**

Paget's disease of bone is the result of an excessive bone breakdown and formation which is followed by disorganized bone remodeling. The affected bones become fragile. The most commonly affected bones are the pelvis, the skull, the spine, and the legs. The diagnosis of the disease is based on the patient's clinical picture, the elevated serum alkaline phosphatase levels, and the characteristic bone appearance on X-rays. Bone reabsorption, enlargement of the affected bone, and bowing of the long bones are evident. Complications of Paget's disease of the bone include bone fractures, hearing loss, and pinched nerves of the spine. There is no curative therapy for the disease, but bisphosphonates can relieve bone pain and disease progression. In severe cases, surgery may be necessary.

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Rheumatic Manifestations: A Compilation

13

Abstract

Autoimmune diseases present with a wide range of symptoms able to affect nearly all body organs. Differential diagnosis of these symptoms can be difficult, as a particular presenting symptom may be encountered in distinct autoimmune diseases, and at the same time many non-rheumatic diseases may share similar clinical manifestations. In the large overlapping field of infections and rheumatology, many autoimmune diseases may present as fever of unknown origin, and on the other hand, many different infectious agents cause signs and symptoms mimicking a systemic autoimmune disease. Clinical manifestations affecting the skin and its annexes, oral cavity, joints, and periarticular structures but also major organs such as the heart and vascular system, lung, liver, spleen, and gastrointestinal tract can be initial symptoms of a systemic autoimmune disease. The good knowledge of underlying pathogenetic mechanisms of particular clinical manifestations, the thorough physical examination, and the accurate use and interpretation of laboratory, serological, and imaging findings are necessary skills in overcoming the challenging differential diagnosis.

1. **Which autoimmune disease patients have the highest incidence to drug allergies**?

   Patients with systemic and organ-specific autoimmune disorders have higher incidence of allergies compared to age-, sex-, and race-matched healthy individuals. It appears that a common variation of the BACH2 gene (the BACH2 protein plays a crucial role in T-lymphocyte maturation) accounts for the coexistence of allergies and autoimmune diseases.

2. **What is the association of systemic autoimmune disorders with autoimmune thyroid diseases?**

   Rheumatoid arthritis, polymyalgia rheumatica, Sjögren's syndrome, psoriatic arthritis, systemic lupus erythematosus, scleroderma, celiac disease, diabetes mellitus, and HCV-related cryoglobulinemia are encountered with increased prevalence in patients with thyroid autoimmune diseases [1].

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3. **In which conditions can Raynaud's phenomenon manifest?**
   - Autoimmune disorders: scleroderma, mixed connective tissue disease, Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, and anti-aminoacyl-tRNA synthetase inflammatory myopathies
   - Hyperviscosity syndromes
   - Use of certain medications (ergotamine/β-blockers)
   - Buerger's disease
   - Smoking
   - Mechanical reasons (repeated action/vibration)
   - Anatomic reasons, such as excessive seventh cervical rib [2]

4. **In which diseases can subcutaneous nodules be observed?**
   - Rheumatoid arthritis
   - Rheumatic fever
   - Systemic lupus erythematosus
   - Erythema nodosum
   - Tophaceous gout
   - Multicentric reticulohistiocytosis
   - Granulomatosis with polyangiitis (Wegener's granulomatosis)
   - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
   - Polyarteritis nodosa
   - Sarcoidosis
   - Type II hyperlipoproteinemia
   - Limited scleroderma (calcinosis cutis)

5. **In which autoimmune conditions can localized lipodystrophy (lipoatrophy) be seen?**

   Lipodystrophy (lipoatrophy) is the local lack of adipose tissue production, as a result of panniculitis. It has been described in patients with systemic lupus erythematosus, Sjögren's syndrome, and morphea.

6. **In which autoimmune conditions can painless mouth ulcers be observed?**

   Painless mouth ulcers can be seen in patients with systemic lupus erythematosus, Sjögren's syndrome, and post-infectious arthritis.

7. **Which are the subjective and objective findings of mouth ulcers in patients with systemic lupus erythematosus, granulomatosis with polyangiitis (Wegener's granulomatosis), and post-infectious arthritis?**
   - Systemic lupus erythematosus: irregularly shaped, raised white plaques, silvery white scarred lesions, and ulcers with surrounding erythema on the soft and hard palate (Fig. 4.7) or buccal mucosa and lips. Oral ulcers are usually painless, and there is not always temporal association with disease activity. Typical discoid lupus lesions with erythema, atrophy, and depigmentation can also occur.
   - Granulomatosis with polyangiitis: two classic mouth lesions can be seen; gum inflammation (strawberry gums) and tongue ulcers, which typically occur on the lateral sides of the posterior tongue (Fig. 8.3). Gum inflammation and tongue ulcers are both painful.
   - Post-infectious arthritis: oral ulcers are usually shallow and painless.

8. **Which are the causes of saddle nose deformity?**

   Saddle nose is characterized by a loss of nose height. The depressed nasal dorsum may be due to destruction of bony, cartilaginous, or both components of the nasal dorsum. It is observed after nasal trauma (most common cause) or in patients with:
   - Congenital syphilis/leprosy
   - Relapsing polychondritis
   - Granulomatosis with polyangiitis (Fig. 13.1)
   - Cocaine abuse

9. **Which conditions are associated with perforation of the nasal diaphragm?**

   Conditions associated with perforation of the nasal diaphragm include systemic lupus erythematosus, granulomatosis with polyangiitis (Wegener's granulomatosis), syphilis, leprosy, sarcoidosis, tuberculosis, neoplastic causes (nasopharyngeal carci-

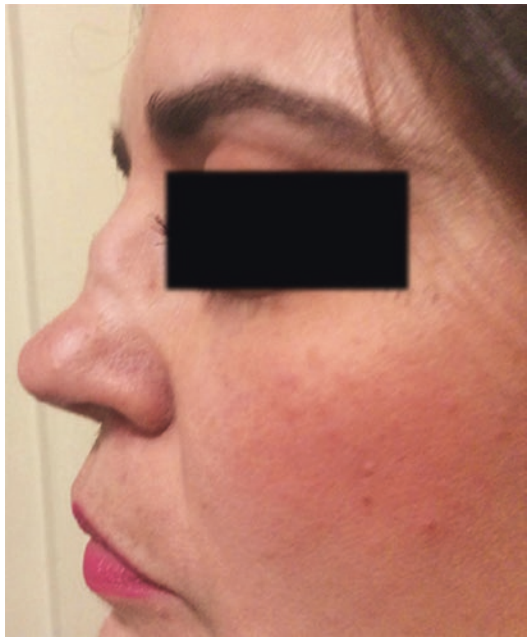

Fig. 13.1 Saddle nose deformity: in a 35-year-old female patient with granulomatosis with polyangiitis (Wegener's granulomatosis)

noma, middle line lethal granuloma), and cocaine sniffing.

10. **Which patients with rheumatic disease develop oral candidiasis?**
    - Immunosuppressed patients with systemic connective tissue diseases
    - Sjögren's syndrome patients with severe xerostomia

11. **What are the telangiectasias and under which conditions can they develop?**

    Telangiectasias form gradually and often in clusters. They are widened venules which cause thread-like red lines or patterns on the skin and mucosae. They are also called "spider veins" because of their fine and weblike appearance. Conditions in which telangiectasias are observed include alcoholism, pregnancy, aging, rosacea, habitual corticosteroid use, limited scleroderma (Fig. 7.2), dermatomyositis, and, in some patients, systemic lupus erythematosus.

12. **Which autoimmune disorders can present with Bell's palsy and uveitis?**

    These are sarcoidosis and Sjögren's syndrome.

13. **Which inflammatory arthritis can affect distal interphalangeal joints?**

    Psoriatic arthritis and gout can affect distal interphalangeal joints.

14. **What is the clinical picture of fibromyalgia?**

    It is a chronic (more than 3 months of duration) noninflammatory, non-autoimmune disorder characterized by multifocal pain (elicited by palpation of specific trigger points above and below the waist), severe fatigue, stiffness, sleep disturbances, cognitive problems, and often psychological distress. The etiopathogenesis of fibromyalgia (FM) is controversial. Genetic predisposition, environmental factors (diet, social distress, poor social relationships), and neuromodulation are considered as possible triggering and perpetuating factors. FM presents with a wide range of manifestations, yet physical examination reveals no signs of articular or muscular disease. Reduction of intraepidermal nerve fiber density in the skin biopsies of patients with fibromyalgia has been recently detected, but the association of this finding with the disease-related symptoms remains to be elucidated. FM may overlap many rheumatic and non-rheumatic diseases. In cases of primary fibromyalgia, laboratory and radiographic tests are normal. It should be differentially diagnosed from chronic pain disorders (e.g., recurrent regional pain syndrome) whose somatic symptoms are similar [3].

15. **Which arthritides can affect the temporomandibular joint?**

    Rheumatoid arthritis, juvenile idiopathic arthritis, degenerative arthritis, and rarely gout can affect the temporomandibular joint.

16. **Which nerve root is affected if a patient presents with back pain and numbness around the left knee, medial shin, and calf and absence of the left knee reflex?**

The L3/L4 root since the knee reflex is mediated by the L3/L4 nerve root. L3 nerve root supplies the dermatome of the anterior aspect of the knee, and the L4 nerve root supplies the medial aspect of calf muscles and skin.

17. **Which are the symptoms and causes of plantar fasciitis?**

The principal symptom of plantar fasciitis is pain in the heel and bottom of the foot. The pain is usually most severe in the morning when the individual gets up from the bed or after a rest period. The symptoms typically come on slowly. The causes of plantar fasciitis are unclear. Risk factors include long periods of standing, strenuous exercise, and obesity. Other conditions in which plantar fasciitis symptoms can manifest include flat feet, osteoarthritis, ankylosing spondylitis, and reactive arthritis. In only one third of patients, both feet are affected.

18. **Which are the therapeutic measures for the management of plantar fasciitis?**

The symptoms of plantar fasciitis resolve with time. Rest, changing the individual's activities, and pain medications can be sufficient to alleviate the symptoms. If, however, these are not effective, physiotherapy, orthotics, splinting, or local steroid injections can be applied.

19. **Which systemic rheumatic diseases can affect the aortic valve?**

- Ankylosing spondylitis
- Cogan syndrome
- Relapsing polychondritis
- Marfan syndrome
- Giant cell arteritis
- Granulomatosis with polyangiitis (Wegener's granulomatosis)
- Reactive arthritis
- Rheumatoid arthritis
- Rheumatic fever
- Antiphospholipid syndrome

20. **Which clinical picture of autoimmune diseases resembles that of the subacute endocarditis?**

Libman-Sacks endocarditis which manifests in systemic lupus erythematosus and antiphospholipid syndrome patients can resemble the clinical picture of subacute endocarditis.

21. **Which cardiac tumor can present as an inflammatory disorder?**

Cardiac myxomas. These are rare benign solitary, pedunculated tumors of all age groups. The majority of these tumors are located in the left atrium, while the minority are located in the right atrium or in both atria and either ventricle. They can present either with symptoms of hemodynamic obstruction or embolization and infarction of peripheral arteries or as an inflammatory syndrome with constitutional symptoms such as fever, malaise, arthralgias/arthritis tachycardia and tachypnea, hyperglobulinemia, and elevated C-reactive protein levels. Two-dimensional echocardiography is the diagnostic procedure of choice. Surgical removal is the therapy of choice.

22. **In which diseases are arterial microaneurysms found?**

- Polyarteritis nodosa
- Ehlers-Danlos disease
- Fibromuscular dysplasia
- Pseudoxanthoma elasticum
- Neurofibromatosis
- Segmental arterial mediolysis

23. **In which systemic autoimmune disorders can pleurisy be the first disease manifestation?**

In men with rheumatoid arthritis, in systemic lupus erythematosus, and rarely in granulomatosis with polyangiitis (Wegener's granulomatosis)

24. **Which findings characterize a body fluid as exudate?**

Appearance: cloudy
Specific gravity >1020
Fluid/serum protein ratio > 0.5
Fluid/serum LDH ratio > 0.6

25. **Which autoimmune patients are at highest risk to develop *Pneumocystis carinii* (*jiroveci*) pneumonia?**

Pneumocystis jiroveci (formerly known as *Pneumocystis carinii*) pneumonia (PCP) occurs frequently in patients with autoimmune inflammatory diseases older than 60 years of age and on steroid treatment.

26. **Which autoimmune diseases may present with alveolar hemorrhage?**

Alveolar hemorrhage should be suspected in patients with progressive dyspnea accompanied by alveolar opacities on chest imaging that cannot be otherwise explained. Hemoptysis is a typical sign but is often absent. A drop of blood hemoglobin over a few days without hemolysis or any overt blood loss should raise the suspicion of diffuse alveolar hemorrhage. Bright red fluid obtained from bronchoalveolar lavage is diagnostic. It can occur in the following autoimmune diseases:

- Systemic lupus erythematosus
- Different types of vasculitis (mainly microscopic polyangiitis or granulomatosis with polyangiitis and, exceptionally, eosinophilic granulomatosis with polyangiitis)
- Antiphospholipid syndrome
- Goodpasture syndrome
- Idiopathic pulmonary hemosiderosis

27. **When should a physician think that a patient has pulmonary arterial hypertension?**

Pulmonary arterial hypertension (PAH) should be ruled out in a patient presenting with dyspnea and fatigue, which cannot be attributed to heart, lung, or blood disorders. There are few signs of early PAH, but there are several important physical examination findings that suggest the presence of advanced PAH, such as features of right heart dysfunction, including lower extremity edema, murmur of tricuspid regurgitation, jugular vein distension, and hepatomegaly. Right heart catheterization is the gold standard for the diagnosis of PAH.

28. **In which autoimmune rheumatic disorders can pulmonary arterial hypertension develop?**

It can develop in scleroderma patients and less frequently in patients with systemic lupus erythematosus, mixed connective tissue disease, and Sjögren's syndrome.

29. **Which conditions (autoimmune and others) present with hemophagocytic syndrome?**

- Still's disease
- Systemic lupus erythematosus
- EBV/CMV infection
- Brucellosis
- Tuberculosis
- Leishmaniasis

30. **In which autoimmune patient group is the incidence of splenomegaly higher?**

Incidence of splenomegaly is higher in patients with Still's disease, autoimmune hemolytic anemia, and Felty's syndrome.

31. **Which autoimmune disorders can manifest clinical, laboratory, and histopathologic features of autoimmune hepatitis? What autoantibodies can these individuals have in their serum?**

Autoimmune hepatitis is classified as type 1 and type 2 based on expression of different autoantibodies. Patients with type 1 autoimmune hepatitis are mainly females and can have other associated autoimmune disorders like rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, inflammatory bowel disease, and autoimmune thyroid diseases. In their serum autoantibodies against nuclear antigens, cellular antigens (particularly against anti-Ro/SSA), and smooth muscle antigens (ASMA) are

present. Type 2 autoimmune hepatitis is mainly a pediatric disease. It is characterized by the presence of anti-liver kidney microsomal antibody type 1 (LKM-1) and/or anti-liver cytosol type 1 (LC-1) autoantibodies.

32. **Which drugs can be responsible for the development of autoimmune liver disease?**

Well-established associations are minocycline, nitrofurantoin, oxyphenisatin, alpha-methyl-dopa, clometacin, statins, and anti-TNF biologic agents. Less compelling associations (infrequent reports) include diclofenac, fenofibrate, dihydralazine, and benzarone.

33. **In which rheumatic diseases can esophageal motility disorders be seen?**

They can be seen in the majority of systemic sclerosis patients, but they can also be seen in patients with polymyositis/dermatomyositis, undifferentiated connective tissue diseases/mixed connective tissue disease, and Sjögren's syndrome.

34. **In which rheumatic disorders can microscopic colitis develop?**

Microscopic colitis is a clinicopathologic entity of middle-aged, predominantly female, patients which presents with chronic, intermittent, or recurrent episodes of watery diarrhea and abdominal cramps. The colonic mucosa of patients with microscopic colitis appears normal in colonoscopy, while the tissue taken during colonoscopy reveals two distinct histopathologic forms: the collagenous and the lymphocytic. Patients with celiac disease, autoimmune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and spondyloarthropathies can manifest symptoms and signs of microscopic colitis. In these rheumatic disorders, collagenous microscopic colitis is the more frequent histopathologic form.

35. **Which is the clinical picture of ischemic colitis and what are the underlying causes?**

Ischemic colitis is the result of reduced blood flow in the colon. The colon tissue damage can range from inflammation and superficial injury to necrosis of the full wall thickness. Classically ischemic colitis affects individuals in their sixties to seventies. Clinically it presents acutely with colicky abdominal pains accompanied with bloody bowel movements.

Underlying causes of ischemic colitis can be:

- Atherosclerosis/diabetes mellitus leading to: thrombosis/emboli
- Arterial hypoperfusion/hypovolemia (septic shock, hemorrhagic shock, cardiopulmonary bypass, hemodialysis, hemorrhagic pancreatitis)
- Hypercoagulable state (severe dehydration, thrombophilia, sickle cell disease)
- Drugs (antihypertensives, digitalis, estrogens, pseudoephedrine, simvastatin, interferon-ribavirin)
- Cocaine abuse
- Cardiac myxoma
- Polyarteritis nodosa
- Amyloidosis
- Postradiation

36. **In which systemic autoimmune diseases can mesenteric vasculitis occur?**

Mesenteric vasculitis is defined by inflammation of medium-size mesenteric arteries. Most often it affects branches of the celiac, superior, and inferior mesenteric arteries. It occurs in patients with polyarteritis nodosa, Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis.

37. **Which autoimmune conditions are responsible for nephrocalcinosis?**

Sjögren's syndrome with chronic untreated interstitial kidney disease and sarcoidosis are the autoimmune conditions responsible for nephrocalcinosis.

38. **What can be the causes of interstitial nephritis?**

- Drugs: nonsteroidal anti-inflammatory drugs, antibiotics (penicillin, fluoroquinolones), proton-pump inhibitors, rifampicin, sulfa drugs, diuretics, allopurinol, and phenytoin

- Autoimmune diseases: Sjögren's syndrome (early in the disease), sarcoidosis (granulomatous interstitial nephritis), and IgG4-related diseases
- Acute transplant rejection
- Infections: bacterial (obstructive uropathy), viral (CMV, HIV, HBV), parasitic (leishmaniasis), and fungal (histoplasmosis)
- Genetic: Alport syndrome
- Endemic: Balkan nephropathy

39. **In which autoimmune conditions is interstitial cystitis observed? What are the main clinical manifestations?**

Interstitial cystitis can be associated with Sjögren's syndrome, inflammatory bowel disease, and systemic lupus erythematosus. Common symptoms include urgency/frequency to urinate, bladder pressure and pain that gets worse when the bladder is full, as well as pain in the lower abdomen and lower back, pelvis, or urethra. In women pain in the vulva/vagina occurs during intercourse.

40. **What is the etiology and clinical picture of Alport syndrome?**

Alport syndrome is a hereditary disease caused by mutations that affect the production and/or function of type IV collagen, the major constituent of mature basement membranes in the glomerulus, cochlea, cornea, lens, and retina. It is a rare syndrome, yet it accounts for about 1% of patients on hemodialysis. The earliest clinical manifestation of Alport syndrome is hematuria. Anterior lenticonus, discolored retina, and hearing loss are extrarenal manifestations.

41. **What is Balkan nephropathy?**

Balkan nephropathy is a familial chronic tubulointerstitial disease. It presents insidiously and slowly progresses to end-stage renal disease. It is frequently related to upper urothelial cancer. Its cause remains largely unknown. Polygenic susceptibility to the disease in interaction with multiple environmental factors is assumed. Chronic intoxication with Aristolochia (family of plants) or long-term exposure to organic toxins (lignite) is considered a major environmental risk factor [4].

42. **What are the rheumatologic manifestations of amyloidosis and in which type of amyloidosis can they occur more often?**

Rheumatic manifestations occur more frequently in AA amyloidosis, and they include muscle weakness (myopathy); arthropathy of shoulders, knees, wrists, as well as the small joints of the hands; bone lesions (osteopathy); and carpal tunnel syndrome. In contrast to AL, transthyretin (ATTR), and beta-2 microglobulin (A beta-2 m) amyloidoses, musculoskeletal manifestations due to amyloid deposition are subtle, subclinical, and only apparent in tissue biopsy. Rarely, sicca syndrome can develop.

43. **In which chronic medical conditions can AA amyloidosis develop?**
- Chronic infections: tuberculosis
- Autoimmune-inflammatory diseases: rheumatoid arthritis, inflammatory bowel disease, and periodic fever syndromes (familial Mediterranean fever)

44. **Which autoimmune diseases can develop in individuals with IgA deficiency?**
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Immune thrombocytopenic purpura
- Thyroid autoimmune disorders
- Inflammatory bowel disease

45. **In which other autoimmune diseases, in addition to Sjögren's syndrome, can trigeminal neuralgia manifest?**

Trigeminal neuralgia can manifest in scleroderma and sarcoidosis.

46. **In which autoimmune conditions is leukopenia prevalent?**

Leukopenia is prevalent in systemic lupus erythematosus, Sjögren's syndrome, autoimmune thyroiditis, and Felty's syndrome.

47. **In which systemic autoimmune diseases can migraine headache manifest?**
   - Systemic lupus erythematosus
   - Antiphospholipid syndrome
   - Sjögren's syndrome
   - Limited scleroderma

48. **In which autoimmune diseases can Devic's syndrome (neuromyelitis optica) manifest?**

   Devic's syndrome can manifest in systemic lupus erythematosus, Sjögren's syndrome, scleroderma, myositis, autoimmune thyroid diseases, inflammatory bowel disease, psoriasis, and pemphigus.

49. **In which disorders can cerebrospinal fluid (CSF) monoclonal bands be found? Are they disease specific?**

   They can be found in the CSF of patients with multiple sclerosis but also of patients with systemic lupus erythematosus and acquired immunodeficiency syndromes, particularly when the patients from the two later groups have central nervous system involvement.

50. **In which autoimmune patients can pseudo-pseudo Meigs syndrome (PPMS) develop?**

   Pseudo-pseudo Meigs Syndrome (PPMS) is a very rare and of uncertain etiology phenomenon seen in patients with systemic lupus erythematosus. It manifests with ascites, pleural effusions, and elevated serum CA-125 levels. PPMS is not associated to benign or malignant pelvic tumors. Due to the rarity of the condition, the underlying pathophysiology of ascites in PPMS is still uncertain. It is suggested that severe, uncontrolled inflammation related to the underlying systemic lupus erythematosus could be the cause. Therefore immunosuppressives to treat lupus flare are used for treating PPMS.

51. **In which autoimmune patients are contraceptives contraindicated?**

   Contraceptives containing estrogens can exacerbate systemic lupus erythematosus and can increase the risk of thrombosis in patients with antiphospholipid syndrome.

52. **Which autoimmune conditions can develop in individuals with silicone breast implants?**

   Sjögren's syndrome, rheumatoid arthritis, and Raynaud's phenomenon can develop in these individuals [5].

53. **What is the impact of bariatric surgery on patients with rheumatoid arthritis?**

   In a recent study, rheumatoid arthritis patients underwent bariatric surgery (Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, or sleeve gastrectomy) at two medical centers. Twelve months following surgery, subjects lost substantial weight (41.0 ± 17.3 kg), rheumatoid arthritis disease activity and inflammatory indexes significantly improved, and the patients were on less rheumatoid arthritis-related medications. The authors suggest that the improvement noticed in rheumatoid arthritis patients who underwent bariatric surgery can be attributed to the improved efficacy of rheumatoid arthritis medications, to increased physical activity, and to metabolic changes [6].

54. **Which are the rheumatologic manifestations in HIV-infected individuals?**
   - Post-infectious arthritis (Reiter's syndrome)
   - Idiopathic polymyositis or zidovudine-induced myositis
   - Sicca syndrome
   - Psoriasis and psoriatic arthritis

55. **What adverse musculoskeletal effects are caused by the use of performance-enhancing drugs?**

   Performance-enhancing drugs (PEDs) are pharmacologic agents that athletes and non-athlete weight lifters use to enhance performance. There are several categories of PEDs that are currently popular. The most frequently used anabolic drugs causing musculoskeletal disorders are:

- Androgenic-anabolic steroids (AAs): can cause rhabdomyolysis and tendon ruptures (attributable both to the disproportionate strength of hypertrophied muscles and to possible deleterious effects of AAs on the architecture of the tendons themselves)
- Growth hormone: can cause acral enlargement, arthropathy, and carpal tunnel syndrome

56. **Which are the clinical manifestations and histopathologic findings of Kikuchi-Fujimoto disease (histiocytic necrotizing lymphadenitis)?**

Kikuchi-Fujimoto disease (KFD) is a rare benign and self-limiting cause of lymphadenopathy, mainly cervical. It classically affects young women during the third decade of life. Although an infectious etiology has been suggested, a definitive causative agent has not been recognized. Typical symptoms include localized lymphadenopathy, fever, and odynophagia. Laboratory findings are usually normal except for mild increase of inflammatory markers and/or mild cytopenias. Biopsy of affected lymph nodes shows features of distortion of the lymph node architecture with patchy areas of necrosis, profuse karyorrhexis, and proliferation of histiocytes, plasmacytoid dendritic cells, and CD8+ T cells around foci of necrosis. Granulocytes and plasma cells are typically absent. Immunohistochemical analysis is useful to rule out malignant lymphoma [7].

57. **With which autoimmune systemic disease is Kikuchi-Fujimoto disease associated?**

Kikuchi-Fujimoto disease is associated with the development of systemic lupus erythematosus (SLE). Presence of weight loss, arthralgias, skin manifestations, and high titers of antinuclear antibodies in patients with Kikuchi-Fujimoto disease have been shown to be associated with the development of SLE.

58. **What rheumatic and/or autoimmune manifestations can develop in cancer patients receiving immunotherapy with checkpoint inhibitors (CPIs)?**

Cancer immunotherapy with checkpoint inhibitors is the latest therapeutic modality used for cancer treatment. The immune system has several checkpoints (stimulatory or inhibitory), where ligand–receptor interactions are critical in maintaining self-tolerance and preventing the immune system from attacking cells indiscriminately. Such inhibitory checkpoints are the programmed cell death 1 and 2 pathways (PD-1 and PD-2) which limit T-cell activity at the time of an inflammatory response and the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) which counteracts the activity of T-cell co-stimulatory receptor CD28. Tumor cells can use these checkpoints to protect themselves from immune system attacks.

In the last few years, monoclonal antibodies targeting the molecules of immune checkpoints, and thereby restoring antitumor immune responses, have been developed. Currently the ones approved are: Ipilimumab, a CTLA-4 inhibitor; nivolumab and pembrolizumab, PD-1 inhibitors; and atezolizumab, avelumab, and durvalumab, programmed cell death-ligand 1 (PDL-1) inhibitors. They are used for treatment of several types of cancer, such as metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer, head and neck cancer, and Hodgkin's lymphoma.

Cancer patients treated with CPIs can exhibit the following rheumatic and autoimmune adverse events:

- Arthralgias, tenosynovitis, myalgias
- Rheumatoid and psoriatic-like arthritis
- Myositis
- Sicca syndrome
- Vitiligo, psoriasiform or lichenoid reactions, bullous pemphigoid
- Autoimmune hypothyroidism more common than hyperthyroidism

- Hypophysitis
- Type 1 diabetes mellitus
- Inflammatory bowel disease, enteritis/colitis
- Pneumonitis
- Multiple sclerosis
- Myasthenia gravis

The use of CPIs may result in disease exacerbation in approximately one-quarter of patients with pre-existing autoimmune disease [8].

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Part IV

Treatment and Management of Rheumatic Diseases

14 Medications, Therapeutic Modalities, and Regimens Used in the Management of Rheumatic Diseases

Abstract

Therapy of systemic autoimmune rheumatic diseases can still be a challenge for clinicians despite enormous progress made in the last decades on the understanding of the pathophysiological mechanisms involved in these diseases. The use of biologic targeted therapies as an adjunct to disease-modifying antirheumatic drugs (DMARDs) for the treatment of autoimmune rheumatic diseases has completely changed standard of care and is still expanding.

Indications, therapeutic schemes, and specific side effects are presented for the classical disease-modifying antirheumatic drugs (DMARDs). In addition, contemporary therapeutic modalities and biologic therapies targeting key effector cells and cytokines implicated in different autoimmune diseases are thoroughly addressed. The major targets of most biologic therapies that we now possess to treat systemic autoimmune diseases are cytokines, B cells, and co-stimulation molecules. Tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-17 belong to the cytokines targeted. B-cell depletion includes use of anti-CD20 antibodies and B-cell receptor modulation by the B-lymphocyte stimulator (BLyS). Although some of the biologic therapies have been found to be useful in more than one disease, others are specific for a single disease. Latest indications and therapeutic schemes involving biologic therapies in autoimmune rheumatic as well as in autoinflammatory diseases are given in this chapter. Up-to-date treatment guidelines for osteoporosis in men and women are presented. Finally, questions and answers addressing matters of special interest, such as the use of anti-inflammatory and immunosuppressive agents during pregnancy and lactation as well as vaccination recommendations in immunocompromised patients, are an interesting part of this chapter.

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1. **How do (a) methotrexate, (b) leflunomide, (c) cyclosporine-A, and (d) D-penicillamine exert their anti-inflammatory/immunosuppressive action?**
   (a) **Methotrexate (MTX)** is an antimetabolite which exerts its anti-inflammatory action through:
   - Inhibition of purine and pyrimidine synthesis.
   - Suppression of transmethylation reactions with accumulation of polyamines.
   - Inhibition of T-cell activation.
   - Suppression of inter-cellular adhesion molecule expression by T cells.
   - Selective downregulation of B cells.
   - Increase of the CD95 sensitivity of activated T cells [CD95 (Fas/Apo1) and CD95 ligand (CD95L) have been known as the death receptor/death system which induces apoptosis (programmed cell death), maintains immune homeostasis, and eliminates virally infected and neoplastic cells].
   - Inhibition of methyltransferase activity.

   All these actions lead to deactivation of enzyme activity relevant to immune system function, which stimulates adenosine release. Adenosine is a potent neutrophil function inhibitor and has strong anti-inflammatory properties. Another mechanism of methotrexate action is the inhibition of interleukin-1 beta binding to its cell surface receptor. Possibly, the combination of these mechanisms is responsible for the anti-inflammatory effects of methotrexate. The adenosine-mediated methotrexate's anti-inflammatory effect is supported by in vitro, in vivo, and clinical data.

   (b) **Leflunomide** exerts its immunomodulatory action by inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase, which plays a key role in the de novo synthesis of uridine monophosphate. Uridine monophosphate is required for the synthesis of DNA and RNA. Through this mechanism leflunomide inhibits the reproduction of rapidly dividing cells, especially lymphocytes.

   (c) **Cyclosporine-A** exerts its immunosuppressive action by binding to the cytosolic protein cyclophilin (immunophilin) of lymphocytes, especially T cells. This cyclosporine/cyclophilin complex binds to calcineurin and inhibits calcineurin-calmodulin interaction, which, under normal circumstances, is responsible for activating the transcription of interleukin (IL)-2. In T cells, T-cell receptor activation normally increases intracellular calcium, which via calmodulin activates calcineurin. Calcineurin thereafter dephosphorylates the nuclear transcription factor of activated T cells, which translocates to the T-cell nucleus and increases the activity of gene coding for IL-2, leading to a reduced function of effector T cells. Cyclosporine-A does not have cytostatic activity.

   (d) **D-penicillamine**: initially it was shown that it decreases the serum levels of circulating rheumatoid factors and immune complexes, affects macrophage functions, and decreases the ability of lymphocytes to proliferate. Subsequently, it has been shown that D-penicillamine increases the rates of apoptosis through a p53 oncogen-mediated mechanism and arrests angiogenesis by chelating with copper which is a cofactor for this process. Furthermore, D-penicillamine interferes with fibroblast proliferation and inhibits the cross-linking of collagen and elastin fibers.

2. **How do (a) hydroxychloroquine, (b) thalidomide, (c) dapsone, and (d) danazol exert their anti-inflammatory action?**
   (a) **Hydroxychloroquine**: its anti-inflammatory/immunomodulatory action is the result of its interference with the "antigen processing" in macrophages and other antigen-presenting cells. It diminishes the formation of peptide-MHC protein complexes, a signal necessary for CD4+ T-cell activation, and thus results in downregulation of the immune response against autoantigens. Hydroxychloroquine can suppress the lupus-related mucocutaneous manifestations, may reduce the risk

of flares, allows the reduction of the dosage of steroids, reduces organ damage, and prevents the thrombotic effects of antiphospholipid antibodies.

The anti-inflammatory action of hydroxychloroquine differs from the action of other anti-inflammatory medications; thus its effectiveness increases when prescribed in combination with other anti-inflammatory medications.

(b) **Thalidomide**: its anti-inflammatory/immunomodulatory actions are mediated through:

- Inhibition of leukocyte chemotaxis to the site of inflammation
- Decreased phagocytosis by polymorphonuclear leukocytes
- Increased production of interleukin (IL)-4 and IL-5 by mononuclear cells
- Inhibition of interferon-γ production
- Selective inhibition of tumor necrosis factor (TNF)-α production by monocytes and macrophages

(c) **Dapsone** belongs to the group of synthetic sulfones. Its effects on inflammatory effector cells, cytokines, and/or mediators have been investigated mainly in vitro:

- Inhibition of the enzyme myeloperoxidase accounts for its anti-inflammatory action.
- It inhibits chemotaxis, but only when certain stimuli are applied.
- It has an inhibitory effect on prostaglandin synthesis and release.
- It inhibits leukotriene (LT) C_4 production, which could explain its corticosteroid-sparing effect in asthma patients.

(d) **Danazol** is a synthetic anabolic steroid with androgenic properties. It can be beneficial in the treatment of refractory autoimmune hemolytic anemia and thrombocytopenia complicating systemic lupus erythematosus, or when there are contraindications to splenectomy and/or corticosteroids. It is relatively well tolerated and may decrease the duration of glucocorticoid therapy. The effects of danazol are based on several immunomodulatory properties:

- Downregulates the expression of Fcγ receptor on monocytes, which in turn decreases platelet phagocytosis.
- Reduces the proliferation of lymphocytes.
- Alters lymphocyte differentiation by increasing the percentage of helper T lymphocytes.
- In mice danazol decreases the production of pro-inflammatory cytokines (IL-2, IFN-γ) and increases anti-inflammatory cytokines (IL-10).

3. **In which immunologic conditions is danazol indicated?**

It is indicated in hereditary angioedema as well as in autoimmune hemolytic anemia and thrombocytopenia.

4. **How do (a) azathioprine, (b) mycophenolate mofetil, and (c) cyclophosphamide exert their immunosuppressive action**?

(a) **Azathioprine** is a purine analog, and the accepted mechanism of its action is at the level of DNA. Both in vitro and in vivo, azathioprine is metabolized to 6-mercaptopurine (6-MP). Ultimately, azathioprine can be incorporated into replicating DNA, blocking the *de novo* pathway of purine synthesis and thus leading to both cytotoxicity and reduced cellular proliferation. This action is thought to contribute to the relative specificity of azathioprine for lymphocytes due to their lack of a salvage pathway.

(b) **Mycophenolate mofetil (MMF)** is a prodrug of mycophenolic acid. Mycophenolic acid:

- Inhibits the proliferation of T and B lymphocytes, thereby diminishing cell-mediated immune responses and antibody formation
- Inhibits the recruitment of lymphocytes and monocytes into sites of inflammation
- Decreases the production of nitric oxide (NO) by inducible NO synthase

(c) **Cyclophosphamide** is a nitrogen mustard, one of the most potent immunosuppressive drugs available. It is an inactive

prodrug which is metabolized via the cytochrome-P450 enzymatic system. Phosphoramide mustard and acrolein are its main active and inactive metabolites, respectively. The former is spontaneously degraded, whereas the latter is excreted into the urine. Acrolein, the main inactive metabolite of cyclophosphamide, is responsible for the unwanted drug effects such as hemorrhagic cystitis and bladder neoplasia.

Cyclophosphamide exerts its immunosuppressive action through:

- Attachment of alkylated bases to DNA, resulting in DNA fragmentation by repair enzymes and ultimately stopping DNA synthesis and RNA transcription from the affected DNA
- Formation of cross-links in the DNA, which prevents DNA from being separated for synthesis or transcription
- Induction of mispairing of the nucleotides leading to mutations

5. **Based on which scientific grounds was anti-tumor necrosis factor-α (TNF-α) therapy established for the treatment of inflammatory arthritis?**

The rationale for the development of anti-TNF-α therapy was based on the following laboratory, experimental animal, and clinical studies:

Initially, abundance of TNF-α was found in inflamed synovial tissues from rheumatoid arthritis patients. Subsequently, it was observed that synovial membrane cell cultures from rheumatoid arthritis patients produce, over several days, in the absence of extrinsic stimulation, pro-inflammatory cytokines. The addition of anti-TNF-α antibodies to the cultures markedly reduced the production of other pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF). These observations led to the concept that TNF-α holds a dominant position in a pro-inflammatory cytokine within the rheumatoid arthritis joint.

Another group of investigators constructed TNF-α transgenic mice which develop arthritis resembling human rheumatoid arthritis. Treatment of these animals with anti-TNF-α antibodies resulted in amelioration of arthritis. An independent group of investigators treated mice with collagen-induced arthritis using anti-TNF-α antibodies, resulting in amelioration of disease activity. All the above studies indicated that TNF-α drives a multi-cytokine, multicellular chronic disease and can be an ideal therapeutic target. Initially anti-TNF-α antibodies were administered, in an open label study, in rheumatoid arthritis patients, and the encouraging results led to the development of controlled multicenter studies which documented the therapeutic efficacy of anti-TNF-α antibodies for rheumatoid arthritis. The success of anti-TNF-α treatment efficacy in rheumatoid arthritis prompted its study in other related diseases such as juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and psoriasis. In all of these, the effect on patients has been very satisfactory and has greatly improved their quality of life. The limitations for the use of this biologic agent are the high cost and the unwanted side effects.

6. **What is the rationale for the use of CTLA4-Ig as a therapeutic agent in patients with rheumatoid arthritis?**

Following antigen recognition via the major histocompatibility complex on antigen-presenting cells by the T-cell receptor, T cells require a second, co-stimulatory signal to become activated. CTLA4-immunoglobulin-Fc (CTLA4-Ig) fusion protein selectively modulates T-cell co-stimulation. It binds to both CD80 and CD86 (B7 molecules) and prevents interaction with their counter-receptors, expressed on T cells, CD28, and CTLA4, respectively. This interferes with T-cell-antigen-presenting cell interaction and limits T-cell activation, a process that plays a central role in the immunopathogenesis of rheumatoid arthritis. In addition, CTLA4-Ig can bind to B7 molecules expressed on dendritic cells and activate a pathway of tryptophan catabolism that indirectly leads to inhibition of lymphocyte activation and T-cell death. Recently it has been shown that the effects of CTLA4-Ig are

mediated by regulatory T cells (Tregs) and transforming growth factor β and require macrophage-derived nitric oxide.

7. **Which is the rationale of interleukin-6 signaling pathway blockade for the treatment of patients with inflammatory arthritis?**

Interleukin (IL)-6 has many physiologic functions and plays an active role in inflammatory responses, bone metabolism, arthritis, and neoplasia. In several inflammatory disorders such as rheumatoid arthritis and systemic-onset juvenile idiopathic arthritis, overproduction of IL-6 has been documented. Interruption of the IL-6 signaling pathway was evaluated as a treatment option for these diseases. Furthermore mice lacking the IL-6 gene were protected from collagen-induced arthritis and in susceptible mice strains antibodies with specificity for IL-6 receptor ameliorate collagen-induced arthritis. On the basis of these studies and observations, clinical trials were initiated with humanized monoclonal anti-IL-6 receptor antibody and indicated that this biologic therapy dramatically improves disease activity and is rather well tolerated.

8. **On what basis led inhibition of IL-17A or IL-17 to its use as a therapeutic agent for rheumatoid arthritis?**

Two experimental observations suggested that IL-17A may play an important role in mediating joint degradation in rheumatoid arthritis. Firstly, in collagen-induced arthritis, a widely accepted experimental arthritis mouse model, IL-17A overexpression accelerated development, enhanced severity of synovial inflammation and bone erosions. Blocking IL-17A with a soluble IL-17 receptor fusion protein suppressed arthritis development and joint damage. Secondly, in human rheumatoid synovial and bone explants, IL-17A enhanced collagen degradation, bone resorption, and blocked collagen synthesis and bone formation. Blocking IL-17A protected against all these effects. In human studies however, IL-17 inhibition either with anti-IL-17 monoclonal antibodies or with monoclonal antibody against IL-17 receptor failed to show a significant therapeutic effect. The therapeutic failure of IL-17 inhibition in rheumatoid arthritis contrasts the significant therapeutic effect of IL-17 inhibition in psoriasis, psoriatic arthritis, and ankylosing spondylitis.

9. **What is the rationale of interleukin-1 signaling pathway blockade for the treatment of patients with inflammatory arthritis and autoinflammatory syndromes?**

Interleukin (IL)-1 (IL-1α and IL-1β) is a master pro-inflammatory cytokine implicated in both local and systemic inflammation. Both IL-1α and IL-1β act on IL-1 receptor and are inhibited by IL-1 receptor antagonist (IL-1Ra). IL-1Ra is a naturally occurring member of the IL-1 family, which blocks the IL-1 receptor type 1. This receptor is expressed on all nucleated cells; therefore, IL-1Ra hinders systemic inflammation induced by IL-1. Infants born with a loss of function mutation in the naturally occurring endogenous IL-1 receptor antagonist (IL-1Ra), a condition called deficiency of interleukin-1 receptor antagonist (DIRA), present overwhelming sterile inflammation of the skin, joints, and bone. This constituted unequivocal evidence of the role of IL-1 in orchestrating inflammation. Mice deficient in IL-1Ra are similarly affected in that they develop spontaneous inflammation resembling rheumatoid arthritis and can succumb to lethal arteritis. The best evidence for the role for IL-1 (either IL-1α or IL-1β) in disease comes from specific blockade, and inhibiting IL-1 by manipulating IL-1Ra became an attractive therapeutic strategy in rheumatoid arthritis (RA) and other chronic inflammatory diseases. The IL-1 receptor antagonist (anakinra) blocks the IL-1 receptor and therefore reduces the activity of IL-1α and IL-1β. Canakinumab is a fully human monoclonal antibody targeting IL-1β, while rilonacept is a soluble decoy receptor. IL-1α is expressed as a precursor and is constitutively present in most cells of healthy subjects. In contrast, IL-1β is not detected in health; is a product of blood monocytes, tissue macrophages, and dendritic cells; and is first synthesized as an inactive precursor. The precursor requires cleavage by caspase-1, which is

activated following the oligomerization of the intracellular protein complex termed inflammasome. Autoinflammatory diseases are due to mutations in the intracellular proteins that control caspase-1, and they constitute a group of rare genetic disorders which are effectively treated with IL-1 blocking therapies. Amyloidosis is a destructive process affecting several organs due to the deposition of amyloid fibrils. IL-1, which is commonly elevated in several chronic inflammatory diseases, is an inducer of serum amyloid A (SAA). Left untreated, IL-1-mediated diseases result in organ failure due to amyloid deposits.

A growing number of chronic inflammatory disorders without a known genetic basis, where IL-1 contributes significantly to the inflammation, respond to reducing IL-1 activity. In adult-onset Still's disease, monotherapy with anakinra is highly effective. Systemic-onset juvenile idiopathic arthritis and macrophage activation syndrome are affectively treated with anakinra. Crystal arthritides (gout and calcium pyrophosphate crystal arthritis) with recurrent attacks and unresponsive to other standards of therapy are highly responsive to anakinra or canakinumab.

10. **On the basis of which facts were anti-CD20 antibodies developed as therapeutic agents for rheumatoid arthritis patients?**

Rituximab, a monoclonal chimeric anti-CD20 antibody originally used in non-Hodgkin's lymphoma, recognizes a determinant expressed on intramedullary pre-B- to B-memory stage lymphocytes. It induces antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis of B cells in various developmental stages leading to their transient but almost complete depletion in peripheral blood, although only partially in the bone marrow and synovial tissue niches. Eliminating B cells by targeting the CD20 cell surface differentiation antigen may remove a large population of cells loaded with pathophysiologically important cytokines, such as TNF-α and IL-6. Concurrent depletion of CD20+ non-B cells and prevention of antigen presentation by eliminating B cells may offer additional effect by leading to a reduction in T-cell activation without primarily affecting co-stimulation. In many rheumatoid arthritis patients, synovial extrafollicular germinal centers develop, where B cells play an important role in local inflammation and the generation of memory B cells and plasma cells. These local processes lead to activation of the immune system and ultimately to joint destruction in rheumatoid arthritis. Administration of anti-CD20 monoclonal antibodies in rheumatoid arthritis patients appears to influence many B-cell functions, such as depletion of memory B cells, interruption of immune activation, antigen-presentation, and production of inflammatory cytokines. The beneficial effect of B-cell depletion therapy of rheumatoid arthritis patients substantiates the notion that B cells are important players in the pathogenesis of the disease.

11. **Which evaluations are mandatory prior to anti-CD20 (Rituximab) monoclonal antibody administration?**

Exclude hepatitis B and C as well as latent tuberculosis infections, and make sure that the patient has been immunized with influenza and pneumococcal vaccines.

12. **On what basis was inhibition of B-lymphocyte-activating factor (BAFF) developed as a therapeutic agent of systemic lupus erythematosus?**

B-lymphocyte-activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS), belongs to the family of tumor necrosis factor ligands. It is expressed by many cell types including hematopoietic and stromal cells. Increased circulating levels of BAFF were found in the sera of patients with systemic autoimmune disorders. Furthermore, inhibition of BAFF in murine experimental systemic lupus erythematosus models resulted in delayed disease onset. These observations led to the development of a human monoclo-

nal antibody (belimumab) which inhibits soluble but not transmembrane BAFF. Clinical studies have shown that belimumab decreases disease activity of patients with moderate active systemic lupus erythematosus.

13. **In which systemic lupus erythematosus patients is anti-BLyS (belimumab) monoclonal antibody administration indicated**?

Belimumab administration is indicated in systemic lupus erythematosus patients that display a mild-to-moderate active disease with acute mucocutaneous and musculoskeletal manifestations, active serology, and disproportionate corticosteroid intake having overall a relapsing-remitting course, despite receiving standard therapy. It is not indicated for systemic lupus erythematosus patients with active neuropsychiatric lupus, severe lupus nephritis, or life-threatening-related manifestations. It has not been studied in combination with other biologics or cyclophosphamide [1].

14. **How do high doses of intravenous immunoglobulins (IVIg) exert their immunomodulatory action?**

IVIg therapy is widely used and is an effective treatment for many autoimmune disorders (idiopathic thrombocytopenia, Kawasaki disease, and inflammatory myopathies). The exact immunomodulatory mechanism(s) of IVIg high doses remains speculative. The proposed immunomodulatory mechanisms include modulation of complement activation, suppression of idiotypic antibodies, saturation of Fc receptors on macrophages, blockade of IgG receptors on phagocytic cells, and blockade of FcRn receptors in endothelial cells, which prevent internalization and catabolism of immunoglobulins in the endosome; thus IVIg by saturating FcRn receptors enables a rapid catabolism of endogenous and possibly pathogenic immunoglobulins in the endosome; in addition IVIg decreases MHC I molecule expression and cytokines, downregulation of transforming growth factor β1, and suppression of various inflammatory mediators, including cytokines, chemokines, as well as metalloproteinases. These mechanisms are not mutually exclusive and may act simultaneously in order to modulate the immune system response.

15. **Which are the specific side effects of the commonly used antirheumatic drugs?**

The majority of antirheumatic, immunomodulatory, and immunosuppressive medications can produce to the patients gastrointestinal discomfort, allergic reactions, and bone marrow suppression and increases their susceptibility to infections. The specific side effects of the commonly used antirheumatic drugs are:

(a) **Methotrexate:** oral ulcers, hepatotoxicity, acute pneumonitis, flu-like symptoms, worsening nodulosis and leukocytoclastic vasculitis in seropositive rheumatoid arthritis patients, and teratogenicity.
(b) **Leflunomide:** hypertension, hepatotoxicity, skin rash, neutropenia/thrombocytopenia, alopecia, and teratogenicity.
(c) **Cyclosporine-A:** hirsutism, gum hypertrophy, hypertension, hyperuricemia, decreased renal function, anemia, lymphoma (EBV-related), and bone pain.
(d) **Hydroxychloroquine:** retinal toxicity, hyperpigmentation of skin, and myopathy.
(e) **Azathioprine:** hepatotoxicity, pancreatitis, hypersensitivity syndrome (rash, fever, hepatitis, renal failure within the first 2 weeks of use), and warfarin resistance. Azathioprine is converted to its active metabolite 6-mercaptopurine by xanthine oxidase and thiopurine methyltransferase (TPMT). In patients concomitantly treated with allopurinol (inhibits xanthine oxidase), it should be used with caution or not at all due to increased toxicity of azathioprine. The activity of TPMT is affected by genetic polymorphisms. Individuals with low enzymatic activity are at risk for severe myelosuppression, in particular 4–10 weeks after onset of treatment with

azathioprine, and in these patients TPMT phenotype activity should be measured.

(f) **Cyclophosphamide**: bladder toxicity (hemorrhagic cystitis, carcinoma), premature menopause, and amenorrhea.

(g) **Anti-TNF drugs** (infliximab, adalimumab, etanercept, golimumab, certolizumab pegol): injection site reactions (for subcutaneous administration of TNF inhibitors), infusion reactions for infliximab (hypotension, headache, nausea, vomiting), infections (reactivation of latent tuberculosis, hepatitis B/C, varicella zoster virus, *Pneumocystis carinii*), demyelinating syndromes (multiple sclerosis-like, Guillain-Barre polyradiculopathy), autoimmune phenomena (some patients will develop positive ANA, anti-dsDNA, and a small number of drug-induced lupus), anti-drug antibodies in patients treated with infliximab (patients may lose response to infliximab and may experience more severe infusion reactions), and psoriasiform rashes.

(h) **IL-1 receptor antagonist** (anakinra): injection site reactions, neutropenia, and infections.

(i) **Anti-IL6 receptor antibody** (tocilizumab): infusion reactions (intravenous administration), infections (rheumatoid arthritis patients with increased baseline DAS28 and peripheral blood absolute neutrophil counts, negative anti-citrullinated peptides, and concomitant leflunomide treatment are at higher risk to develop serious infections after initiation of treatment with anti-IL-6 antibody [2]), elevated hepatic enzymes, neutropenia, lipid elevations (LDL), gastrointestinal tract perforation (rare), and macrophage activation syndrome (in 3% of treated systemic juvenile idiopathic arthritis patients).

(j) **Anti-CD20** (rituximab)**:** infusion reactions, serum sickness, infections, viral infections (reactivation of hepatitis B, JC virus, VZV), hypogammaglobulinemia (after repeated infusions), and late-onset neutropenia (3–4 month post-therapy).

(k) **Intravenous Immunoglobulins (IVIg):** headache, hypotension, flushing, aseptic meningitis, serum sickness, severe anaphylactic reaction in patients with IgA deficiency, acute renal failure especially when sucrose is used as excipient to stabilize the protein in the solution (sucrose-containing IVIgs) and when the patient is concurrently treated with angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, and pseudohyponatremia (due to hyperproteinemia and increased serum viscosity following IVIg infusion).

(l) **D-penicillamine:** dysgeusia, drug-induced lupus, membranous glomerulonephritis, antibody-mediated myasthenia gravis, and Lambert-Eaton myasthenic syndrome, which can persist even after its withdrawal.

(m) **Danazol:** androgenic side effects: hirsutism, acne, irreversible deepening of the voice, adverse blood lipid profiles, breast atrophy and decreased breast size, hot flashes, elevation of liver enzymes, and mood changes.

(n) **Thalidomide:** sensory polyneuropathy, blood clot formation, teratogenic (phocomelia), sedation, and constipation.

(o) **Dapsone:** hemolysis, leucopenia, liver toxicity, and peripheral neuropathy.

(p) **Injectable gold salts:** coloring of the skin in shades of mauve to a purplish dark grey when exposed to sunlight (if the salts are taken on a regular basis over a long period of time). Saturation of skin tissue and organs by gold compounds, a condition known as chrysiasis (can ultimately lead to acute renal failure, severe heart failure, and hematologic toxicity).

(q) **Pilocarpine hydrochloride:** vision changes, increased sweating, dizziness, diarrhea, headaches, increased or frequent urge to urinate, and exacerbation of peptic ulcer.

16. **Hydroxychloroquine retinopathy: what are the risks of toxicity and how often is screening recommended?**

The risk of hydroxychloroquine (HCQ) toxicity is dependent on daily dose and duration of treatment. At recommended doses (≤5.0 mg/kg body weight), the risk of toxicity up to 5 years is less than 1% and up to 10 years is less than 2%, but it rises to almost 20% after 20 years of use. The most significant risk factors for HCQ-related retinopathy are the high dose and long duration of use. Other major factors are concomitant renal disease or use of tamoxifen. A baseline fundus examination should be performed in all patients starting treatment with HCQ to rule out preexisting maculopathy. Annual screening should begin after the first 5 years of use for patients on acceptable doses and without major risk factors. The primary screening tests are automated visual fields and spectral-domain optical coherence tomography. Retinopathy is not reversible, and there is no therapy at present. Recognition at an early stage is important to prevent central visual loss. Patients should be informed about risk of toxicity, proper dose levels, and the importance of annual screening [3].

17. **Which drugs used for the therapy of rheumatic diseases can cause gynecomastia?**
- Methotrexate
- Cyclophosphamide
- Prednisone
- H_2 histamine receptor blockers (cimetidine)

18. **To which patients should acetylsalicylic acid (ASA) not be given?**

Patients most at risk to develop hypersensitivity reactions to ASA are severe asthmatics with nasal polyps (Samter's triad = asthma, nasal polyps, and aspirin sensitivity). Up to 78% of these patients may have a reaction to aspirin. This is considered sensitivity and not allergy because it is not IgE mediated. Inhibition of COX-1 by aspirin diverts the arachidonic precursors down the leukotriene (LT) pathway resulting in excessive production of LTC4, LTD4, and LTE4, which are effective chemoattractants and activators of inflammatory cells. This induces topically chronic sinonasal inflammation resulting in mucosal overgrowth characterizing nasal polyps.

19. **Which nonsteroidal anti-inflammatory and immunosuppressive agents are permitted and which should be avoided in pregnant patients**?

Based on current evidence, nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) are recommended to be used during pregnancy as follows:
- Nonselective cyclooxygenase (COX) inhibitors can be continued during the first and second trimesters. Selective COX II inhibitors should be avoided in pregnancy.
- Glucocorticoids can be continued at the lowest effective dose (preferably less than 10 mg daily) throughout pregnancy. Fluorinated glucocorticoids are less metabolized by the placenta and should be used with caution only to treat fetal problems. Intravenous glucocorticoids can be given, when required.
- Conventional synthetic DMARDs compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, and cyclosporine–A.
- Colchicine can be used throughout pregnancy.
- Intravenous immunoglobulin (IVIg) can be used throughout pregnancy.
- Tacrolimus can be continued throughout pregnancy at the lowest effective dose.
- Leflunomide has been recently shown not to be associated with significantly increased risk of major congenital malformations, prematurity, low birth weight or spontaneous abortions when used during pregnancy [4].
- Methotrexate should be withdrawn 1–3 months before a planned pregnancy.
- Cyclophosphamide must be withdrawn before a planned pregnancy.

- Mycophenolate mofetil (MMF) should be withdrawn 1.5 months before a planned pregnancy.
- Tofacitinib should be stopped 2 months before conception.

20. **Which nonsteroidal anti-inflammatory drugs and immunosuppressive agents are permitted and which should be avoided in lactating patients?**
    - Nonselective COX inhibitors are compatible with breastfeeding, while from the selective COX II inhibitors, only celecoxib should be used during lactation.
    - Glucocorticoids are compatible with lactation, yet they should be taken 2–4 h before breastfeeding.
    - Hydroxychloroquine, cyclosporine, sulfasalazine (caution in cases of premature children, G6PD deficiency, and hyperbilirubinemia), tacrolimus, colchicine, and intravenous immunoglobulin are compatible with breastfeeding.
    - Methotrexate, leflunomide, cyclophosphamide, MMF, and tofacitinib should be avoided during breastfeeding.

21. **Which biologic agents are permitted and which should be avoided in pregnant patients?**

    Biologics differ significantly in structure, half-life, and placental passage. Their placental transfer is low during organogenesis but increases steadily after the 13th week of gestation. Those biologic agents that extensively transfer through the placenta reach high serum levels in the fetus when administered after the 30th week of gestation, thus increasing the risk of postnatal infection.
    - Infliximab and adalimumab can be continued up to the 20th week of gestation. If absolutely indicated, they can be used throughout pregnancy.
    - Etanercept can be used up to 30–32 weeks of gestation, and if strongly indicated, it may be considered for use throughout pregnancy due to its low rate of transplacental passage.
    - Certolizumab may be considered for use throughout pregnancy due to its low rate of transplacental passage.
    - Golimumab should not be considered for treatment during pregnancy because of limited evidence.
    - Rituximab can be used early in gestation only in exceptional cases. Its use at later stages of pregnancy bares the risk of B-cell depletion and other cytopenias in the neonate.
    - Anakinra can be used before and during pregnancy only when there are no other options available for treatment.
    - Tocilizumab, abatacept, and belimumab should be avoided during pregnancy.

    It should be noted that neonates exposed to biologics before gestational week 22 can receive vaccinations according to standard protocols including live vaccines. Whereas, children exposed to biologics at the late second and during the third trimester can follow vaccination programs but should not receive live vaccines in the first 6 months of their life.

22. **Which biologic agents are permitted and which should be avoided in lactating patients?**
    - Infliximab, adalimumab, golimumab, etanercept, and certolizumab are compatible with breastfeeding.
    - Rituximab anakinra, tocilizumab, abatacept, and belimumab should be avoided during breastfeeding.

23. **Are vitamin K antagonists indicated during pregnancy?**

    Vitamin K antagonists (VKAs), such as warfarin, cross the placenta. During the first trimester of pregnancy, especially beyond the eighth week after last menstrual period, VKAs at doses >5 mg daily may account for adverse outcomes, such as miscarriage, stillbirth, and embryopathy. Although warfarin has much lower fetal toxicity at doses ≤5 mg/day than at higher doses, when the dose to achieve the target INR exceeds 5 mg/day, substitution with low molecular weight

heparin (LMWH) during the first trimester, the critical phase of organogenesis, is recommended [5].

LMWH does not cross the placenta and is cleared entirely by the kidneys. In that sense fixed, weight-based dosing tends to underperform as the pregnancy advances, due to the increase in glomerular filtration rate (and clearance of LMWH) throughout pregnancy. Therefore, when LMWH is used during pregnancy, peak anti-Xa level should be checked 4–6 h post-dose, and LMWH carries a low risk of thromboembolic complications when the levels are kept between 1.0 and 1.2 U/ml [6].

24. **Which precautions and measures should be taken before vaccination is administered in adult patients with autoimmune rheumatic diseases?**
    - The vaccination status of the patients should be assessed and documented at the earliest after diagnosis, and recommended vaccinations should be administered as soon as possible, preferably before initiation of immunosuppressive therapy.
    - It is generally safe to administer inactivated vaccines to patients with autoimmune rheumatic diseases under immunosuppressive treatment; the immunogenicity may be reduced.
    - Live attenuated vaccines (MMR, measles, mumps, and rubella; varicella zoster) should only be given before initiation of immunosuppressive treatment (at least 4 weeks).
    - In already treated autoimmune patients, vaccines should ideally be administered when immunosuppressive therapy is at the lowest levels and during stable disease.

25. **How does methotrexate influence the antibody production after seasonal flu vaccine and what immunization protocol is recommended?**

Methotrexate, a widely used immunosuppressant, is known to lower vaccine efficacy in people with rheumatoid arthritis (RA). In a prospective, multicenter, randomized, parallel-group trial comprising 316 RA patients who were taking a stable methotrexate dose it was shown that holding methotrexate for two weeks after vaccination with the seasonal, quadrivalent influenza vaccine (containing H1N1, H3N2, B-Yamagata, and B-Victoria), the vaccine response was significantly improved in RA patients who stopped their regular methotrexate dosing for two weeks after receiving influenza vaccination compared to those who stayed on the medication, without increasing disease activity. Therefore, patients should be advised to hold methotrexate for two weeks after vaccination [7].

26. **Which vaccines are recommended for adult patients with autoimmune rheumatic diseases?**

It is well known that patients with autoimmune rheumatic diseases under immunosuppressive therapy have an increased risk for influenza infection, invasive pneumococcal disease, and for herpes zoster infection. The risk of human papillomavirus (HPV) infection is increased in systemic lupus erythematosus patients, especially with the high-risk (oncogenic) subtypes of the virus, since systemic lupus erythematosus patients demonstrate a decreased spontaneous clearance of the virus leading to an increased risk of developing cervical cancer.

Vaccination recommendations include:

- Annual influenza vaccination.
- Vaccination with the 13-valent pneumococcal conjugate vaccine.
- Vaccination against hepatitis B is encouraged in all patients.
- Vaccination against human papillomavirus in female patients aged 11–26 years should be considered.
- Vaccination can be administered during the use of DMARDs and TNF-inhibitors but before starting rituximab.
- Tetanus toxoid vaccination should be administered in accordance with recommendations for the general population.
- In hyposplenic/asplenic patients, influenza, pneumococcal, hemophilus influenza B,

and meningococcal C vaccinations are recommended.

27. **What are the vaccination recommendations before elective splenectomy and what antibiotic prophylaxis scheme is recommended post-splenectomy?**

In patients with thrombocytopenia (SLE/APS/ITP) not responsive to steroids and newer immunosuppressives (anti-CD20 antibodies and thrombopoietin mimetics), at times elective splenectomy is performed. In these patients it is important to follow a strict pre- and post-splenectomy vaccination schedule in order to minimize the risk of severe infections.

Pre-splenectomy: Initial vaccinations to be given 4–6 weeks before elective splenectomy:

- **Pneumococcus:** since there is no record of previous vaccination in her medical file: Conjugate vaccine (Prevenar 13) 0.5mL IM and after 8 weeks Polysaccharide (Pneumovax 23) 0.5mL IM/SC. One more dose of Polysaccharide (Pneumovax 23) 0.5mL IM/SC 5 years later.
- **Meningococcus:** Conjugate ACWY (Menveo, Menactra, Nimenrix) 0.5mL IM and Recombinant B + (Bexsero) 0.5mL IM followed by a second dose of both 8 weeks later.
- **Haemophilus influenzae type b:** Conjugate Hib (Liquid PedvaxHIB, Hiberix) 0.5mL IM single dose.
- **Influenza:** quadrivalent Influenza vaccine and thereafter yearly every October.

Post-splenectomy:

- **Antibiotic Prophylaxis:** since in the patient's medical history Penicillin allergy (not verified) is mentioned – roxithromycin 150 mg once daily or erythromycin 250 mg once daily or clarithromycin 250mg twice daily should be given lifelong (immunocompromised patient)
- **Emergency plan:** instruct/educate the patient to immediately increase roxithromycin to 300 mg a day or erythromycin 1 gram four times a day (and take all capsules at once) if signs of bacterial infection occur especially if not able to receive prompt medical review [8].

28. **Which vaccines should not been administered in patients with autoimmune rheumatic diseases?**

(a) Live vaccines with a high potential of replication (e.g., yellow fever vaccine) should generally be avoided in patients with autoimmune rheumatic diseases under treatment with immunosuppressive therapy.
(b) BCG vaccination.

29. **Which is the therapeutic algorithm for the treatment of seropositive and seronegative polyarthritis?**

The cornerstone therapeutic agent used initially for both entities is methotrexate (0.2–0.3 mg/kg/week) alone or in combination with small prednisone doses (<7.5 mg/day). If this therapeutic scheme after 3 months of follow-up does not place the arthritis into remission, then another disease-modifying agent should be added to the above therapeutic scheme; either leflunomide (20 mg/qd) or sulphasalazine 2 gm/day or cyclosporine-A (1–3 mg/kg/day) can be used. If this combination is not effective, then in the seropositive polyarthritis group, an anti-CD20 monoclonal antibody or an anti-TNF biologic agent can be prescribed. In the seronegative group, an anti-TNF biologic agent is a preferred therapeutic modality. In a small percentage of either seropositive or seronegative polyarthritis patients that do not respond to the above therapeutic schemes, anti-interleukin-6 receptor monoclonal antibody therapy can be beneficial.

30. **Does anti-TNF therapy increase the risk of lymphoma in rheumatoid arthritis patients?**

Patients with rheumatoid arthritis (RA) have a two times higher risk for lymphoma (both Hodgkin's and non-Hodgkin's lymphomas) development compared to the general population. To date, there is no evidence whether treatment with anti-TNF agents influences the risk of lymphoma development over the background risk in subjects

with rheumatoid arthritis or whether it affects the risk of specific lymphoma subtypes. In a recent large collaborative prospective analysis of European registries, it was shown that cases of non-Hodgkin's lymphoma (NHL) were more frequent than Hodgkin's lymphoma in RA patients and diffuse large B-cell lymphoma (DLBCL) was the most frequent B-cell NHL subtype. Nevertheless, although the lymphoma subtype distribution was different between RA patients and the general population, there was no evidence of any change of the distribution of lymphoma subtypes in patients with RA treated with anti-TNFs compared to patients never having received biologics [9].

31. **An adult patient with rheumatic fever: For how long should the patient be on prophylactic antibiotic therapy?**

All individuals who have had an initial attack of rheumatic fever, whether or not they have rheumatic heart disease, should receive chronic administration of an antibiotic to prevent infection of the upper respiratory tract by group A streptococci. Secondary prophylaxis has been documented to reduce significantly the risk of recurrent attacks and associated morbidity and mortality. Regular intramuscular injection of repository penicillin (benzathine benzylpenicillin) is the most effective available treatment. Although classically given every 4 weeks, recent data indicate that 1,200,000 units of benzathine benzylpenicillin given every 3 weeks is more effective in preventing recurrences of rheumatic fever, especially in high-risk patients.

32. **Which are the therapeutic steps to treat adult-onset Still's disease?**

In mild to moderate disease, prednisolone 0.5–1 mg/kg/day in combination with methotrexate (0.2–0.3 mg/kg/week) is initiated. Methotrexate is added as an anti-inflammatory and steroid-sparing agent. In severe disease with poor prognostic factors, high doses of steroids (prednisolone 1 mg/kg/day) in combination with methotrexate (0.2–0.3 mg/kg/week) and biologic agents, either anti-IL-1 receptor antagonist (anakinra) or anti-IL-6 receptor antibody (tocilizumab), should be given [10, 11].

33. **In which systemic lupus erythematosus manifestations is methotrexate indicated?**

It is predominantly indicated in arthritis. The administration of methotrexate significantly reduces systemic lupus erythematosus disease activity index (SLEDAI) and the average daily dose of corticosteroids in adult patients with systemic lupus erythematosus [12].

34. **In which systemic lupus erythematosus patients is monthly pulse intravenous cyclophosphamide indicated alone or in combination with methylprednisolone?**

It is indicated in systemic lupus erythematosus patients with life- or major organ-threatening disease, like proliferative glomerulonephritis, central nervous system involvement, mesenteric vasculitis, and diffuse pulmonary hemorrhage. It is more effective when given in combination with methylprednisolone intravenous pulses.

35. **Describe the evidence-based therapeutic intervention for the induction and maintenance therapy of lupus nephritis classes III, IV, and V.**

In general, for the treatment of lupus nephritis, immunosuppressive agents are recommended in class III_A or $III_{A/C}$ and IV_A or $IV_{A/C}$ nephritides and also in pure class V nephropathy if proteinuria exceeds 1 g/24 h despite the optimal use of renin-angiotensin-aldosterone axis blockers. Treatment should aim for complete renal response with proteinuria <0.5 g/24 h and normal or stable glomerular filtration rate (GFR). Response to treatment defined as ≥50% reduction in proteinuria and stability or improvement in GFR should be achieved by 6–12 months after initiation of treatment.

Induction therapy

- *Class III/class IV lupus nephritis:*

– IV pulse methylprednisolone (0.5–1 g) daily for 3 days followed by prednisolone 1 mg/kg/day (if crescents are present in the biopsy) or 0.5 mg/kg/day (if no crescents present in the biopsy) tapered after a few weeks to lowest effective dose.

plus

– mycophenolate mofetil (MMF) 2–3 g/day for 6 months (preferred to cyclophosphamide in African-American and Hispanic patients)

or

– cyclophosphamide (CYC): high-dose IV (0.5–1 g/m^2 body surface area monthly × 6 doses) or low-dose IV (500 mg every 2 weeks × 6 months).
– Patients who fail to improve on MMF should be switched to CYC. Patients who fail CYC are switched to MMF. Patients who fail to respond to both are candidates for rituximab (RTX) or calcineurin inhibitors (cyclosporine, tacrolimus).

- *Class V lupus nephritis*:

– Oral prednisolone 0.5 mg/kg/day for 6 months plus MMF 2–3 g/day for 6 months.
– Patients who fail to improve on MMF are switched to high dose CYC IV for 6 months.

Maintenance therapy

Azathioprine (2 mg/kg/day) or MMF (2 g/day). Each of these drugs is given in association with a dose of prednisolone to control extrarenal manifestations, and prednisolone is tapered over time. Although there are no strict guidelines on the duration of maintenance treatment, it is recommended for at least 3 years. RTX has also been used as maintenance therapy when patients fail or cannot tolerate azathioprine or MMF.

Adjunctive therapy

In cases of active lupus nephritis, the following should be added to treatment:

– Hydroxychloroquine
– Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker if proteinuria ≥0.5 g/24 h
– Control blood pressure (≤130/80)
– Statin therapy if LDL >100 md/dL
– Counsel against pregnancy while nephritis is active [13]

36. **Which are the predictors of sustained amenorrhea from intravenous cyclophosphamide pulses in premenopausal women with systemic lupus erythematosus?**

Sustained amenorrhea is difficult to be avoided in women 32 years or older, even with very short intravenous cyclophosphamide courses. In these patients alternative regimens should be considered. In younger women treated with a monthly intravenous cyclophosphamide regimen, sustained amenorrhea may occur predominantly in those with the recognized adverse predictors like longer systemic lupus erythematosus disease duration and autoantibodies to Ro/SSA and U1RNP autoantigens [14].

37. **What is the oral anticoagulation treatment used in a patient with primary antiphospholipid syndrome?**

Treatment for antiphospholipid syndrome (APS) patients is based on the patient's clinical status, levels of antiphospholipid antibodies (aPL), and history of thrombotic events.

– In case of an asymptomatic patient with aPL positivity without previous thrombotic events, the treatment is mainly focused on reduction of modifiable vascular risk factors (smoking, lipid profile, hypertension, diabetes mellitus, birth control pills). In these patients the use of acetylsalicylic acid (ASA) is controversial.
– APS patients who have had a venous thrombosis, after initial low-molecular-weight heparin (LMWH) therapy, should be placed on life-long anticoagulation with warfarin at a target INR of 2.5 (range 2.0–3.0).
– In APS patients with a history of cerebral arterial thrombosis, combination of antiplatelet agents (ASA plus clopidogrel) or warfarin plus ASA is used based on the risk assessment for recurrence.
– In APS patients with a previous noncerebral arterial thrombotic event, ASA plus clopidogrel or ASA plus warfarin is used in cases of noncardiac arterial thrombus, while in cases of cardiac arterial thrombus and high risk of recurrence war-

farin, ASA and clopidogrel are the combination treatment preferred.
- Direct oral anticoagulants, which inhibit directly a single enzyme of the coagulation cascade, such as a direct thrombin inhibitor (dabigatran etexilate) and direct anti-Xa inhibitors (rivaroxaban, apixaban, and edoxaban), are currently available. Existing evidence suggests that the use of direct oral anticoagulants for secondary thromboprophylaxis for APS patients with previous venous thrombotic event could be promising. Yet, until new data are available from ongoing clinical trials, there is not enough evidence to consider using them in patients with APS and previous arterial events [15].

38. **What is the evidence-based therapeutic intervention in order to prevent maternal morbidity in a female with antiphospholipid syndrome?**

As soon as pregnancy is achieved in an antiphospholipid syndrome patient, in order to prevent abortion, intrauterine growth retardation of the embryo, or stillbirth, daily administration of acetylsalicylic acid (aspirin) 80 mg daily should be started as well as hydroxychloroquine 200–400 mg/day. Subcutaneous administration of small molecular weight heparin (prophylactic or therapeutic doses) is usually started at 8 weeks of pregnancy.

39. **What are the benefits from hydroxychloroquine administration in an antiphospholipid syndrome patient?**

It prevents thrombotic episodes and pregnancy morbidity [16].

40. **Which is an effective therapeutic scheme for acute dermatomyositis (DM)?**

Standard therapeutic approach for DM consists of high prednisolone dose (1 mg/kg) either p.o. or intravenously in combination with immunosuppressive agents (methotrexate or azathioprine or cyclosporine-A) which will reduce inflammation and will permit to taper the prednisolone dose. Methotrexate 1.5–3 mg/kg body weight/week and cyclosporine-A 1–3 mg/kg body weight/day have similar therapeutic effect. Azathioprine 1.5–3 mg/kg/day is equally effective to methotrexate, but its therapeutic effects are delayed by 2–3 months.

In serious cases monthly administration of intravenous immunoglobulin pulses (2 g/kg body weight) in 2 consecutive days for 6 months should be added to the above regimen and can speed recovery. When the acute phase subsides, physical therapy should be instituted to prevent muscle atrophy, regain muscle strength, and range of motion.

41. **In which types of inflammatory myopathies have intravenous monthly pulses of immunoglobulins been proven to be effective?**

Intravenous monthly pulses of immunoglobulins has been proven to be effective in different types of dermatomyositis. In polymyositis some effectiveness has been shown in uncontrolled studies. In sporadic inclusion body myositis, it does not improve muscle symptoms, but it may only improve dysphagia.

42. **In which Sjögren's syndrome patients can hydroxychloroquine be beneficial?**

It is usually prescribed for fatigability and arthralgias/arthritis in Sjögren's syndrome patients, despite the fact that double-blinded, placebo-controlled studies have shown that hydroxychloroquine is not superior to placebo. The only definite hydroxychloroquine effect is the decrease of serum immunoglobulin levels in Sjögren's syndrome patients with hypergammaglobulinemia [17].

43. **Which therapeutic agents are used in the treatment of rapidly progressive systemic sclerosis?**
- Cyclophosphamide (CYC) treatment has been shown to stabilize or mildly improve—in terms of lung volume measurements in pulmonary function tests—systemic sclerosis (SSc) patients with rapidly progressive interstitial lung disease. However, the beneficial effects of

CYC do not persist more than 12 months following its cessation.
- D-Penicillamine is known to exert a strong anti-fibrotic effect by interfering with collagen cross-linking and by accelerating collagen turnover even at low doses and is used for rapidly progressive cutaneous involvement in SSc.
- Mycophenolate mofetil (MMF) has been effectively used for rapidly progressive cutaneous involvement in SSc. Of note, SSc patients with shorter disease duration seem to obtain greater benefit from MMF therapy, showing more pronounced improvement in skin fibrosis.
- Methotrexate can be used for less severe skin progression and for patients unable to tolerate mycophenolate.
- Rituximab has been shown to induce improvement in SSc-cutaneous and lung involvement, but results from prospective double-blind RCTs are still waited.
- Novel agents involved in the fibrotic and inflammatory pathways of SSc pathogenesis, including tocilizumab, pirfenidone, tyrosine kinase inhibitors, lipid lysophosphatidic acid 1, and NOX4 inhibitors, are currently investigated for the treatment of rapidly progressive SSc [18].

44. **What is the potential pharmacological treatment of Raynaud's phenomenon associated with systemic sclerosis?**

Besides general measures, such as avoidance of cold exposure, maintaining high core body temperature, use of gloves and socks, and cessation of smoking, systemic sclerosis (SSc) patients with Raynaud's phenomenon could benefit from some pharmacological intervention:
- Calcium channel blockers (e.g., nifedipine) demonstrate a moderate reduction in frequency and severity of attacks of Raynaud's phenomenon in patients with SSc and do not seem to reduce digital ulceration. Diltiazem has also been trialled as a treatment for Raynaud's phenomenon but does not seem to be effective in SSc-associated Raynaud's phenomenon. Common side effects include hypotension, headache, and peripheral edema.
- Angiotensin receptor antagonists, angiotensin-converting enzyme inhibitors, and α-adrenergic receptors have not been effective in the management of SSc-associated Raynaud's phenomenon.
- Intravenous iloprost (prostacyclin), a potent vasodilator that is effective in the treatment of Raynaud's phenomenon, reduces the frequency and severity of attacks and the development of digital ulcers. The most common side effects are headache, flushing, hypotension, and nausea, which can be controlled by reducing the rate of infusion.
- Phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, tadalafil) increase cyclic guanosine monophosphate-dependent microvascular and macrovascular vasodilation. Several case reports and small studies suggest improvement in Raynaud's phenomenon in patients treated with phosphodiesterase inhibitors. Adverse side effects include headache, flushing, and dizziness, but they are generally well tolerated.
- The endothelin receptor antagonist bosentan is used for the treatment of pulmonary arterial hypertension. It has an emerging role in the treatment of Raynaud's phenomenon and digital ulcers in SSc patients. A multicenter, randomized, placebo-controlled, double-blind study showed that bosentan may be effective in preventing new digital ulcers; however, no benefit was demonstrated for healing of existing ulcers. Both phosphodiesterase inhibitors and endothelin receptor antagonists are approved for the treatment of pulmonary arterial hypertension, which may coexist in patients with SSc [19–21].

45. **What is the treatment of giant cell arteritis and polymyalgia rheumatica?**

The cornerstone for giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) treatment are glucocorticoids (GC). In line with consensus-based recommendations, ini-

tial therapy for PMR is 12.5–25 mg/day prednisone or equivalent and 40–60 mg/day for GCA, followed by individualized tapering regimens in both diseases. Intramuscular methylprednisolone can be considered as an alternative to oral GCs in some cases of PMR. There are few studies supporting the use of methotrexate in addition to GCs, particularly in patients at a high risk for relapse and/or prolonged therapy as well as in cases with risk factors, comorbidities, and/or concomitant medications where GC-related adverse events are more likely to occur, yet its efficacy is controversial. In a recent placebo-controlled trial, more GCA patients receiving subcutaneous tocilizumab, weekly or every other week, compared to the placebo group remained relapse-free after 52 weeks. The use of tocilizumab led to a significantly lower cumulative prednisolone dose in the tocilizumab group versus the placebo group. However, further studies are needed to substantiate the use of tocilizumab as a therapeutic modality for GCA.

46. **What is the role of biological agents in the management of large vessel vasculitis (LVV)?**

Giant cell arteritis (GCA) and Takayasu arteritis (TKA) affect both large vessels. Since prolonged treatment with high doses of glucocorticoids used in LVV causes serious side effects and therapeutic effects of conventional immunosuppressive agents (methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide) have overall been disappointing, biological agents have been tried in the treatment of LVV. Tumor necrosis factor (TNF)-α blockers are ineffective in GCA, while observational evidence and a phase 2 randomized trial support the use of tocilizumab in relapsing GCA. Observational evidence strongly supports the use of anti-TNF-α agents and tocilizumab in TKA patients with relapsing disease. However well-designed studies are desperately needed in order to increase our understanding of the potential role of biological agents in the management of LVV [22–24].

47. **How is granulomatosis with polyangiitis treated?**

The induction therapy for granulomatosis with polyangiitis (GPA) with major organ involvement consists of: IV methylprednisolone pulses (1 g) for 3 consecutive days plus monthly IV pulses of cyclophosphamide (0.5–1 mg/m^2 body surface area) for 6 months. Another equally effective alternative to cyclophosphamide is rituximab (two doses of 1000 mg given 2 weeks apart). After 6 months of induction therapy and if remission has been achieved, less toxic immunosuppressives can be used to maintain remission, such as azathioprine (2 mg/kg/day). In addition to immunosuppressive therapy, oral trimethoprim/sulfamethoxazole should be used prophylactically for recurrent Staphylococcus aureus sinus infections that can exacerbate GPA.

48. **Which is the preferred therapeutic agent for induction therapy in Churg-Strauss vasculitis and which agent is prescribed to spare steroid side effects?**

The treatment of choice for induction therapy in Churg-Strauss vasculitis are glucocorticoids. In patients with more than one risk factor (serum creatinine >1.6 mg/dL, proteinuria >1 g/24 h, central nervous system involvement, gastrointestinal tract involvement, myocardial involvement), cyclophosphamide monthly pulses should be added (0.5–1 mg/mm^2 body surface area). Those with severe presentations may benefit from plasmapheresis. Milder cases may be treated with azathioprine (2 mg/kg/day), methotrexate (0.2–0.3 mg/kg/week), or mycophenolate mofetil (2–3 g/day). In refractory cases, rituximab and interferon-a have been used with some success.

49. **How is panuveitis of Behcet's syndrome treated?**

If the patient has severe eye disease defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease (retinal vasculitis or macular involvement), it is recommended to receive either cyclosporine-A (2–3 mg/kg body weight/day) or infliximab

in combination with azathioprine (1–3 mg/kg body weight/day) and corticosteroids. Alternatively interferon (IFN)-α with or without corticosteroids can be used.

50. **How are the acute episodes of gout and pseudogout treated?**

Gout:

- Nonsteroidal anti-inflammatory drugs, e.g., Indomethacin 50 mg, four times daily for 24–48 h, and then 50 mg, three times daily for 48 h; taper and discontinue after the attack subsides.
- Oral colchicine: 1 mg followed by 0.5 mg 1 h later. Most effective within the first 36 h of the attack. Contraindicated in elderly with significant renal/hepatic insufficiency, avoid concomitant use with other P450 inhibitors (e.g., cyclosporine-A).
- Systemic corticosteroids: prednisolone 0.5 mg/kg/day for 5–10 days or for 2–5 days and then taper for 7–10 days or triamcinolone acetate IM 60 mg (can be repeated once).
- Intra-articular steroids**:** first septic arthritis should be excluded, and then triamcinolone or methylprednisolone (40 mg for large joints, 10–20 mg for small joints/bursae) can be administered. Effective within the first 24 h of the attack.
- Canakinumab as an IL-1β blocking agent has been shown to reduce the risk of acute gouty arthritis flares during initiation of allopurinol treatment and has been proven to be a valuable therapeutic agent for patients with limited treatment options.

Pseudogout: Administration of nonsteroidal anti-inflammatory drugs or colchicine or intra-articular triamcinolone or triamcinolone intramuscular. All the above agents are known to interrupt acute pseudogout attacks. In addition, treatment or elimination of offending agents or pathologies (hyperparathyroidism, hypomagnesemia, hemochromatosis, hypophosphatasia, drugs causing hypercalcemia/hypophosphatemia: loop-thiazide diuretics, proton pump inhibitors, cyclosporine-A, tacrolimus, intravenous bisphosphonates) is mandatory.

51. **Is the maintenance therapy for gout and pseudogout similar or different? What are the sequelae if these disorders are left untreated?**

Gout: life-long therapy with an antihyperuricemic drug is indicated in cases of: (a) more than two to three acute gouty attacks occurring in 1–2 years, (b) renal stones (urate or calcium), (c) tophaceous gout, and (d) established gout with chronic kidney disease. A xanthine oxidase inhibitor (allopurinol, febuxostat) is first-line therapy (starting dose of allopurinol 100 mg/day, with gradual upward titration, maximum daily dose 800 mg always adjusted to glomerular filtration rate). The goal of treatment is to maintain the serum uric acid <6 mg/dL or <5 mg/dL in tophaceous gout. If gout is untreated, urate nodules (tophi) under the skin can develop in several areas (fingers, elbows, Achilles tendons), and bony erosions, urate nephropathy, uric acid nephrolithiasis, and heart disease are possible sequelae.

Pseudogout: Most patients only have few attacks that are widely separated in time; thus prophylaxis is not required against pseudogout. For patients with frequent attacks, colchicine at a dose of 0.5 mg twice daily prevents recurrences.

52. **How effective are oral glucosamines for the treatment of osteoarthritis?**

Although widely used, oral glucosamine treatment for osteoarthritis (OA) has been strongly debated for several years, and open trial data are not available. In a recent meta-analysis, it has been shown that any oral glucosamine substance used in patients with clinically or radiographically defined hip or knee OA was no better than placebo for altering pain severity or function restriction neither after short- (3 months) nor after long-term (24 months) follow-up [25].

53. **How should the therapeutic regimen of adult patients on traditional disease-modifying antirheumatic drugs, biologic agents, and glucocorticoids be modified if they undergo elective total hip or total knee arthroplasty?**
    - For patients with rheumatoid arthritis (RA), spondyloarthropathies (SpA, including ankylosing spondylitis and psoriatic arthritis), juvenile idiopathic arthritis (JIA), or systemic lupus erythematosus (SLE) undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA):
    - The current dose of methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine should be continued.
    - For SLE patients not treated (induction or maintenance) for severe organ manifestations:
    - The current dose of mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus should not be given 1 week prior to elective THA or TKA surgery.
    - For RA, SpA, JIA, or SLE patients on biologic agents:
    - All biologic agents should be discontinued prior to surgery in patients undergoing elective THA or TKA, and the surgery should be planned at the end of the dosing cycle for each specific biologic.
    - Biologics in these patients can be restarted once wound healing is established (approximately 14 days), all sutures/staples are out, and there is no clinical evidence of surgical and nonsurgical site infections.
    - For RA, SpA, or SLE patients on glucocorticoids:
    - The current daily dose should be continued in these patients undergoing THA or TKA, rather than administering perioperative supraphysiologic glucocorticoid doses (the so-called stress dosing).
    - An increased arthroplasty-related infection risk exists with long-term use of prednisone (or equivalent) dose >15 mg/day. Therefore careful tapering of prednisone dose prior to surgery to <20 mg/day, when possible, is advisable [26].

54. **What is the treatment of fibromyalgia?**

    The treatment of fibromyalgia demands a multidisciplinary approach that involves physical, pharmacological, and cognitive measures. Current evidence suggests that small doses of tricyclic antidepressants, aerobic exercise, cognitive behavioral therapy, and patient education can be effective in treating fibromyalgia. However, poor compliance of fibromyalgia patients to all these measures is an important issue firstly due to slow or unsatisfactory clinical response and secondly due to inadequate patient education [27].

55. **Which are the general measures for osteoporosis treatment in postmenopausal women not on glucocorticoid therapy?**
    - Modify the modifiable risk factors (smoking, alcohol, low body weight, sun exposure, calcium/vitamin D3 intake, low physical activity, amenorrhea).
    - Assess fracture risk using dual-energy X-ray absorptiometry (DEXA) scan (T and Z scores) or FRAX tool.
    - Provide sufficient calcium through diet or supplements: at least 120 mg elemental calcium/day and 800–1000 IU/day vitamin D3 for patients older than 50 years of age.

56. **Which are the indications for treatment of osteoporosis in postmenopausal women not on glucocorticoid therapy?**
    - Treat patients with bone mineral density (BMD) T score ≤ -2.5 at femoral neck or spine.
    - Treat postmenopausal women and men >50 years of age who have osteopenia (T score between -1 and -2.5) and a 10-year probability for hip fracture $\geq 3\%$ or a 10-year probability for major osteoporotic fracture $\geq 20\%$ (as assessed by the FRAX tool).
    - Start therapy for patients with hip or vertebral fracture.
    - Monitor BMD every 5 years.

57. **What is the therapeutic algorithm for the treatment of low bone density or osteoporosis to prevent fractures in men and women?**
    - Women with known osteoporosis should be offered treatment with bisphosphonates (alendronate, risedronate, zoledronic acid) to reduce the risk for hip and vertebral fractures. Women who cannot tolerate bisphosphonates and are at high risk for fragility fractures could benefit from subcutaneous administration of denosumab.
    - Osteoporotic women should be treated with pharmacologic therapy for 5 years, and during that time, bone density monitoring is not necessary.
    - In men with clinically recognized osteoporosis, pharmacologic treatment with bisphosphonates should be offered to reduce the risk for vertebral fracture.
    - It is *not* recommended to use menopausal estrogen therapy alone or in combination with progesterone or raloxifene for the treatment of osteoporosis in women.
    - In the case of patients with severe osteoporosis, especially accompanied by fractures or patients who cannot tolerate bisphosphonates or patients who have not responded to other drugs, teriparatide is indicated. Therapy should not exceed 2 years, and it should not be given to patients with bone metastases, Paget's disease, skeletal irradiation, or unexplained increased of serum alkaline phosphatase.
    - Clinicians should decide whether to treat osteopenic women 65 years of age or older, who are at a high risk for fracture based on a discussion of patient preferences, benefits, harms, and costs of medications [28].

58. **In which osteoporotic patients' drug holiday of bisphosphonate therapy is indicated?**

    Patients at high fracture risk should be maintained on bisphosphonate therapy without drug holiday (DH). In low- and moderate-risk osteoporotic patients, DH should be implied after 3–5 years of bisphosphonate use. In these patients, a bone density reevaluation is recommended every 1–3 years depending on the bisphosphonate used. If after drug holiday, assessment shows an increased risk of fracture, patients may benefit from initiating another treatment such as teriparatide or denosumab.

59. **What is the therapeutic algorithm for the treatment of glucocorticoid-induced osteoporosis in premenopausal women and men <50 years of age?**

    The therapeutic approach of glucocorticoid-induced osteoporosis differs according to the age group of the patients:
    - If there is no fragility fracture, there is no strict recommendation, and prevention is based on clinical judgment and assessment of fracture risk factors.
    - If there is a fragility fracture, the approach differs:

    – In women without childbearing potential or men aged <50:
      If glucocorticoid therapy lasts up to 3 months: alendronate or risedronate (for prednisolone ≥5 mg/day) or zoledronic acid (for prednisolone ≥7.5 mg/day)
      If glucocorticoid therapy lasts for more than 3 months: alendronate, risedronate, zoledronic acid, or teriparatide, independently of daily prednisolone dose
    – In women with childbearing potential:
      If glucocorticoid therapy lasts up to 3 months: the decision whether to initiate treatment or not should be based on assessment of fracture risk factors and should be individualized for each patient.
      If glucocorticoid therapy lasts for more than 3 months: alendronate, risedronate, zoledronic acid, or teriparatide, if prednisolone ≥7.5 mg/day.

60. **What is the therapeutic algorithm for the treatment of glucocorticoid-induced osteoporosis in postmenopausal women and men >50 years of age?**

    Initially in patients with an anticipated glucocorticoid therapy duration of ≥3 months, or prevalent duration of at least

3 months, the patient's risk category should be determined. High-, medium-, and low-risk patient classification is based on an approximation of FRAX using age, sex, race, T score, and the presence of glucocorticoids for the calculation.

- **In low-risk patients**: treatment should be initiated if prednisolone ≥7.5 mg/day: alendronate, risedronate, or zoledronic acid.
- **In medium-risk patients**:

– If prednisolone <7.5 mg/day: alendronate or risedronate
– If prednisolone ≥7.5 mg/day: alendronate, risedronate, or zoledronic acid

- **In high-risk patients**:

– If prednisolone <5 mg/day or treatment duration <1 month: alendronate, risedronate, or zoledronic acid
– If prednisolone 5 mg/day for ≤1 month or any dose of glucocorticoids used for >1 month: alendronate, risedronate, zoledronic acid, or teriparatide

61. **Which are the side effects of bisphosphonates?**

Side effects are esophageal irritation (esophagitis) (for the orally administered), osteonecrosis of the jaw, musculoskeletal pains, uveitis (rarely), and atypical femur fractures (subtrochanteric/femur shaft, can be bilateral, often present with a prodromal of thigh pain, typically occurs in patients that have been treated for longer than 5 years). Flu-like symptoms (fever, myalgias, and arthralgias) occur in almost 10% of patients after the first intravenous dose of bisphosphonate.

62. **What therapeutic interventions can be used for acute, subacute, and chronic low back pain?**

The noninvasive pharmacologic and non-pharmacologic interventions for the treatment of **acute** (<4 weeks), **subacute** (4–12 weeks), and **chronic** (>12 weeks) **low back pain in adults** should include the following:

– Since **acute or subacute** low back pain may improve over time regardless of treatment superficial heat, massage, acupuncture, or spinal manipulation should be proposed by clinicians as initial non-pharmacologic approach. If pharmacologic treatment is anticipated, nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants should be preferred.
– Patients with **chronic** low back pain should initially be advised to exercise, take part in multidisciplinary rehabilitation, acupuncture, tai chi, yoga, mindfulness-based stress reduction programs, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation. If this group of patients does not respond adequately to the above interventions, nonsteroidal anti-inflammatory drugs should be used first and thereafter, as second-line treatment, tramadol or duloxetine. Opioids should be considered only in patients who have not responded to any of the aforementioned treatments and only if the potential benefits prevail over the risks for individual patients [29].

63. **What are the effects of repeated intra-articular triamcinolone used in patients with symptomatic knee osteoarthritis?**

In clinical practice, intra-articular corticosteroids are widely considered the most rapidly effective non-surgical therapeutic modality for knee osteoarthritis and typically provide a substantial post-injection pain relief.

However, it has been shown that in patients with symptomatic knee osteoarthritis repeated (every 3 months) intra-articular triamcinolone results, after two years, in significantly greater cartilage loss without significant reduction in knee pain, compared to intra-articular saline injection. These findings do not support the use of frequently repeated intra-articular corticosteroids for treating patients with symptomatic knee osteoarthritis [30].

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