Rheumatic Disease in Geriatrics

Diagnosis and Management

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Chapter 10
Interpretation of Laboratory Tests in a Geriatric Patient with Rheumatic Disease

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10.1 General Considerations on Immunological Biomarkers in Laboratory Diagnostics

Starting with the Jones Criteria for the Diagnosis of Acute Rheumatic Fever (1944), the diagnosis of most autoimmune diseases (AID) was based on clinical and laboratory data, and the value and weight of laboratory criteria are continuing to increase [1]. Nowadays, criteria for most rheumatic AID generally include laboratory tests.

Autoantibodies are immunoglobulins of G, A, and M (IgG, IgM, IgA) classes that bind to antigenic epitopes of the human organism's molecules. Self-epitopes of molecules of the human organism become targets of autoantibodies due to antigenic similarity with exogenous structures [2]. Thus, it is difficult to accurately separate the pathological autoimmune response from the natural reaction of the human immune system.

Sometimes, identification of autoantibodies in patients with AID indicates their involvement in the mechanisms of the pathogenic autoimmune reaction. However, autoantibodies do not always contribute to the development of processes that are characteristic of AID. In such cases, autoantibodies are thought to be "witnesses" of immunological reactions. On the other hand, autoantibodies can carry an independent immune function, for example, participate in the clearance of tissue antigens. Antinuclear antibodies (ANA) are often observed in "graft versus host disease" and in cases of solid tumors, which can be explained by an alloimmune response or antitumor immunity [3]. In these examples, autoantibodies are components of the natural immune response. The induction of autoantibodies synthesis is a normal biological phenomenon, and the binding of immunoglobulins to their self-antigens can be detected in the blood serum of any person. The spectrum of antigenic stimuli

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affecting a person is continually changing, which leads to the formation of low-affinity non-pathogenic autoantibodies. Low titers of low-affinity autoantibodies with multiple reactivities can be detected almost in every individual. Clinically significant levels of autoantibodies may be an accidental finding in clinically healthy adult individuals. As such, ANA can be detected in 3–5% of the population (mostly women), rheumatoid factor (RF)—in 3%, antibodies to thyroperoxidase—in 4%, antibodies to cardiolipin—in 1–5%, antibodies to myocardium—in 5%, and antibodies to skeletal muscle—in 3% (mainly in the elderly). This phenomenon is called "natural autoantibodies", and its biological significance is not well understood [4]. The role of these autoantibodies is not entirely clear, but this phenomenon probably reflects the contribution of the immune system to a process that is commonly called immune surveillance [5].

Aging is associated with the formation of a large number of autoantibodies [6]. The leading cause of increased autoantibody production in elderly persons is believed to be the involution of thymic tissue after the age of 50 years and, therefore, termination of several processes that are important for the formation of immunological tolerance of T cells. There are several other changes in the biology of T and B cells at an older age that are described elsewhere [7].

The frequency of detection of different autoantibodies in elderly persons is presented in Table 10.1. There is some variation in frequencies of autoantibodies detection among scientific reports. That discrepancy is easily explained by differences in test performance, reference ranges, and comorbidities in the tested cohorts, but the average incidence of many autoantibodies in older people is 5–10 times higher than in a healthy young population.

The possibility to utilize specific autoantibodies as a diagnostic marker is determined by their frequency in AID. The prevalence of those autoantibodies that are used for clinical diagnosis of AID is usually more than in 60–80% of patients with the

Table 10.1 Relative frequency of antibodies in older adults without evident autoimmune disease

Autoantibody	Relative frequency in elderly vs. adult	Clinical significance
ANA HEp-2 IIF	11.4% in elderly vs. 3.8% in adults (high titers) [8]	Seropositivity in elderly is related to female gender [9], vitamin D deficiency [10], *HLA* genotype [8]
Anticardiolipin antibodies	12% in elderly vs. 2% in adults (high titers) [11]	Seropositivity in elderly is related to ANA positivity [11], CVD in elderly group [12]
Rheumatoid factor	16.6% in elderly vs. 3.6% in adults [13]	Risk of RA development depends on initial levels of RF and its increase in titer during the time [14]
Gastric parietal cell antibodies	18% in elderly vs. autoantibodies absent in adults [15]	Seropositivity was related to *H.pylori* seropositivity and presence of thyroid diseases
Antibodies to thyroid antigens	26% in elderly vs. 4% in adults [15]	Subclinical hypothyroidism in 4.70% of European population [16]

ANA antinuclear antibodies, *CVD* cerebrovascular disease, *RA* rheumatoid arthritis, *IIF* indirect immunofluorescence, *RF* rheumatoid factor

specific disorder and, optimally, less than 5% in healthy controls and relatively rare in patients with other diseases. The proper clinical and laboratory parameters of many autoantibodies allow us to consider them as laboratory markers of AID with exceptional diagnostic information. Specific serological markers are those autoantibodies that are found exclusively in studied disease. As such, highly-specific serological markers include antibodies to double-stranded DNA (anti-dsDNA) and anti-Sm antibodies, that are used for diagnosis of systemic lupus erythematosus (SLE), and antibodies to the Scl-70 antigen, that are used for systemic sclerosis (SSc) diagnosis.

The identification of specific autoantibodies in AID can predict the characteristic features of the clinical course of the disorder. The best example of that phenomenon is the presence of specific autoantibodies in inflammatory myopathies that readily characterize unique features of muscle involvement, rate of progression, and occurrence non-muscular symptoms. Even low-prevalent autoantibodies typically specify some peculiar disease manifestation valuable for clinical classification and prognosis. So-called disease phenotypes are generally characterized by the presence of a specific set (or spectrum) of antibodies. Antibody profiling, which means the investigation of a wide range of autoantibodies, is an essential tool for personalized medicine in the field of autoimmunity. Furthermore, during differential diagnosis, a combination of positive antibody test results makes the final diagnosis more convincing. Therefore, the determination of some autoantibodies allows the physician not only to predict, but sometimes also to prevent the development of complications.

In AID, specific antibodies are synthesized in high concentration and usually have high affinity. However, high concentrations of low-affinity autoantibodies can sometimes give a more reliable signal than a low concentration of high-affinity specific autoantibodies. The detection of nonspecific binding of autoantibodies in some immunological tests and the detection of low titers of autoantibodies often require the creation of a “gray zone”, or a range of doubtful results. Low titers are not considered disease-specific like, for example, in the cases of low titers of antibodies against cardiolipin in APS, low titers of RF, and ACPA in RA. From a clinical point of view, at low concentrations, the interpretation of the result of autoantibodies low concentration depends on the clinical risk of AID.

Despite specific difficulties in interpreting the results of the immunological tests, as well as a large amount of information that must be taken into account analyzing the results of the test, the clinical significance of immunological tests is very high.

10.2 Antinuclear Antibodies Testing in Systemic Autoimmune Rheumatic Diseases

ANA is a family of autoantibodies directed against various cellular structures, including the nucleus, nuclear membrane, mitotic apparatus, components of the cytoplasm and organelles of the cell, as well as cell membranes. Since ANA antigens are not only found in the nucleus, the term ANA may be misleading and outdated.

There was an attempt to re-name the ANA into “anti-cellular” antibodies; however, the term ANA is presented in a large number of specialized literature and recommendations for many medical specialties, and therefore it is not easy to replace it. The detection of ANA represents an indispensable approach for early diagnosis of the main systemic AID, autoimmune liver diseases, rheumatic diseases in pediatrics, and other conditions.

Because of the diversity of antigenic targets of ANA, there is no universal method for the detection of all clinically significant autoantibodies. A sequence of tests should be performed to determine the spectrum of antibodies and to confirm the diagnosis. The screening laboratory test for ANA detection is based on the binding of the antibodies to internal antigens of the HEp-2 cell line. HEp-2 cells are epithelial in origin, have a relatively large polyploid nucleus, several nucleoli rich in the cytoplasm, and are characterized by a high division rate. Because of these characteristics, they represent the best substrate for detection ANA with indirect immunofluorescence (IIF). The sensitivity of the HEp-2 IIF ANA test is up to 100% in the diagnosis of classical autoimmune systemic diseases like SLE and SSc. In novel ACR/EULAR criteria of SLE of the 2019 year HEp-2 IIF ANA test is considered to be an initial diagnostic test for SLE confirmation, so negative result virtually excludes SLE. The specificity of the test dramatically depends on the upper reference range (cut-off) that are used. International recommendations for ANA testing suggest that the initial screening at the dilution of serum at 1:160 is optimal for the adult population. On the other hand, the ACR / EULAR SLE classification criteria recommend an initial dilution of 1:80 to exclude the diagnosis of SLE. It should be noted that at low dilution, the specificity of ANA IIF testing is very low. If low dilutions of serum (1:40–1:80) would be used, up to 25% of sera from apparently healthy individuals can be ANA positive [17]. The ability to diagnose a systemic autoimmune rheumatic disease substantially depends on the level of positivity of the ANA IIF test. Low positive titers (1:80–1:160) are usually not associated with any AID, and, usually, it is impossible to determine the antigenic specificity of ANA at these concentrations. At medium positive titers (1:320–640), the probability of detecting an AID, and a specific antigenic target ANA increases to 30%. With high titers of more than 1:1280 (up to 1:1,000,000 in some cases), the probability of systemic rheumatic disease is over 50%, and there is a high probability of detecting specific autoantigens of antibodies.

The antigens of ANA are distributed across different cellular structures, and 30 patterns of ANA immunofluorescence patterns were described. New nomenclature of ANA patterns links them with the antigenic targets and diseases, dramatically increasing the clinical value of ANA IIF testing [18]. There are up to 100 described targets of ANA that are commonly called antibodies to the extractable nuclear antigen (ENA). Historically, many of antigens of ANA were described using crude called ENA. Although ENA is not currently used to detect ANA antibodies, the term has been retained and has become the general name used to describe ANA antigens.

Due to unknown clinical significance, low frequency, and methodological problems, only a limited number of anti-ENA antibodies are tested in clinical laboratories. Although the presumable spectrum of autoantibodies can be predicted from clinical symptoms and ANA IIF screening results, the patient’s serum is usually

tested on a panel of specific autoantigens. The so-called "multiplex approach" for detecting anti-ENA and other autoantibodies has become a valuable tool for immunological testing. It can increase diagnostic "hit rate" because many reactions are carried out in a single test, and can also help to capture rare autoantibodies important for the classification and prognosis of the disease.

Typically, anti-ENA antibodies are tested if initial ANA IIF screening is positive. However, sometimes the result of ANA IIF testing can be false-negative, especially in the presence of several particular ENAs, that may be lost from the nucleus of HEp-2 cells during the fixation process (e.g., SSA, or Ro-52). Also, an ANA directed to cytoplasmic antigens or antigens, expressed only on mitotic cells, can be easily missed during IIF testing even by an experienced laboratory specialist. In cases when clinical suspicion is high, it is recommended to order the ENA multiplex test even in cases of ANA negative IIF result. This is especially true for ANAs associated with inflammatory myopathies when special detection of myositis-specific antibodies should be performed regardless of the results of ANA IIF [19].

Anti-dsDNA autoantibodies are very important for the diagnosis of SLE. Antibodies against dsDNA formally do not belong to antibodies against ENA and should be separately ordered in patients with symptoms of SLE. Several methods are recommended for their laboratory detection: ELISA, immunofluorescent test on protozoan Crithidia Lucilia (CLIFT), and radioimmune Farr assay. Among all of these methods, ELISA is the less specific, but the most sensitive one. Antibody levels against dsDNA measured with ELISA that exceed twice the threshold value are considered highly positive and are important for the diagnosis and prognosis of SLE [20]. To confirm the specificity of the ELISA test-results in a controversial clinical situation, other anti-dsDNA detection methods can be used, namely the CLIFT and Farr assays [21].

10.3 Interpretation of Antinuclear Antibodies Testing in Geriatric Patients with Systemic Autoimmune Rheumatic Diseases

The assessment of the diagnostic value of ANA in elderly patients is challenged by the fact that ANA is relatively prevalent in healthy older adults. A gradual increase in the incidence of ANA from 5.6% in persons under 60 to 24% in people aged 71–80 years has been demonstrated [13]. Incidence of positive ANA IIF >1:50 was 23% in a large cohort of older people over 85 years old without AID [9]. The prevalence of positive results of ANA tests in older people with other prevalent AIDs, such as autoimmune thyroiditis or RA, is even higher.

Other factors contributing to the higher prevalence of ANA positivity in older people include female gender, vitamin D deficiency [10], and malignancy [22]. The reported frequency of ANA titer ≥1:160 in the elderly was approximately 5–10%. In most patients with ANA titer more than 1:200, researchers were unable to detect antigenic specificity of autoantibodies [9], although some authors detected anti-ssDNA and anti-histone antibodies in older people without the AID [8]. Other

authors reported that fine speckled pattern of ANA IIF can be associated with anti-DFS-70 antigen antibodies not related to any of AID. In general, ANA is found in older people more often, but frequently is not associated with any particular antigen, particularly if detected in low and medium titers.

The importance of ANA testing is supported by recently published 2019 EULAR/ACR classification criteria for SLE [23]. In accordance with recommendations, the diagnosis of SLE is based on a set of 11 criteria, which includes five laboratory and six clinical or morphological findings, which are evaluated in accordance with their diagnostic weight. To fulfill the criteria, the score should be equal to or bigger than ten. A new feature of these criteria is that the ANA HEp-2 IIF test results are used as the entry criterion for the initial patient selection. The titer ANA HEp-2 IIF test used for initial screening remains highly controversial, especially in the elderly population. The ANA titer of 1:80 had 97.8% sensitivity with 74.7% specificity, while after the increase in the level of titer to 1:160, meta-regression analysis showed a 95.8% sensitivity and an 86.2% specificity. The authors evaluated the diagnostic value of 1:80 titer of ANA in juvenile-onset SLE; however, the analysis of diagnostic parameters in the late-onset SLE was not reported to date [24].

Late-onset SLE diagnosed after 50 years of age is not a rare disease and represents approximately one-tenth of all cases of SLE [25]. Late-onset SLE patients have a specific autoantibody spectrum with significantly lower prevalence of anti-dsDNA antibodies, anti-Sm and anti-RNP autoantibodies, normal complement levels, but relatively more prevalent SSA and SSB antibodies, and RF [26]. The prevalence of ANA was not related to the age of onset of SLE, but the total number of all serological findings in late SLE, including anti-ENA, anti-dsDNA, and aPLA, is lower than that of SLE, which starts earlier [27].

The differential diagnosis of SLE in older adults comprises other systemic inflammatory rheumatic diseases, including Sjogren syndrome (SjS), SSc, and idiopathic inflammatory myopathies (IIM). Among them, SjS is the most common, affecting up to 6% of adults over 65. Anti-SSA 60 kDa antibodies that belong to the ANA family are frequently found in SjS. The positive result of SSA testing is used in ACR-EULAR 2016 classification criteria of the SjS. Anti-SSA antibodies are typically found together with anti-SSB antibodies, while isolated anti-SSB positivity is rare and is not considered a disease-related marker. Several other autoantibodies are frequently found in SjS, including RF, anticentromere antibodies, antimitochondrial antibodies [28]. SjS can be associated with the presence of polyclonal RF and type III cryoglobulinemia as well. Extra glandular manifestations of SjS and the development of lymphoma correlate with anti-SSA positivity and the presence of RF and IgG class hypergammaglobulinemia. Sometimes, loss of autoantibodies and a decrease in the level of hypergammaglobulinemia can precede the progress to malignant lymphoma. Anticentromere antibodies are increasingly described as specific SjS markers, with molecular targets presumably different from CENP-A/B antigens, found in limited forms of SSc. Low incidence of SSA antibodies and RF is characteristic in patients, positive for anticentromere antibodies.

Antiphospholipid antibodies (aPLA) can also be found in patients with SjS and are associated with increased thrombotic risk and other symptoms of antiphospholipid syndrome (APS). Relatively low frequency of anti-SSA antibodies and RF have been reported in patients, diagnosed with SjS after the age of 70. On the contrary, patients diagnosed with SjS before 45 years of age, had a higher rate of positivity of the autoantibodies, and higher incidence of lymphomas.

Scleroderma or SSc is frequently associated with old age. There are several scleroderma specific autoantibodies, including anti-Scl-70, anti-centromere, and anti-RNA polymerase III. The clinical specificity of their detection is high; that's why they were used in ACR-EULAR 2013 classification of the disease. Anti-Scl-70 antibodies are almost never co-occur together with the anti-centromere antibodies and the anti-RNA polymerase III antibodies. The prevalence of the anti-U1RNP and the anti-PM-Scl antibodies is significantly lower among older patients. These autoantibodies are detected mainly in juvenile or young-onset forms of SSc with a higher frequency of muscle involvement. A higher incidence of lung cancer was reported in Scl-70 positive patients. The close temporal relationship between the onset of cancer and scleroderma in patients with anti-RNA polymerase III antibodies has been reported as well.

The IIM are a heterogeneous group of muscle diseases associated with certain pathomorphological signs, the presence of muscle inflammation, and frequent relationship with systemic AID and cancer. Polymyositis, dermatomyositis, autoimmune necrotizing myopathy, and inclusion body myositis can be found in an elderly patient. Currently, only anti-Jo-1 antibody positivity is used in the 2017 EULAR/ACR classification criteria. Despite this fact, over a dozen myositis specific antibodies and myositis-associated antibodies are widely used for the diagnosis, classification, and prognosis in patients with symptoms of IIM. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, and ferritin levels are higher in the elderly patients with IIM, as compared to their younger IIM counterparts.

10.4 Laboratory Diagnostics in Geriatric Patients with Inflammatory and Non-inflammatory Arthropathies

The prevalence of RA in the general adult population is between 0.2 and 1% with the peak age of disease onset between 40 and 60 years of age. The reported prevalence of RA in persons older than 60 is up to 2% and can be even higher in the age of 85 [29, 30]. The lifetime risk of developing RA in adults is 3.6% for women and 1.7% for men [31].

There are several clinical variants of RA in the elderly population. The first one is elderly-onset RA (EORA) that starts after the age of 60. Classic RA that presents before 60 years of age and persists into the older age is commonly called young-onset RA or YORA. Older patients can have polymyalgia rheumatica

(PMR)-like EORA that is associated with predominant involvement of the axial joints. The PRM-like disease EORA is typically RF negative, has an acute onset, does not cause joint erosions, and has a good prognosis [32].

The 2010 ACR/EULAR diagnostic criteria for RA emphasize the significance of laboratory findings. Most patients who have RA have a positive test for RF and ACPA antibodies, as well as an elevated ESR and CRP. Highly elevated concentration of ACPA or RF together with raised ESR and CRP can provide four out of six points necessary for a diagnosis of RA.

In 60% of EORA patients, ACPA can be determined at the beginning of the disease, and in most of them, the aggressive phenotype of the disease and frequent bone erosions are found. The results of cohort studies revealed a lower incidence of ACPAs in patients with EORA, with reported ACPA positivity in about 60% in RA patients who started their disease at the age of 50–60 years old, 50% in EORA patients at the age of 60–70 years, 40% when the disease started at 70–80 years, and only 30% in very late RA, starting after 80 years [33]. The ACPAs were not different with respect to the titer, isotype distribution, specificity, and avidity index with increasing age of disease onset. Similar observations were made for RF that showed a decrease in frequency with increasing age of onset of the disease [34]. Anti-modified citrullinated vimentin (anti-MCV) antibodies and high sensitive anti-CCP (hsCCP) based on citrullinated vimentine peptides are the other types of ACPAs in RA. They are not as specific as antibodies to cyclic citrullinated peptide (anti-CCP) in the diagnosis of early RA, but in patients positive for anti-CCP, together with anti-MCV (or hsCCP) faster progression of bone destruction was noted.

A pronounced inflammatory response, accompanied by high levels of ESR and CRP is usually observed in patients with EORA. These markers of inflammation, however, are commonly found in other rheumatic diseases as well.

Osteoarthritis (OA) is the most prevalent form of non-inflammatory arthritis in the elderly population. Basic laboratory evaluation is normal in OA and the finding of autoantibodies (like RF or ACPA), alevated inflammatory markers (e.g., CRP) or specific metabolites (e.g., high uric acid) usually indicate another diagnosis.

10.5 Laboratory Diagnostics in Patients with Polymyalgia Rheumatica, Systemic Vasculitis, and Antiphospholipid Syndrome in the Advanced Age

Systemic vasculitis is a heterogeneous group of diseases associated with inflammation in the wall of blood vessels. Among them, several diseases are commonly found in older persons and deserve mention in this chapter. PMR and giant cell arteritis (GCA), or temporal arteritis, are closely related diseases of the elderly. Both diseases often coexist together and are characterized by a dramatic inflammatory

response [35]. Systemic inflammation is a common denominator for PMR and GCA, and in almost 80–90% of patients, ESR is higher than 50 mm/h, and the level of CRP is over 50 mg/L. Other laboratory markers of acute-phase response that are associated with the effects of IL-6 include hypoalbuminemia, hypergammaglobulinemia, thrombocytosis higher than 400,000/μL, mild normocytic anemia, and hyperfibrinogenemia. Autoantibodies directed to anti-N-terminal peptides of the ferritin heavy chain can be found in up to 90% of GCA cases, but they are not specific for the disease. Since the diagnosis of PMR is based on the exclusion of other rheumatic diseases with systemic inflammation, many other tests such as ACPA, RF, ANA, creatine kinase, alkaline phosphatase, and other analyses of bone and liver metabolism should be performed.

ANCAs are associated with small-vessel vasculitis, commonly found in old age. The group of ANCA-associated vasculitis (AAV) consists of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Pauci-immune rapidly progressive necrotizing crescentic glomerulonephritis (RPGN) is also classified as a kidney-limited form of AAV. ANCA is a family of autoantibodies directed against antigens of azurophilic and specific granules of neutrophil cytoplasm. About ten molecular targets of ANCAs have been described; among them proteinase-3 (PR3), and myeloperoxidase (MPO) appear to be the most clinically significant. Non-specific ANCAs that do not target PR3 or MPO antigens have been noted in many chronic inflammatory conditions [36]. Anti-PR3 and anti-MPO ANCAs are characteristic for AAV, and are related to different clinical syndromes. Anti-PR3 antibodies are primary biomarkers of GPA and are essential for the pathogenesis of the disease. Anti-PR3 can be found in both localized and systemic forms of the disease, manifested by granuloma in the airways, and lung damage. Glomerulonephritis is found in about 30% of the anti-PR3-positive GPA. Also, anti-PR3-positive patients have a more recurrent nature of the disease. Anti-PR3 antibody titers frequently change in parallel with the disease activity. Isolated RPGN is more frequent in MPO-positive patients, and kidney involvement is found in 50–90% of MPO-positive MPA. All patients with clinical suspicion of AAV should be tested with a sensitive ELISA method for the detection of anti-PR3 and anti-MPO antibodies. Goodpasture syndrome or anti-glomerular basement membrane disease (anti-GBM disease) is another example of small vessel vasculitis associated with ANCA-positivity that can manifest in older patients. Detection of anti-GBM antibodies directed against the non-collagenous domain of type IV collagen expressed in kidney and lung have 95% sensitivity and specificity in this disease.

Another kind of small vessel vasculitis is so called immune complex-mediated vasculitis. Immune complexes (IC) are formed in the slow bloodstream of small vessels and deposited in the walls of blood vessels of the skin and kidneys. Cryoglobulinemic vasculitis is the most common IC-mediated disease of old age. Cryoglobulins are IC consisting of aggregated immunoglobulin molecules that can reversibly precipitate at temperatures lower than body core temperature (e.g., below

35 °C). The defect in the solubility of IC is attributed to impaired glycosylation of the Fc fragment of immunoglobulin molecules. There are several types of cryoglobulins with slightly variable clinical presentations. Type I cryoglobulinemia consists of monoclonal immunoglobulins (paraprotein) of IgG or IgM classes highly prone to precipitation. Type I disease is manifested with high serum cryocrite levels and severe skin lesions with ulcers in almost half of patients and, in contrast, the decreased incidence of glomerulonephritis. Type II essential mixed cryoglobulinemia is typically related to chronic HCV infection. Cryoglobulins in type II cryoglobulinemia represent a monoclonal RF of the IgM class. Cryoglobulins in type II CSs cryoglobulinemia can be detected almost in 30% of HCV-infected patients, but clinical signs of vasculitis can only be found in 5–15% of patients. Cryoglobulins in type III cryoglobulinemia are polyclonal RF, which bind to self IgG. This is the most clinically indolent type of disease related to joint involvement, myalgia, and Raynaud's phenomenon. RA, SjS, or SLE are the leading causes of type III cryoglobulinemia, and a high prevalence of secondary lymphoma has been noted in cryoglobulin-positive patients with rheumatic diseases [37]. Tests for RF and monoclonal paraprotein are valuable tools for the diagnosis of cryoglobulinemic vasculitis.

Antiphospholipid syndrome (APS) is an antibody-mediated AID that is characterized by hypercoagulation, recurrent miscarriages and obstetric pathology. There are several clinical manifestations closely related to APS and potentially mediated by aPLA; however, the pathogenic mechanisms have not been fully elucidated. The diagnosis of APS can be suspected after receiving positive results of a laboratory panel of serological and coagulation tests, including lupus anticoagulant (LAC), antibodies of IgG and IgM subclasses directed to cardiolipin (aCL) or β-2 glycoprotein I (anti-b2GPI). According to the 2006 classification criteria for APS, persistently elevated levels of these antibodies in medium or high titers and/or presence of LAC, determined by re-evaluation after 12 weeks, are necessary for the confirmation of the diagnosis. Higher titers of aPLA are usually found before the development of thrombosis and slightly decrease immediately after thrombotic events.

At the same time, aCL antibodies are commonly found clinically healthy individuals. The prevalence of aPLA in the general population ranges between 1 and 5%, and goes up to 12% in elderly people. Low titers of aPLA are detected in many diseases, but they are not considered as risk factors for thrombosis [38]. Therefore, the diagnosis of APS in old age can be puzzling because of the high frequency of low positive aPLA, and the presence of other coexisting factors of acquired thrombotic risk. These risk factors for thrombosis include older age (>55 in men, >65 in women), all established risk factors for cardiovascular diseases and atherosclerosis, such as hypertension, diabetes, high LDL cholesterol or low HDL cholesterol, smoking, early onset of cardiovascular diseases in the family, body mass index over 30 kg m^2, as well as microalbuminuria, decreased glomerular filtration rate, congenital thrombophilia, oral contraceptives, nephritic syndrome, tumors, immobilization, and surgery.

Several attempts have been made in order to recognize the individual risk of thrombosis in patients positive for aPLA. Published EULAR guidelines for

the management of APS in adults specially address the issue of so-called “high-risk aPLA profile”, defined as any of the following: multiple (double or triple) aPLA positivity, persistently positive LAC or high aPLA titers, high aPLA score and Global Anti-Phospholipid Syndrome (GAPSS) Score [39, 40]. Additional risk factors for recurrent APS manifestations are coexistence with other systemic AID, especially SLE, a history of thrombotic and/or obstetric APS, and the presence of traditional cardiovascular risk factors including smoking, hypertension, dyslipidemia, diabetes, surgery, hospitalization, prolonged immobilization and the postnatal period. All but the latter factors are highly relevant in older age, so elderly patients with APS almost universally are classified as high-risk patients with more active treatment strategies.

10.6 Conclusion

Immunological laboratory testing is the basis for the diagnosis of most autoimmune and inflammatory rheumatic diseases. The substantial characteristics of the immune system at the older age include a higher frequency of autoantibodies, a predisposition to the inflammatory reactions, and a shift towards the monoclonal production of immunoglobulins. Interpretation of laboratory tests in geriatric patients should consider the unique characteristics of the immune response in older individuals.

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