19.11.1 Introduction 4495 David A. Isenberg and Ia

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CONTENTS 19.11.1 Introduction 4495 David A. Isenberg and Ian Giles 19.11.2 Systemic lupus erythematosus and related disorders 4499 Anisur Rahman and David A. Isenberg 19.11.3 Systemic sclerosis (scleroderma) 4513 Christopher P. Denton and Carol M. Black 19.11.4 Sjögren's syndrome 4532 Wan-Fai Ng 19.11.5 Inflammatory myopathies 4537 Ingrid E. Lundberg, Hector Chinoy, and Robert Cooper 19.11.6 Large vessel vasculitis 4546 Raashid Luqmani and Cristina Ponte 19.11.7 ANCA-associated vasculitis 4556 David Jayne 19.11.8 Polyarteritis nodosa 4569 Loïc Guillevin 19.11.9 Small vessel vasculitis 4573 Richard A. Watts 19.11.10 Behçet's syndrome 4579 Sebahattin Yurdakul, Izzet Fresko, and Hasan Yazici 19.11.11 Polymyalgia rheumatica 4584 Bhaskar Dasgupta and Eric L. Matteson 19.11.12 Kawasaki disease 4590 Brian W. McCrindle

19.11.1 Introduction David A. Isenberg and Ian Giles

ESSENTIALS About 1 in 20 people develop an autoimmune disease, many of which involve the musculoskeletal system. Young women are particularly at risk, but the development at any age of symptoms such as unexplained fever, rash, polyarthritis, Raynaud's phenom- enon, or mouth ulcers should encourage serological screening for autoimmune rheumatic or vasculitic disorder. Aetiology and pathogenesis—common to all of the autoimmune rheumatic diseases is the phenomenon of production of autoanti- bodies by activated B cells. In the primary vasculitides, a pathogenic role has been proposed for antiendothelial cell antibodies and sen- sitized T cells, but undoubtedly the most important role is that of antineutrophil cytoplasmic antibodies. Diagnosis—detection of antinuclear antibodies or rheumatoid factor in high titre favours the diagnosis of an autoimmune rheumatic disease and should lead to a search for more specific autoantibodies; for example, anti-dsDNA linked to lupus, anti-citrullinated peptide/ protein antibodies linked to rheumatoid arthritis, antineutrophil cytoplasmic antibodies linked to granulomatosis with polyangiitis, and microscopic polyangiitis. Well-established and validated classifi- cation criteria exist, and several have been recently revised for all the main autoimmune rheumatic diseases and vasculitides, but there is significant overlap between them. Physicians

treating patients with these conditions need to be constantly aware of the possibility of organ involvement because prompt diagnosis and treatment may be necessary to prevent irreversible damage. Definition and epidemiology The autoimmune rheumatic diseases are a heterogeneous group of disorders characterized by clinical involvement of the joints, con- nective tissues, muscles, internal organs, Raynaud's phenomenon, and cutaneous manifestations. They include a broad clinical spec- trum of disease, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome, scleroderma, derm- atomyositis, polymyositis, antiphospholipid syndrome (APS), and the vasculitides. This latter group of diseases all share inflamma- tion and necrosis of blood vessels as cardinal features, and may be divided into primary (e.g. giant cell arteritis, granulomatosis with polyangiitis, polyarteritis nodosa, and so on), occurring in the ab- sence of a recognized precipitating cause, or secondary to estab- lished disease (e.g. systemic lupus erythematosus or rheumatoid 19.11 Autoimmune rheumatic disorders and vasculitides

 arthritis) or infection (e.g. hepatitis B, C, or HIV). Recent revisions in the commonly used terms for various vasculitides have been pro- posed to reflect increased pathophysiologic understanding of these conditions (see Table 19.11.1.1). In general, autoimmune rheumatic diseases have a predilection for young women and share defects in immune regulation leading to the production of autoantibodies, ac- tivation of the complement system, and generation and deposition of immune complexes. Autoimmune rheumatic diseases affect as many as 1 in 20 people. Some are rare, for example, systemic sclerosis; others are common, rheumatoid arthritis affecting approximately 1% of the popula- tion (see Table 19.11.1.2). Some are severely debilitating or life- threatening illnesses, while others produce minor symptoms that require little, if any, medical intervention. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Diseases most commonly associated with antineutrophil cytoplasmic antibody (antimyeloperoxidase and antiproteinase 3 antibodies), a significant risk of renal involve- ment, and which are most responsive to immunosuppression with cyclophosphamide. Immune complex vasculitis. Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement com- ponents, predominantly affecting small vessels (i.e. capillaries, venules, arterioles, and small arteries). Glomerulonephritis is frequent. Drugs able to induce vasculitis include sulphonamides, penicil- lins, thiazide diuretics, and many others. The clinical spectrum Each of the autoimmune rheumatic diseases is a distinct entity and can be clearly defined clinically, serologically, and in terms of treatment and prognosis. However, many patients with these dis- eases have nonspecific features of malaise, fever, and arthralgia, and about 30% of patients with lupus, myositis, and Sjögren's have at least one other autoimmune rheumatic disease, there being much overlap in terms of multisystem involvement, as shown in Table 19.11.1.3. Organ-specific features (e.g. lung fibrosis, pericarditis, and less frequently glomerulonephritis), can all occur in several of the autoimmune rheumatic diseases and the presence of such a fea- ture is not pathognomonic of an individual disease. The clinical features of each patient must be considered together with the laboratory investigations, which should include an auto- antibody profile. A preliminary 'autoimmune screen' includes a rheumatoid factor and antinuclear antibody test as a bare min- imum, the results of which then guide the need for further autoanti- body testing. Immunologically, the detection of rheumatoid factor or anti-citrullinated peptide antibodies (ACPA) are the most im- portant guide to establishing the diagnosis of rheumatoid arthritis (especially at high titre). Anti-citrullinated peptide antibodies are present in 80% of patients with established rheumatoid arthritis and their specificity is 85–90% with

sensitivity of 50–60%. Furthermore, a positive ACPA predicts the development of erosive rheumatoid arthritis and may also be genuinely pathogenic. It is important to note, however, that the American College of Rheumatology/ Table 19.11.1.1 Classification of systemic vasculitis Dominant vessel involved Primary Secondary Large vessel vasculitis (LVV) Giant cell arteritis Aortitis associated with rheumatoid arthritis Takayasu arteritis Infection (e.g. syphilis) Isolated CNS angiitis Medium vessel vasculitis (MVV) Polyarteritis nodosa Infection (e.g. hepatitis B) Kawasaki disease Small vessel vasculitis (SVV) Granulomatosis with polyangiitis (GPA, previously termed Wegener's granulomatosis) Vasculitis secondary to RA, SLE, and SS Eosinophilic granulomatosis with polyangiitis (EGPA, previously termed Churg–Strauss) Drugs Microscopic polyangiitis (MPA) Infection (e.g. HIV) Anti-glomerular basement membrane (GBM) disease Drugs IgA vasculitis (Henoch–Schönlein) Cryoglobulinaemic vasculitis Infection (e.g. hepatitis B, C) Hypocomplementaemic urticarial vasculitis (Anti-C1q Vasculitis) CNS, central nervous system; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome. Table 19.11.1.2 Occurrence of major autoimmune rheumatic diseases in Western populations aged 15 years and over Diseases Annual incidence per 1000 Point prevalence per 1000 Rheumatoid arthritis 0.5 8.0 Systemic lupus erythematosus 0.05 0.4a Polymyositis 0.005 0.08 Systemic sclerosis 0.01 0.1 Sjögren's syndrome 0.3 0.27 Antineutrophil cytoplasmic antibody-associated vasculitis 0.02 0.2 a There is a considerable variation according to ethnic origin, thus Afro-Caribbean women are five times as likely to get systemic lupus erythematosus as white women.

19.11.1 Introduction 4497 European League Against Rheumatism classification criteria for rheumatoid arthritis may still be fulfilled in the absence of rheuma- toid factor and anti-citrullinated peptide antibodies, and neither of these antibodies are of value in the monitoring of the disease. The presence and pattern of staining of antinuclear antibody is a very useful guide to the presence of disease, as shown in Table 19.11.1.4, with the important proviso that an antinuclear antibody is present in low titre (up to 1 in 80) in about 1 to 2% of the normal population, and more frequently (up to 10%) in healthy people over the age of 75 years. Hence, its presence alone at low titres does not in itself justify the diagnosis of an autoimmune rheumatic dis- ease: the whole clinical picture must be considered. In the case of the vasculitides, the antineutrophil cytoplasmic antibody should be regarded in the same manner as the antinuclear antibody, but it should also be remembered that some autoantibodies may be found in more than one disease, such as anti-U1RNP (in systemic lupus erythematosus and undifferentiated autoimmune rheumatic disease), while others may be found in other diseases 'beyond' the autoimmune rheumatic diseases, such as perinuclear staining (p-) antineutrophil cytoplasmic antibody, which is well recognized in patients with inflammatory bowel disease, some chronic infec- tions, and malignancies. Immunopathogenesis Autoimmune rheumatic disorders The precise aetiologies of the autoimmune rheumatic diseases re- main unknown, but are undoubtedly complex. Inciting agents, such as infection, are involved, as are genetic susceptibility, hormonal fac- tors, and both cellular and immune dysregulation. Common to all of the autoimmune rheumatic diseases is the phenomenon of production of autoantibodies by activated B cells. Most of the pathogenic autoantibodies are of the IgG class and have undergone somatic mutation in their hypervariable re- gions, leading to a gradual increase in specificity and binding affinity of an antibody produced by a particular clone of cells. This latter finding is particularly true of anti-dsDNA antibodies in systemic lupus erythematosus and antiphospholipid antibodies in the antiphospholipid syndrome. The origins of autoantibody production remain an enigma. Mechanisms that have been invoked include antigen-driven T helper cell responses, failure of efficient clearance of nuclear antigens which become surface expressed following cellular

apoptosis, and epitope spreading. These might act alone, in combination with each other, or together with other factors. Each has been proposed to lead to in- creased B-cell activation. Impaired tolerance appears to be the cen- tral defect, and once this has occurred abnormal immunoregulation leads to persistence of the inappropriate self-directed immune response. Cellular mechanisms also play a role in the development of auto- immunity in the autoimmune rheumatic diseases: T-cell dysfunc- tion; impaired macrophage and natural killer cell cytotoxicity; Table 19.11.1.3 The spectrum of the autoimmune rheumatic diseases Disease Major organ/system involvement Principal immunological abnormalities Rheumatoid arthritis Joints, skin, eyes, lungs, heart, neurological, renal Rheumatoid factor, IgM, G, or A, AB to CCP, central role for T and B cells Systemic lupus erythematosus Skin, joints, kidneys, brain, heart, lungs AB to polynucleotides, histones, nucleosomes, ENA, PL, C1q, abnormalities in T and B cells and accessory cells Poly-/dermatomyositis Muscle, skin, blood vessels, Lungs Disease-specific AB (e.g. anti-tRNA Synthetases such as Jo-1) and infiltrates of T cells in muscle Scleroderma Skin, gut, lungs, kidneys, heart, muscle Disease-specific AB (e.g. anti-Scl-70, anticentromere, RNA polymerases, anti-PDGFR); T-cell and cytokine abnormalities Primary antiphospholipid syndrome Blood vessels any size, skin, pregnancy morbidity, neurological AB to PL, β2-GP1, and the lupus anticoagulant Sjögren's syndrome Exocrine glands, notably lacrimal and parotid AB to ENA, SS A/Ro, SS B/La; major infiltrate of T cells in glands Vasculitides (e.g. PAN, GPA, EGPA, MPA, and GCA) Skin, joints, muscles, lungs, central nervous system, kidneys, blood vessels of all sizes Cellular infiltration of blood vessel walls; disease-related AB to c-ANCA or p-ANCA AB, antibody; p-ANCA, perinuclear staining antineutrophil cytoplasmic antibody; c-ANCA, cytoplasmic staining antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss); ENA, extractable nuclear antigen; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis (Wegener's); MPA, microscopic polyangitis; PDGFR, platelet-derived growth factor receptor; PL, phospholipid; PAN, polyarteritis nodosa; SS, Sjögren's syndrome; β2-GP1, β2-glycoprotein 1. Table 19.11.1.4 Antinuclear antibody use in diagnosis Antinuclear antibody pattern Other autoantibodies Disease Nuclear Homogenous Chromatin, dsDNA SLE Histone DIL Speckled Sm, U1RNP SLE Ro, La SS, SCLE, CHB, NL High titre U1RNP Overlap/UARD Nucleolar Speckled Scl-70, RNA Polymerase I DcSSc Homogenous PM-Scl SSc/PM overlap Clumpy U3RNP DcSSc, PHT Centromere Anti-centromere LcSSc CHB, congenital heart block; DcSSc, diffuse cutaneous systemic sclerosis; DIL, drug- induced lupus; LcSSc, localized systemic sclerosis; NL, neonatal lupus; PHT, pulmonary hypertension; PM, polymyositis; SCLE, subacute cutaneous lupus; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome.

 decreased clearance of immune complexes by the mononuclear phagocytic system; increase in the number of activated B cells; cyto- kine dysregulation; and up-regulation of adhesion molecules have all been reported. Genetic factors are important, especially in the case of systemic lupus erythematosus, where there is a higher rate of concordance in monozygotic twins (25%) than dizygotic (3%). The best described of the genetic contributions to autoimmune rheumatic disease is the increased risk associated with particular human leucocyte antigen (HLA) class II molecules. The HLA DR4 (the Dw4 and Dw14 sub- types, notably the DR1*0404 allele) and HLA DR1 (Dw1) are par- ticularly associated with rheumatoid arthritis. These subtypes share a similarity of the amino acid sequence in the third hypervariable re- gion of the DR1 chain, the shared epitope that has been proposed as the underlying unit of susceptibility to rheumatoid arthritis. There are, however, conflicting data proposing that this epitope is better related to the severity of disease. In systemic lupus erythematosus, among white people, the haplotype A1 B8 DR3 is associated with an approximately tenfold increase in risk,

although the primary link may be with the complement C4 null allele with which there is linkage disequilibrium. Human leukocyte antigen associations are not only seen with autoimmune rheumatic disease, but also with certain autoanti- bodies. Anti-Ro and La are strongly correlated with HLA DR3 and DQ, an association that is stronger than that seen with the disease in which these autoantibodies are most frequently encountered (sys- temic lupus erythematosus and Sjögren's syndrome). Vasculitides Human leukocyte antigen class I and class II associations are seen throughout the primary vasculitides, whereas infectious agents and circulating immune complexes are pathogenic in the secondary vas- culitides. In the primary vasculitides a pathogenic role has been pro- posed for antiendothelial cell antibodies and sensitized T cells, but undoubtedly the most important role is that of the antineutrophil cytoplasmic antibody. Immunofluoresence studies have localized the antigen to the cytoplasm of granulocytes in the azurophilic granules, and two patterns of staining are seen: cytoplasmic (c-) ANCA, of which 90% of sera recognize proteinase 3; and perinuclear staining p-ANCA that is directed against myeloperoxidase (MPO) in 70% of patients with p-ANCA vasculitis. A positive c-ANCA is strongly associated with granulomatosis with polyangiitis, although 10% of these patients may be p-ANCA positive, while anti-MPO antibodies occur in necrotizing glomerulonephritis (65%), eosino- philic granulomatosis with polyangiitis (Churg–Strauss) (60%), and microscopic polyangiitis (45%). Clinical features As mentioned previously, the presentation of an autoimmune rheumatic disease may be variable and nonspecific, with fatigue and arthralgia frequently the major features. In this instance, sys- temic review should enquire for the presence of alopecia, mouth ulcers, Raynaud's phenomenon, rash, sicca symptoms, and lymph- adenopathy. The presence of these would lend an autoimmune flavour to the illness, but not necessarily help to make a precise diagnosis. The history should also seek a possible trigger such as a preceding infection, drugs (for example hydralazine, isoniazid, procainamide in drug-induced lupus), or environmental exposure to chemicals, as may be seen in scleroderma-like illnesses. A family history must pay particular attention to the presence, not only of other autoimmune rheumatic diseases, but also other autoimmune diseases such as diabetes, pernicious anaemia, and thyroid disease, which are often found in association with the autoimmune rheum- atic diseases. The protean clinical manifestations mean that an autoimmune rheumatic disease may present not only to a rheumatologist but to many other specialists, including those in nephrology, dermatology, and less commonly neurology, cardiology, haematology, or even ob- stetrics, in the case of recurrent miscarriages in antiphospholipid syndrome. In many cases it is not possible to make a precise diagnosis on the first encounter with a patient. In those with mild disease, symptom- atic relief can be obtained with a nonsteroidal anti-inflammatory drug (NSAID), while the results of baseline investigations and an 'immunological screen' of antinuclear antibody and rheumatoid factor are awaited. Modern management of rheumatoid arthritis, however, mandates prompt diagnosis so that a disease-modifying drug can be used as early as possible and treatment escalated to achieve a target of remission or very low disease activity to prevent the development of erosive, destructive joint disease. Since the autoimmune rheumatic diseases are systemic dis- orders, it is always important to search for evidence of involve- ment of any of the major organ systems. Baseline investigations must therefore include urinalysis, a full blood count, simple blood tests of renal and liver function, measurement of serum inflammatory markers, an electrocardiogram (ECG), and a chest radiograph. The simple bedside test of urinalysis is particularly important: the finding of proteinuria and haematuria imme- diately identifies those who require renal investigation—often urgently—and whose prognosis may be chiefly determined by the extent of renal involvement. Damage to major organ systems can be part of the presenting illness in a patient with an autoimmune rheumatic disease, but may also occur in a previously diagnosed patient with 'stable' disease. Myocardial infarction can occur as the result of a vasculitic

illness, or accelerated atherosclerosis in systemic lupus erythematosus. Pericarditis can lead to tamponade (e.g. in systemic lupus erythematosus or rheumatoid arthritis), while myocarditis may in- duce complex arrhythmias or even heart failure (e.g. in systemic lupus erythematosus or polymyositis). Seizures or a disturbed level of consciousness can occur due to cerebral infarction or meningo- encephalitis (e.g. in systemic lupus erythematosus, antiphospholipid syndrome, or granulomatosis with polyangiitis). Rapidly progressive glomerulonephritis (systemic lupus erythematosus, granulomatosis with polyangiitis or microscopic polyangiitis) may be associated with pulmonary haemorrhage, while hypertension requires ur- gent treatment in scleroderma renal crisis. Pneumonitis or myositis due to systemic lupus erythematosus may be life-threatening if not recognized and treated appropriately with adequate immunosup- pression. Venous or arterial thromboses are likely to complicate the antiphospholipid syndrome, which in its primary form may be catastrophic and characterized by widespread microvascular dis- ease with adult respiratory distress syndrome (ARDS), profound thrombocytopenia, and acute renal failure.

Revision #1
Created 2026-01-22 16:40:37 UTC by Omar Ayman
Updated 2026-01-22 16:40:37 UTC by Omar Ayman