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Immunological Aspects of Cardiovascular Diseases

Implications for Treatment

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Summary

The immunological cardiovascular diseases are a very diverse group of clinical entities that generally are of either unknown aetiology or of unproven pathophysiology. Most of the conditions with a proven, or strongly suspected, aetiology are caused by infections, with the best examples being acute rheumatic fever and Lyme disease. However, even with these diseases, the primary pathophysiological mechanisms have not been irrefutably established. In addition to the importance of infectious agents in the immunological cardiovascular diseases, other factors have been identified that are associated with or modify these diseases. These factors include age, genetic background and coexisting inflammatory diseases.

The proposed immunological mechanisms important in the immunological cardiovascular diseases include: (a) immune mimicry, in which antigens of an infectious agent crossreact with self antigens; (b) modification of self antigens by infections or other inflammatory processes; (c) introduction of self antigens to the immune system following a traumatic or inflammatory event; and (d) dysregulation of an autoimmune response. The immunological effector mechanisms

include: (a) passive deposition of immunoglobulin or immune complexes in cardiovascular tissues with resulting inflammation; (b) autoantibodies that damage the cardiovascular system directly or indirectly; and (c) cell-mediated immune responses to antigens within the cardiovascular system.

The clinical diagnosis of the immunological cardiovascular diseases is facilitated by clinical criteria and by selective laboratory tests in certain diseases. Laboratory tests, other than histology, do not usually provide definitive answers but serve to confirm suspected diagnoses. The vague, often systemic, symptoms associated with many of the disorders add to the clinical confusion of diagnosis.

Despite the lack of clearcut aetiologies, the classification of these diseases does facilitate therapeutic decision making. This is particularly important since the prognosis of some of these conditions, such as acute rheumatic fever, Lyme disease, Wegener's granulomatosis, systemic necrotising vasculitis and temporal arteritis, is significantly improved by treatment. Classification schemes for vasculitis remain primarily descriptive, but are useful for dividing the entities into categories with similar response to treatment. Significant progress and improvement in the treatment of the immunological cardiovascular disorders await better definition of the aetiologies and primary pathophysiological mechanisms involved.

The terms for immunological diseases of the cardiovascular system are carditis, involvement of the heart, and vasculitis, involvement of the blood vessels and surrounding tissues. The histological characteristics of these disorders are deposition in the affected tissue of immunoglobulin and complement and/or an inflammatory cellular infiltration. The proposed mechanisms of immune injury include: (a) tissue modification or immunological exposure of self antigens by preceding infection or trauma, resulting in an autoimmune process; (b) immunological response to unrelated antigens crossreacting with vascular or cardiac antigens; and (c) passive involvement with blood-borne immune reactants.[1]

Cognate recognition of the endothelium of the cardiovascular system by immune cells is a necessary process to facilitate regulated movement of cells and products of the immune system. This cellular interaction is facilitated by membrane proteins and their ligands such as addressins, integrins and selectins. The relative infrequency of immunological diseases of the cardiovascular system reflects the effectiveness of regulation of these interactions.[2,3] The aetiology and principal pathophysiological mechanism of most of the immunological cardiovascular diseases are unknown. Therefore, the classification scheme is descriptive but, nevertheless, useful therapeutically.

1. Carditis

Carditis is a descriptive term for inflammation of any one of the 3 tissues of the heart, specifically pericarditis, myocarditis and endocarditis, or of all 3 (pancarditis). Symptoms and signs suggest the portion of the heart involved: chest pain and accumulation of pericardial fluid in pericarditis, dysrhythmia and heart failure in myocarditis, and valvular dysfunction with changing murmurs in endocarditis. Carditis associated with transplant rejection is not discussed in this general review.

1.1 Acute Rheumatic Fever

Acute rheumatic fever (ARF) is an inflammatory, multisystem disease that occurs 2 to 3 weeks to 6 months after a group A streptococcal pharyngitis. The frequency and severity of ARF have diminished dramatically in North America and Europe during the past 90 years because of improved social conditions, antibiotic therapy and a decline

of the rheumatogenicity of the streptococcus. Outbreaks of ARF in several sites in the US in 1985 are attributed to the reappearance of rheumatogenic strains of group A streptococci.[4] Rheumatic heart disease remains the leading cause of cardiac death in the 5- to 24-year-old age group in most parts of the world, and outbreaks continue to occur in North America and Europe.[5]

The pathophysiology of ARF remains speculative. The most widely held theory is that cross-reacting antibodies, i.e. antibodies that react with *Streptococcus*, particularly the M protein, cross-react with human cardiac myocytes, cartilage, chondrocytes, synovial cells, and thalamic and subthalamic nuclei of the central nervous system.[6] However, crossreactive antibodies, albeit in lower titre, occur in patients with streptococcal pharyngitis uncomplicated by ARF. Furthermore, the time course of ARF does not always coincide with the rise of streptococcal antibody levels. Thus, the aetiological importance of crossreacting antibody remains uncertain. Superantigen, a substance that activates up to 10% of all T cells, has been identified in M protein and erythrogenic toxins A and B. Superantigens from streptococci or streptococcal products could activate and expand pathogenic lymphocyte clones, contributing to disease.[7] Genetic predisposition to ARF, as demonstrated by the increased frequency of the B cell alloantigen 883 in patients with ARF, suggests that a particular immune response to the streptococcus is important for disease development.[8]

The diagnosis of ARF requires differentiation from other immunological and infectious diseases. The Jones criteria facilitate this distinction (table I).[9] The pancarditis associated with ARF is rarely severe; however, acute cardiac failure and even death can occur. The incidence of carditis in the first attack of ARF varies inversely with age. It is 90 to 92% in children less than 3 years old, 50% in children 3 to 6 years old, 32% in adolescents 14 to 17 years old, and as low as 15% in adults.[10]

The most common murmur of ARF is mitral regurgitation, with aortic insufficiency noted about one-third as often. The major complications of the carditis usually occur years after the ARF episode and include mitral and/or aortic valve dysfunction from postinflammatory scarring.

Table I. Revised Jones criteria for the diagnosis of rheumatic fever.[9] Two major criteria or 1 major and 2 minor criteria plus evidence of a preceding group A streptococcal pharyngitis (positive throat culture, increased antibody titres such as anti-streptolysin O or anti-deoxyribonuclease B, or recent history of scarlet fever) are considered diagnostic of rheumatic fever

Major manifestations
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules
Minor manifestations
Clinical: previous rheumatic fever or heart disease, fever, arthralgias
Biochemical: increased erythrocyte sedimentation rate, increased C-reactive protein, leucocytosis
Electrocardiographic: prolonged PR interval

The arthritis of ARF is a migratory joint disease, usually affecting fewer than 6 joints simultaneously, and generally lasting less than 4 to 6 weeks. The arthritis affects adults more commonly than adolescents and children (95 to 100%, 82% and 66%, respectively).[11] Likewise, the incidence of chorea is affected by age. It occurs only rarely after puberty, and almost never in adults.

An increase in streptococcal antibodies, such as anti-streptolysin O (ASO) and anti-deoxyribonuclease B, supports the diagnosis of ARF, with peak levels occurring 4 to 5 weeks after the pharyngitis.

ARF lasts an average of less than 3 months, and less than 5% of attacks persist for more than 6 months. The prompt response of the arthritis and fever to aspirin 40 to 100 mg/kg/day is so characteristic that it strengthens the clinical diagnosis. Anti-inflammatory therapy masks inflammation but tends to prolong the duration of the attack, with rebounds of inflammatory activity occurring when therapy is tapered or discontinued. Thus, analgesics such as codeine are the treatment of choice for mild episodes. Systemic glucocorticosteroids should be reserved for the most severe carditis.

ARF does not occur when streptococcal infections are prevented or treated. Penicillin, either (a) a single intramuscular injection of 1.2MU of benzathine benzylpenicillin (penicillin G), or (b) potassium phenoxymethylpenicillin (penicillin V) 125 to 250mg orally 4 times a day for 10 days, is the drug of choice for treatment. Erythromycin is used for penicillin-allergic individuals. Since recurrent streptococcal pharyngitis may reactivate the carditis, continual prophylactic therapy to prevent streptococcal disease is recommended for 5 to 10 years or longer after an attack of ARF. Effective regimens include: (a) intramuscular benzathine benzylpenicillin 1.2MU every 4 weeks; (b) sulfadiazine 500 to 1000mg orally once daily; (c) phenoxymethylpenicillin 250mg orally twice daily; or (d) erythromycin 250mg orally twice daily.

The purification of the M protein of the streptococcus, and evidence of its immunogenicity and absence of rheumatogenicity, offer the prospect of a vaccine to prevent ARF.[12] The occurrence of ARF without the herald of pharyngitis and the potential development of antibiotic resistance of the streptococcus increase the importance of vaccine development.[13,14]

1.2 Viral Myocarditis

Unsuspected myocarditis is detected in almost 10% of routine autopsies, and 2.5 to 12% of endomyocardial biopsies of patients with dilated cardiomyopathy show myocarditis.[15] The incidence of lymphocytic myocarditis in unexplained heart failure varies from 0 to 80%.[16] Viral-specific RNA sequences have been detected in myopathic hearts without histological evidence of inflammation, without culturable virus and without the presence of viral-specific antigens.[17] Techniques such as dot-blot hybridization, *in situ* hybridization and polymerase chain reaction amplification of viral DNA have been used to confirm the presence of viral genetic material in 25% of patients with myocarditis and 15% with dilated cardiomyopathy.[18]

Coxsackie B, poliomyelitis and other enteroviruses, influenza, mumps, rubella, Epstein–Barr and lymphocytic choriomeningitis virus are the most frequently suspected viral pathogens. The role of viral myocarditis in the development of lymphocytic myocarditis is unknown in humans, but is suspected based upon animal data and indirect evidence.[19] During human epidemics of coxsackie B viral infection, as many as 10% of infected individuals manifest clinical signs of cardiac involvement, and a few of these ultimately develop dilated cardiomyopathy.[20] The role of the host immunological response in viral-induced carditis is suggested by the biphasic clinical pattern of acute viral illness, initial improvement, and clinical deterioration with carditis 10 days to weeks later. The primary role of the immune system in the disease is supported by:

- the development of antibodies specific for the cardiac myocyte sarcolemma and myosin;[21]
- expression of immune cell receptors such as intercellular adhesion molecule-1 (ICAM-1), interleukin (IL)-2 receptor and major histocompatibility complex (MHC) class II molecules on myocytes from affected hearts;[22]
- the presence of activated lymphocytes in the myocardium;[23]
- activation of endothelial cells in coronary vessels from affected hearts;[24]
- changes in circulating lymphocyte populations;[25]
- the absence of replicating virus during the inflammation.[17]

Anti-inflammatory therapy with glucocorticosteroids, cytotoxic agents and immunomodulators reduces the inflammation within the myocardium and results in functional improvement in animal models and in selected patients in human disease. Patients who are candidates for such therapy include those with malignant arrhythmias with or without heart failure, those with positive ^{111}In-labelled antimyosin antibody scans, and those with recent onset congestive heart failure without other explanation. Endomyocardial biopsy is useful to confirm clinical suspicion of the diagnosis. The cytotoxic immunosuppressive agents used for myocarditis include azathioprine, cyclophos-

phamide and cyclosporin. The immunomodulating therapies that may be of value include anti–IL-2, anti–tumour necrosis factor-α (TNFα), interferon, and immunoglobulin specific for myocyte receptors or the suspected virus. Although current therapy for viral myocarditis is supportive, i.e. control of arrhythmias, treatment of heart failure, and perhaps prolonged bed rest to enhance healing, an intriguing possibility is that more aggressive anti-inflammatory therapy in the early phase of post-viral myocarditis might prevent late onset refractory congestive cardiomyopathy.[26,27]

1.3 Pericarditis Following Cardiac Trauma or Ischaemic Injury

Pericarditis may occur after cardiac surgery, myocardial infarction, or blunt or penetrating chest trauma. An immune pathogenesis is suggested by some of the same features implicating the immune response in the viral syndromes described above, including the development of cardiac autoantibodies. The pathological importance of cardiac autoantibodies is unknown, since these antibodies are found in similar quantities in patients without pericarditis following cardiac injury. The time between the injury and onset of the pericarditis varies from 4 days to 12 months, but is usually 4 to 8 weeks. The incidence varies from 5% after myocardial infarction to 30% following surgery or trauma.

The symptoms of pericarditis usually respond to aspirin or equivalent anti-inflammatory therapy, although symptoms may reappear when therapy is discontinued. Rarely, pericardial tamponade or constrictive pericarditis may complicate the clinical management.[1]

1.4 Carditis Associated with Connective Tissue Diseases

Carditis associated with various connective tissue diseases occurs more frequently than recognised clinically. Systemic lupus erythematosus (SLE) is the most common associated connective tissue disease. Postmortem examinations demonstrate pericarditis in approximately 80% of all patients with SLE of all ages, with approximately 50% having symptoms at some point during their disease.[28]

The prevalence of pericarditis in rheumatoid arthritis varies from 1% of hospitalised patients having symptoms, to 20% of patients in an outpatient clinic who were examined by echocardiographic screening, to 50% of subjects with seropositive nodular rheumatoid arthritis. The pericardial fluid is characterised by a high cell count, with a low glucose level. Serosal lining cells proliferate in affected hearts from patients with rheumatoid arthritis. Beneath the pericardium is an infiltrate of inflammatory cells, including lymphocytes and plasma cells. Localised fibrinoid necrosis occurs on the visceral pericardial surface, with surrounding palisades of histiocytes resembling a rheumatoid nodule.

Pericarditis probably occurs less frequently in systemic-onset juvenile rheumatoid arthritis (Still's disease) and mixed connective tissue disease.

Myocarditis occurs with rheumatoid arthritis, systemic sclerosis, systemic-onset juvenile rheumatoid arthritis and SLE. The histology of myocarditis in the connective tissue diseases is characterised by a mononuclear cell infiltrate and fibrosis. Granulomatous lesions are more specific for rheumatoid arthritis. The granulomas resemble those found in subcutaneous nodules, with palisading histiocytes and fibroblasts, monocytes and central necrosis. Myocarditis has been associated with antibodies to the extractable nuclear antigen ribonucleoprotein (RNP).[29] Neonatal lupus in children of mothers with anti-Ro (Sjögren's syndrome–associated antigen A), and possibly with anti-La (Sjögren's syndrome–associated antigen B), antibodies is characterised by heart block with transient myocarditis.[30]

Myocarditis associated with connective tissue diseases is suspected in the presence of a resting tachycardia disproportionate to body temperature, electrocardiographic abnormalities, unexplained cardiomegaly with or without congestive heart failure, and conduction system abnormalities and arrhythmias.

Endocarditis is not unusual in the connective tissue diseases. Valvular disease occurs more commonly than is recognised clinically, particularly in SLE.[31] Systolic murmurs are noted in up to 44% of patients with SLE, and diastolic murmurs in 1 to 3%. Echocardiography is useful to detect verrucous endocarditis (Libman-Sachs endocarditis). Verrucae usually occur in proximity to the mitral, aortic or tricuspid valve leaflet margins. The verrucae consist of aggregates of immune complexes, mononuclear cells, haematoxylin bodies, fibrin and platelet thrombi. Rarely, valve dysfunction results from scarring, and valvular insufficiency from rupture of chordae tendineae or leaflet perforation.

An association between aortic and mitral valvulitis, typical of Libman-Sachs endocarditis, and antiphospholipid antibody has been reported.[32] Antiphospholipid antibody and antiphospholipid syndrome, characterised by a prolonged prothrombin time and spontaneous non-inflammatory arterial thrombosis, deep vein thrombosis, thrombocytopenia and/or recurrent fetal loss, can occur with or without SLE. Symptomatic individuals are treated with anticoagulants, but the optimal choice among aspirin, heparin, warfarin or a combination of these therapies has not been determined.[33,34] Glucocorticosteroid therapy and immunosuppressive agents are not indicated unless active SLE is noted.[35] Treatment of asymptomatic antiphospholipid-positive individuals is not indicated without a past history of thrombosis or fetal loss.[36]

Treatment for the carditis associated with connective tissue disease is to intensify the treatment of the systemic disease, with glucocorticosteroids and/or nonsteroidal anti-inflammatory drugs (NSAIDs) used to ameliorate the symptoms of carditis.

1.5 Lyme Carditis

Lyme disease is a complex multisystem disease that results from the immunological response to infection with the spirochaete *Borrelia burgdorferi*.[37] The skin, heart, central and peripheral nervous systems and joints may be affected. Original reports of the syndrome from Europe were from Sweden in 1919, and the disease was described as acrodermatitis chronica atrophica and meningopolyneuritis (Bannwarth's syndrome). There are regional variations in disease manifestation. The syndrome usually develops in the late summer or early autumn, typically with a rash (erythema chronicum migrans) 3 to 30 days after a bite from a tick infected with the causative organism. The rash first occurs in the vicinity of the tick bite, but is usually more diffuse in later stages of the disease. Within days to weeks of the inoculation, the infection disseminates to distal skin sites, the heart, the nervous system, the liver and spleen and the synovium and muscle. Systemic immune complexes are almost uniformly present, often with cryoglobulins.

Approximately 5% of infected individuals develop cardiac involvement.[38] The most frequent clinical abnormality is fluctuating degrees of atrioventricular block, varying from first degree block to complete heart block.[39] Rarely, patients will have myopericarditis, left ventricular dysfunction and cardiomegaly. The duration of cardiac dysfunction is usually brief, 3 days to 6 weeks. Complete heart block rarely persists for more than 1 week.

The diagnosis of Lyme disease is based upon clinical manifestations, exclusion of other immunological diseases that emulate Lyme disease, and suspected exposure to tick bite(s) in an endemic area. Routine serological testing for antibodies against *B. burgdorferi* is not sensitive or specific and, therefore, not generally helpful for screening but useful for confirming the diagnosis. IgM antibody against *B. burgdorferi* characteristically is first detected 2 to 4 weeks after the onset of the erythema chronicum migrans, peaks after 3 to 6 weeks and usually declines to background levels after 4 to 6 months. IgG antibody levels increase 6 to 8 weeks after the onset of the disease, peak after 6 to 8 months and remain increased indefinitely in patient with chronic infection.

The methods of serological confirmation of Lyme disease remain nonstandardised. Immuno-

blots showing antibody to proteins of 21, 28 and 94kD are most specific for infection with *B. burgdorferi*. Indiscriminate or screening laboratory testing for antibodies against *B. burgdorferi* will result in a high rate of false positive results.

Oral and parenteral antibiotic therapy is effective in the early phase of the arthritis or dermatitis, but improvement of the carditis with such treatment is less well substantiated. Oral administration of amoxicillin 500mg 4 times daily for adults and 250mg 4 times daily for children less than 8 years old is used for treatment of first-degree heart block. Treatment should be administered for 10 to 30 days. Tetracycline or erythromycin are alternatives if penicillin is contraindicated. Intravenous ceftriaxone 2g once daily for 14 to 30 days is the drug of choice for high-degree atrioventricular block or left ventricular dysfunction. Benzylpenicillin 20MU/day or vancomycin 1g twice daily are alternatives but may be less effective.[37,40] NSAIDs provide limited relief of the symptoms that are unresponsive to antibiotics.

2. Vasculitis

Vasculitis is inflammation within blood vessels. This often results in a narrowing of the vessel lumen and causes ischaemia. The ischemia causes the major manifestations of the vasculitic syndromes and determines the prognosis. Since any size, location and type of blood vessel may be involved, the vasculitic syndromes are a heterogeneous group of diseases.[41-43] Vasculitis was a primary diagnosis in 1 per 300 patients admitted to a tertiary university teaching hospital in the US.[44] Thus, vasculitis is uncommon but not rare.

The inflammation of vasculitis usually results from the passive involvement of the vasculature and not from a specific immune response to vascular antigens. However, antibody specific to endothelial cells (AECA) also contributes to immune vasculopathy.[45,46] AECAs may contribute to thrombosis by inhibiting production of anticoagulant factors by the endothelial cell. Immunological responses to the vascular endothelium may also be important in the initiation of the common atherosclerotic plaque.[47]

2.1 Systemic Necrotising Arteritis

Systemic necrotising arteritis (SNV) is a broad group of vasculitic syndromes characterised by intense inflammation of small to medium-sized muscular arteries, defined as having a diameter greater than 2mm with a well-defined muscularis layer as well as internal and external elastic membrane. This inflammation results in vascular obstruction with extensive tissue ischaemia and infarction. The latter is responsible for the high mortality and morbidity if SNV is untreated. Typical complications include bowel ischaemia with perforation, renal failure, mononeuritis multiplex and cerebrovascular accident. The individual entities are distinguished by the presence or absence of tissue granuloma and the distribution of vessel involvement. They will be discussed as a group because they all require aggressive treatment with glucocorticosteroids and cytotoxic agents to prevent complications.[41,42]

2.1.1 Polyarteritis Nodosa

Polyarteritis nodosa (PAN) represented 7% of all forms of vasculitis in a prospective study of 1020 patients over 5 years.[48] PAN is systemic but does not usually affect the aorta, the primary branches of the aorta or the elastic pulmonary arteries. Historically, visible or palpable aneurysmal nodules of the muscular arteries were responsible for the term 'periarteritis nodosa'. Small (1 to 5mm) aneurysmal dilatations of affected arteries are common, but palpable nodules are rarely seen in modern times. The decrease in the occurrence of nodules is probably due to recognition of the disease in an earlier stage and the application of more effective treatment that suppresses the development of aneurysms in cutaneous arteries. The histology of the disease is characterised by a transmural pleomorphic cellular infiltrate, fibrinoid necrosis, thrombosis and aneurysm formation.

The aetiology of PAN is unknown. A subset of PAN, in some studies as large as 50%, is associated with hepatitis B antigenaemia.[43] Immune com-

Table II. Criteria for the classification of polyarteritis nodosa.[49] The presence of 3 or more criteria suggests a diagnosis of polyarteritis nodosa

Bodyweight loss ≥ 4 kg
Livedo reticularis
Testicular pain or tenderness
Myalgias, weakness, or leg tenderness
Diastolic blood pressure > 90 mm Hg
Elevated blood urea nitrogen or creatinine
Hepatitis B antigenaemia
Arteriographic abnormality not due to arteriosclerosis, fibromuscular dysplasia or other noninflammatory causes
Biopsy of small or medium-sized muscular artery showing granulocytes or granulocytes and mononuclear leucocytes in the arterial wall

plexes containing hepatitis B surface antigen and specific IgG and IgM have been demonstrated in the circulation and within the arterial lesions of some patients with PAN. In addition, antigens of streptococci, staphylococci and mycobacteria have been recognised in the arterial lesions or in the peripheral blood of affected patients. The quantity of antigen and the affinity of the antibody in the circulating immune complexes may influence the development of PAN.

The symptoms of patients with PAN are vague and nonspecific. They include malaise, fatigue, abdominal pain, fever, weight loss, peripheral nerve deficits with mononeuritis multiplex, and stroke.[41,42] The American College of Rheumatology criteria for distinguishing PAN from other conditions and forms of vasculitis are provided in table II. The presence of 3 or more of these criteria has a sensitivity of 82% and a specificity of 86% in differentiating PAN from other forms of vasculitis.[49]

2.1.2 Allergic Angiitis and Granulomatosis

Allergic angiitis and granulomatosis (AAG) resembles PAN in that systemic small to medium-sized muscular arteries are affected with an intense destructive inflammation characterised by fibrinoid necrosis. Distinguishing differences between the two include: (a) the predominant peripheral eosinophilia (usually > 1.5×10^9/L and > 10% of peripheral leucocytes as eosinophils) and tissue eosinophilia of AAG; (b) the tendency of AAG to occur in individuals with preceding bronchial asthma, respiratory allergy and chronic sinusitis; (c) the wide variability in AAG of the size of affected vessels, ranging from venules to muscular arteries; (d) the presence, though not in all cases, of tissue granuloma in AAG; and (e) the involvement of the pulmonary vessels in AAG.[50]

The American College of Rheumatology criteria for diagnosis of AAG are listed in table III.[51] The presence of 3 or more of these criteria distinguish AAG from other forms of vasculitis with a sensitivity of 85% and a specificity of 99.7%. Pulmonary symptoms of asthma precede the vasculitis by an average of 13 years. Gastrointestinal and cardiac involvement are more common than renal involvement.

The eosinophilia, elevation of IgE (200 to 220 IU/ml) and association with allergic disease suggest that an accelerated Type I Coombs and Gell allergic mechanism is important in the pathogenesis of AAG. The primary role of the eosinophil is suggested by the observation that AAG may occur in nonatopic hypereosinophilic diseases, such as parasitic infestation, and may be cured by treating the underlying disease and resolving the hypereosinophilia.[52] The differential diagnosis includes Wegener's granulomatosis (see below), the hypereosinophilic syndrome, eosinophilic pneumonia and bronchocentric granulomatosis.

2.1.3 Overlap Syndrome

The occurrence of the clinical features of both PAN and AAG in a single individual is termed the overlap syndrome. This observation suggests that

Table III. Criteria for the classification of allergic granulomatosis and angiitis (Churg-Strauss syndrome).[51] The presence of 4 or more criteria suggests the diagnosis of allergic granulomatosis and angiitis

Asthma
Eosinophilia > 10%
Neuropathy, mono- or poly-
Pulmonary infiltrates, nonfixed
Paranasal sinus abnormality
Extravascular eosinophils

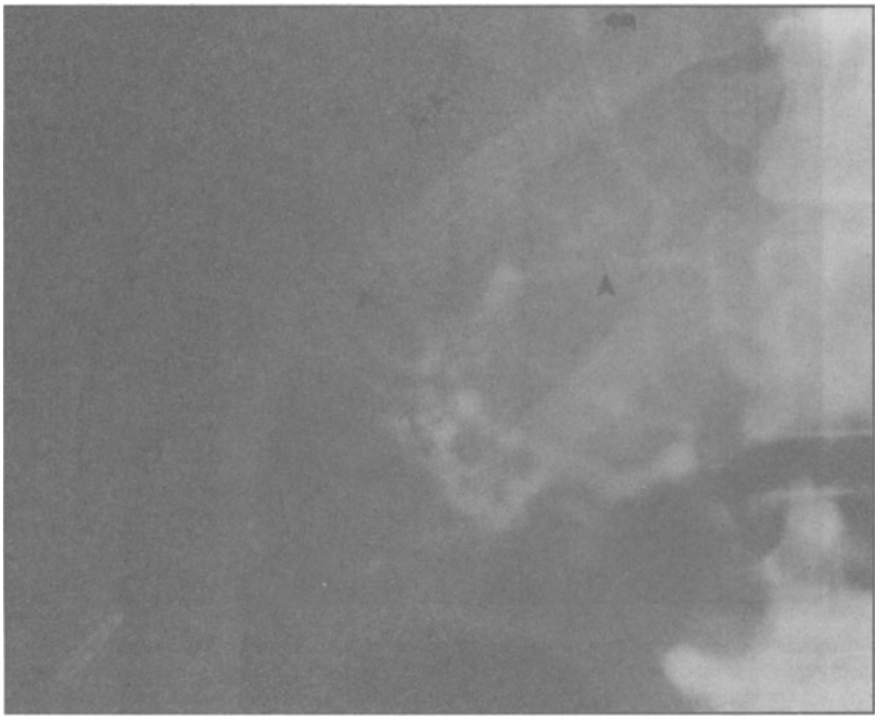

Fig. 1. Abdominal angiogram of patient with polyarteritis nodosa demonstrating irregular vessel narrowing (arrowheads) and multiple 1 to 5mm aneurysmal dilatations of the medium-sized, muscular arteries (arrows).

PAN and AAG may represent portions of the spectrum of SNV rather than distinct entities.[53]

2.1.4 Diagnosis

The diagnosis of SNV requires the histopathological demonstration of necrotising vasculitis of muscular arteries with compatible clinical manifestations. The selection of tissue for biopsy should be based upon clinical evidence of involvement, since random biopsy has an unacceptably low yield.[54] Typical safe biopsy sites include sural nerve, skin, muscle and rectum. More invasive biopsy sites, selected only if other laboratory tests indicates involvement, include kidney, lung and bowel.

Angiography, demonstrating multiple 1 to 5mm diameter aneurysms and irregular vessel narrowing, may be helpful in establishing the extent of disease and suggesting the diagnosis of SNV (fig. 1). The presence of aneurysms correlates positively with more severe and widespread vasculitis, hepatitis B antigenaemia, and increased severity of hypertension. A normal angiography does not exclude the diagnosis, since abnormalities are detected in only 80% of patients with SNV. Non-vasculitic entities associated with multiple aneurysms include thrombotic thrombocytopenic purpura, atrial myxoma, mycotic aneurysms with endocarditis, fibromuscular dysplasia and pseudoxanthoma elasticum. The role of angiography in diagnosing AAG is not defined since the frequency of aneurysm development is unknown.

The demonstration of necrotising vasculitis at a single site does not necessarily establish the diagnosis of SNV. Necrotising vasculitis limited to the appendix, uterus or skin has been described.

Cutaneous PAN is a necrotising vasculitis limited to the subcutaneous tissue, with sparing of the visceral arteries. Systemic symptoms such as fever and arthralgias may occur with cutaneous PAN. The long term prognosis is generally benign and similar to that for patients with hypersensitivity

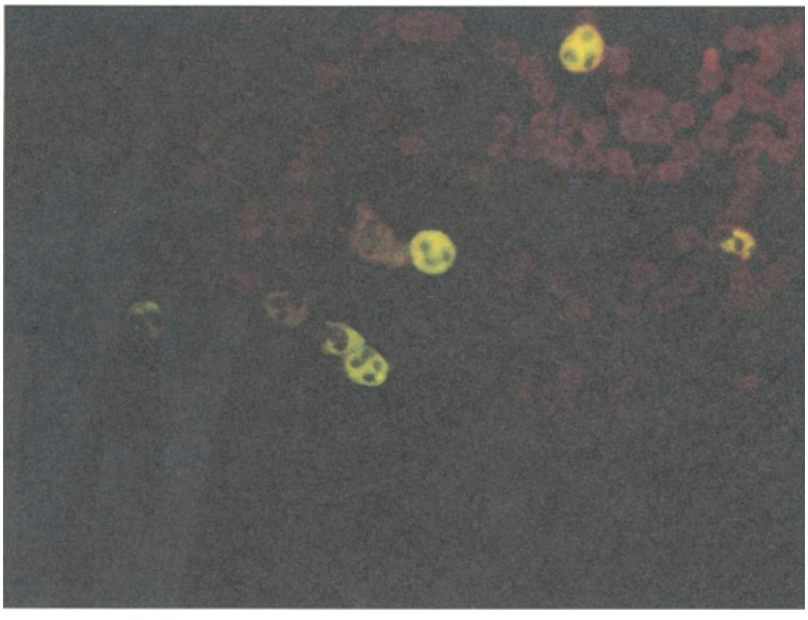

Fig. 2. Fluorescent photomicrograph demonstrating cytoplasmic fluorescence typical of the granular, cytoplasmic staining of anti-neutrophil cytoplasmic antibody in the sera of patients with Wegener's granulomatosis. The cells with the fluorescence are polymorphonuclear leucocytes. The unstained cells are crenated red blood cells. Notice that the nuclei are not stained, which contrasts with the antinuclear antibody of systemic lupus erythematosus. The staining is distributed throughout the cytoplasm with peripheral predominance in a few of the cells. This pattern contrasts with that of perinuclear cytoplasmic fluorescence detected in some cases of glomerulonephritis.

vasculitis. Therefore, aggressive therapy is usually not indicated.

Other laboratory tests are not particularly helpful in making or confirming a diagnosis of SNV. Elevated ESR and other acute phase reactants, anaemia, thrombocytosis, leucocytosis and reduced serum complement are typical, but nonspecific, and reflect the systemic effects of inflammation.

2.1.5 Treatment

The 5-year survival rate for untreated PAN is 4 to 13%. Monotherapy with systemic glucocorticosteroids increases the 5-year survival rate to 50 to 80%. The addition of cytotoxic therapy enhances the response to glucocorticosteroids and helps minimise their adverse effects by permitting a reduction of dosage. Oral cyclophosphamide 2 mg/kg/day in conjunction with oral prednisone 1 to 2 mg/kg/day is the treatment of choice.[55] The prednisone is tapered to an alternate day regimen within the first 2 to 3 months of therapy. Prednisone therapy is further tapered and can be discontinued after 4 to 8 months if the response continues. The cytotoxic therapy should be adjusted to maintain a neutrophil count of 1000 to 1500 cells/μl and is tapered after 6 to 12 months if the remission is sustained.

In chronic hepatitis B infection, interferon-α may theoretically decrease the amount of circulating viral antigen by suppressing viral replication. This could reduce immune complex formation and possibly ameliorate the vasculitis. There are no studies of interferon therapy of PAN, although there are reports of beneficial effects in hypersensitivity vasculitis with essential mixed cryoglobulinaemia, another condition associated with hepatitis B.[56]

Treatment of AAG and overlap syndrome is the same as that of PAN. AAG may respond more readily to glucocorticosteroid therapy and require lower dosages of cytotoxic therapy than PAN.

2.2 Wegener's Granulomatosis

Wegener's granulomatosis (WG) is a clinical triad of granulomatous vasculitis of the upper and lower respiratory tract, glomerulonephritis, and variable degrees of a small-vessel vasculitis.[57] Limited forms of the disease occur with airway involvement only. WG occurs with approximately the same frequency as PAN and develops in all age groups, although characteristically in the fourth or fifth decade.

A role for humoral immunity in the pathophysiology of WG is suggested by:

- increased levels of serum immunoglobulins;
- vascular deposits of immunoglobulin and complement;
- increased numbers of circulating B lymphocytes;
- the presence of autoantibodies, such as IgM rheumatoid factor and antineutrophil cytoplasmic antibody (ANCA).

ANCAs are detected in 60 to 70% of patients with WG, and the level of this antibody often fluctuates with the activity of disease.[58] The pathophysiological importance of ANCAs may be to activate neutrophils, which contribute to the vascular injury. ANCAs have also been detected in glomerulonephritis without WG, but the pattern of fluorescence is distinguished by perinuclear staining rather than the granular cytoplasmic fluorescence seen in WG (fig. 2).[59]

The cytoplasmic antigen recognised by ANCAs in WG is probably proteinase 3; the antigen recognised by perinuclear ANCAs is myeloperoxidase in 90% of patients.[59,60] The specificity of a positive granular cytoplasmic ANCA approaches 99%, but the sensitivity ranges from 50 to 96%, increasing with the systemic extent and activity of disease.[61]

The histology of WG is necrosis of small arteries and veins with fibrin deposition (fibrinoid necrosis), mononuclear cell infiltration with necrotising granulomas containing giant cells, and healing with fibrosis. Renal involvement, present in 80% of affected patients, is typically a glomerulonephritis of variable severity ranging from minimal disease to progressive renal insufficiency.

Table IV. Criteria for the classification of Wegener's granulomatosis.[62] The presence of 2 or more criteria suggests the diagnosis of Wegener's granulomatosis

Nasal or oral inflammation
Abnormal chest radiographs (nodules, fixed infiltrates, or cavities)
Urinary sediment (> 5 erythrocytes per high power field, or red cell casts)
Granulomatous inflammation on biopsy

Patients with WG usually present with complaints localised to the airway, most commonly sinusitis and/or nasal obstruction. Other frequent symptoms and signs include otitis media and ear pain, decreased auditory acuity, epistaxis and nasal septal cartilage necrosis, laryngitis and cough with sputum production and haemoptysis.

The American College of Rheumatology criteria for the diagnosis of WG are listed in table IV.[62] Two or more of these criteria suggest a diagnosis of WG, with a sensitivity of 88% and a specificity of 92%. The diagnosis of WG depends on an adequate tissue biopsy specimen showing necrotising granulomas and vasculitis. An open lung biopsy is the most likely site to have the characteristic pathological findings. Other biopsy sites, such as the nasopharynx, sinus mucosa, gingiva, or skin, may also be helpful but frequently exhibit nonspecific chronic inflammation. Vasculitis and granulomas are infrequently detected on renal biopsies, with renal histological abnormalities usually limited to glomerulonephritis. Detection of serum ANCA is helpful in supporting a diagnosis, but alone is not diagnostic. Other supportive laboratory findings include an increase in acute phase reactants, positive rheumatoid factor in 50% of patients, and haematuria with or without casts and proteinuria. Abnormal sinus roentgenograms occur in more than 95% of patients, and roentgenograms of the chest frequently reveal ill-defined infiltrates, single or multiple nodules and/or the more characteristic cavitary lesions (fig. 3).

The differential diagnosis of WG includes other forms of vasculitis, particularly AAG; syphilis;

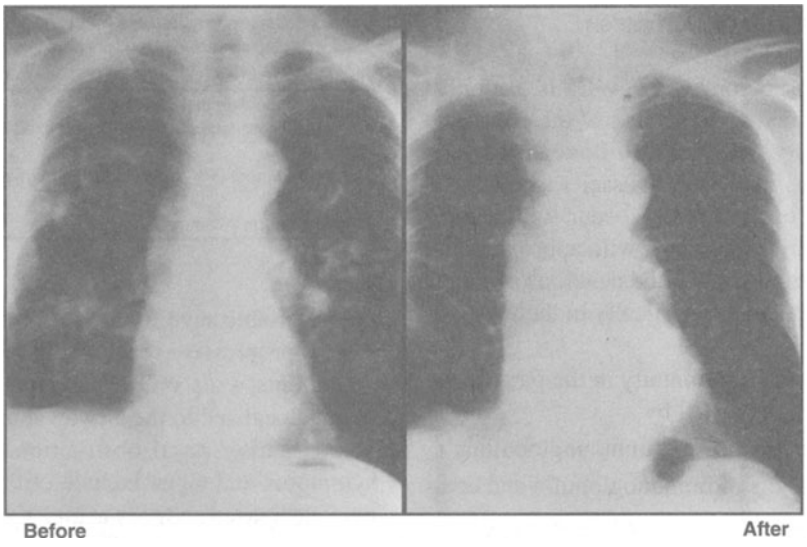

Fig. 3. Chest x-rays of a patient with Wegener's granulomatosis before and after treatment. Before: bilateral nodular infiltrates with cavitation in middle and upper lung fields. After: the same patient showing almost complete resolution of abnormalities after 2 months of treatment.

midline granuloma; Goodpasture's syndrome; streptococcal pneumonia with glomerulonephritis; malignancies of the airway, particularly nasal pharyngeal carcinoma and lymphoma; and granulomatous diseases, such as sarcoidosis, berylliosis, tuberculosis, and fungal infection.

Untreated patients with WG have a mean survival of 5 months with a 90% mortality in 2 years. Treatment is effective, with improvement in 75 to 90% of patients and possible cure in some. The treatment regimen is the same as described with PAN, although glucocorticosteroid monotherapy may be effective in selected patients. Individuals with localised disease, sparing the kidneys, would be candidates for this simplified therapy. Other cytotoxic agents, such as azathioprine, are effective and particularly useful if haemorrhagic cystitis develops with cyclophosphamide therapy.

The antimetabolite methotrexate has been shown to be effective in 1 study.[63] Methotrexate is administered once a week at doses of 15 to 50mg, and may be better tolerated than cytotoxic agents in most patients. Finally, there are anecdotal reports of the effectiveness of therapy with the antibiotic cotrimoxazole (trimethoprim/sulfamethoxazole).[64] An implication of the efficacy of antibiotic therapy is that an infectious agent, possibly with an airway portal of entry, may be important in the aetiology of WG. A prospective randomised trial comparing this less toxic form of treatment with the glucocorticosteroid/cytotoxic combination is needed before antibiotic therapy is accepted as standard care.

2.3 Microscopic Polyarteritis

Microscopic polyarteritis (MPA) is a small vessel necrotising vasculitis affecting the lung. It causes serious pulmonary haemorrhage. MPA may be an atypical form of WG,[65] although this is controversial. MPA also typically affects the kidney and abdominal viscera, and nasopharyngeal and oral involvement may occur. Rapidly progressive crescentic glomerulonephritis, often more fulminant than in WG, is typical of the renal disease. Granulomas do not usually occur in MPA, but ANCAs are frequently detected. The isotype of the ANCA in arteritis may help to distinguish clinical subsets of the disease.[66] IgM ANCA is associated with vasculitis and pulmonary haemorrhage, IgA ANCA with a syndrome resembling Henoch-

Schönlein purpura, and IgG ANCA with vasculitis in the context of antiendothelial cell antibody. Survival after diagnosis is shorter with MPA than WG. The treatment of MPA is the same as for WG, although intravenous immunoglobulin may be effective in patients with ANCA.[67] However, no controlled trial data on immunoglobulin therapy of MPA is available.

2.4 Giant Cell Vasculitis and Takayasu Arteritis

2.4.1 Giant Cell Vasculitis

Giant cell vasculitis (GCV), also referred to as temporal arteritis, is a generalised vasculitis affecting large and medium-sized arteries with a well defined elastic lamina. Temporal arteritis is a misnomer, since any arterial bed may be affected, but extracranial branches of the carotid arteries are the most commonly affected and ischaemia from GCV is rarely noted below the neck.

The incidence of GCV increases about 30-fold from 50 to 80 years of age. It occurs rarely before the age of 50 years. The importance of genetic factors is suggested by: (a) the predominance of GCV in White populations, particularly of northern Europe and North America; (b) familial aggregation; and (c) association with HLA-DR4. GCV is 2 to 3 times more prevalent in women than in men.[68] The aetiology is unknown, but a cell-mediated autoimmune response against the vascular wall, particularly the elastic lamina, is a potential explanation. Associated immunological changes include a decrease in peripheral T suppressor cells when the disease is active.[69]

The histological appearance of affected vessels is a segmental, predominantly mononuclear, cell infiltrate of macrophages and T helper lymphocytes with giant cell formation (fig. 4). The major site of involvement is the vascular media, with smooth muscle necrosis and interruption of the internal elastic membrane. Variable intimal prolifer-

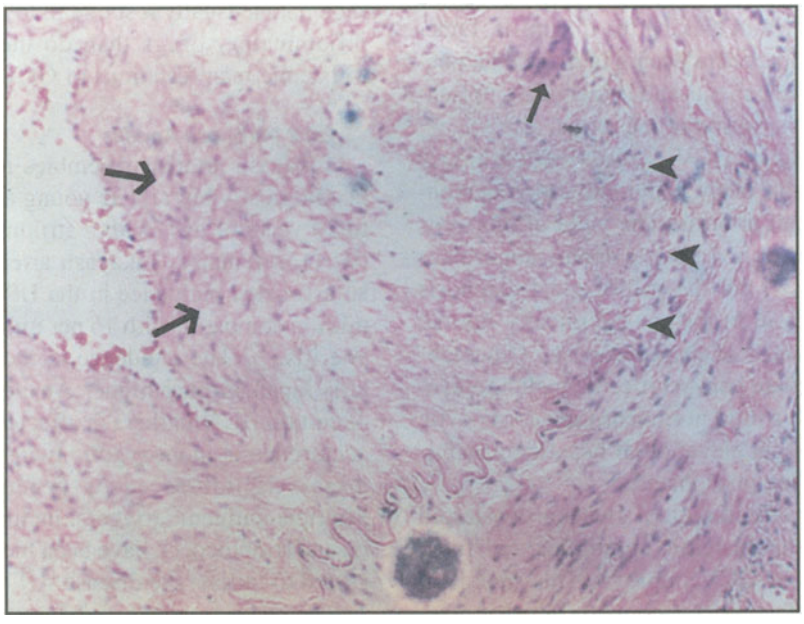

Fig. 4. Photomicrograph of temporal artery biopsy specimen in a patient with temporal arteritis (giant cell arteritis). An intense, destructive inflammatory process is demonstrated with a predominance of mononuclear cell infiltration, macrophages and monocytes, and T helper lymphocytes, with giant cell formation (small arrow). The inflammation is diffuse but somewhat focused on the elastic lamina with disruption of the elastic tissue (arrowhead). Intimal proliferation is a significant contributor to the obstruction of the vessel (large arrow). Stained with haematoxylin/eosin, magnification × 160.

Table V. Criteria for the classification of temporal (giant cell) arteritis.[70] The presence of 3 or more criteria suggests the diagnosis of temporal arteritis (giant cell vasculitis)

Age at disease onset ≥ 50 years
New headache
Temporal artery abnormality (tenderness to palpation or decreased pulsation unrelated to arteriosclerosis of cervical arteries)
Elevated erythrocyte sedimentation rate (≥ 50 mm/hour by the Westergren method)
Abnormal artery biopsy (vasculitis with a predominance of mononuclear cells or granulomatous inflammation, usually with multinucleated giant cells)

ation may progress to vessel occlusion, with the resultant ischaemia responsible for the major morbidity.

The symptoms of GCV include headache, fatigue, anorexia, fever, visual impairment and diplopia, and jaw claudication (ischaemic pain when chewing or talking). The American College of Rheumatology criteria for the diagnosis of GCV are listed in table V.[70] The presence of 3 or more of these criteria yields a sensitivity of 94% and a specificity of 91% in making the diagnosis. Functional visual impairment occurs in more than one-third of untreated patients and is secondary to ischaemia in the distribution of the retinal artery.

The diagnosis of GCV is made with a biopsy specimen, usually of the temporal artery, demonstrating giant cell arteritis. The yield of biopsy is enhanced if performed upon palpable abnormalities of the vessel, but the pathological diagnosis can be made from biopsies of clinically normal vessels in 30 to 40% of suspected cases. Other laboratory findings are nonspecific, but include elevation of the ESR, a mild normochromic normocytic anaemia, and slight elevation of hepatic transaminases and alkaline phosphatase.

Within days of initiation of glucocorticosteroid therapy, both the systemic symptoms and focal manifestations of GCV improve. This treatment also prevents the most frequent cause of irreversible morbidity, visual loss. Treatment is initially with oral prednisone 40 to 60mg daily (1 mg/kg/day), and the clinical findings and ESR are monitored. The dosage usually can be tapered to 5 to 10 mg/day over 6 to 12 months, but low-dosage therapy may be necessary for several years with a mean duration of disease approximately 24 months. Cytotoxic therapy may be useful if the adverse effects of glucocorticosteroids cause problems. Oral cyclophosphamide 1 to 2 mg/kg/day as a single daily dose or azathioprine 1 to 2 mg/kg/day have been used without proof of efficacy.

Consideration should also be given to pulse intravenous methylprednisolone 20 mg/kg/day administered over 30 to 60 minutes for 3 days, or 1 gram every 12 hours for 5 days, for acute onset ischaemic retinal disease.[71] This intravenous therapy is followed by daily oral glucocorticoids as described above.

Polymyalgia rheumatica is a syndrome that may be associated with GCV and is characterised by proximal myalgias, periarticular stiffness and pain, weight loss and fever. Some 40 to 50% of patients with polymyalgia rheumatica have GCV of the temporal artery even though they may have no head symptoms. The symptoms of polymyalgia rheumatica usually respond to lower doses of anti-inflammatory drugs than do the symptoms and ischaemic manifestations of GCV.

2.4.2 Takayasu Arteritis

Takayasu arteritis resembles temporal arteritis histologically but affects young adults, usually 15 to 20 years of age, with a striking preponderance (9 : 1) in females. Takayasu arteritis is rare, with an estimated incidence in the US of 2.6 cases per million compared with 16 per million for temporal arteritis.[72] The incidence in the Orient, particularly Japan, is much higher. An increased incidence of certain HLA markers in affected patients and its occurrence in monozygotic twins suggest that the disease is influenced by genetic factors.[73-76] Multiple antigenic triggers, including mycobacteria and streptococci, have been inconclusively suggested to initiate the disease.[77]

The disease characteristically has 3 phases. Typically, systemic symptoms develop, resolve over several weeks and are followed by arteritis, usually affecting the aortic arch and its major branches. The arteritis also resolves, with an ensu-

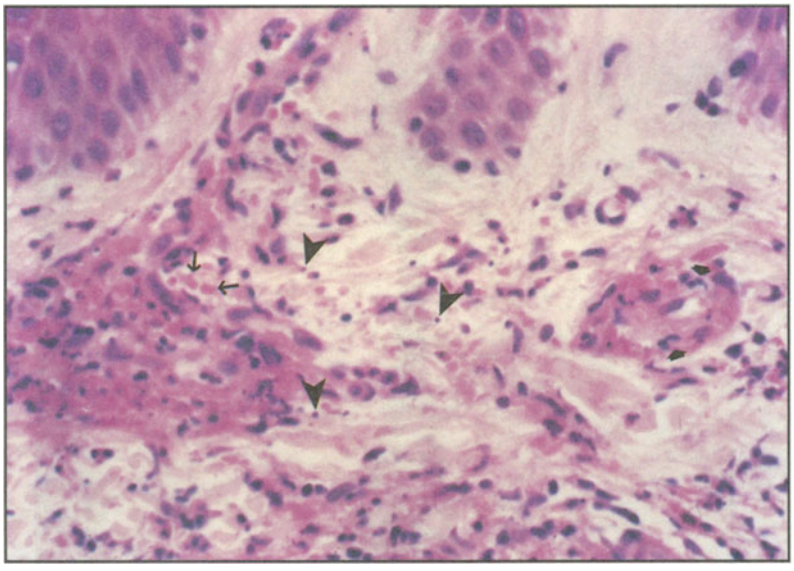

Fig. 5. Photomicrograph of skin biopsy of a patient with hypersensitivity vasculitis. The cellular infiltrate results in a 'busy, smudged' appearance. Small arterioles are infiltrated with neutrophils (small arrow head), red blood cells are extravasated (small arrow), and fragments of nuclear debris (nuclear dust) result in a basophilic stippling of the specimen (large arrow head). Fibrin strands in the affected vessels, not seen in this photograph, are another important histological finding of hypersensitivity vasculitis. Stained with haematoxylin/eosin, magnification × 158.

ing asymptomatic period (mean of 8 years) before vaso-occlusive signs and symptoms develop. The signs of the obstructive vasculopathy include an absence of or decreased arterial pulses and bruits of the aorta and/or its major branches. The pulmonary tree is affected in about half of affected patients.[78]

Routine laboratory studies generally are not helpful in making the diagnosis, although increased ESR, anaemia and hypergammaglobulinaemia are frequently noted in the early phase of the disease. Arteriography is central to the diagnosis, with findings of irregular vessel narrowing, occlusion and aneurysms.

Glucocorticosteroids are somewhat effective in suppressing the arteritis, but their efficacy in prolonging life and reducing morbidity and mortality is unknown. Current recommendations are that initial therapy with oral prednisone 40 to 80 mg/day should be reduced to alternate day therapy over several months and then tapered.[79] Cytotoxic therapy with cyclophosphamide 2 mg/kg/day, azathioprine 2 mg/kg/day, or possibly methotrexate 0.2 mg/kg orally once weekly, has been shown to be of benefit in selected patients with active disease not responding to glucocorticosteroids. Vascular surgery to relieve arterial obstruction should be considered after the inflammatory disease has abated. The presence of ischaemic retinopathy, severe hypertension, significant aortic valvular insufficiency or aortic or other large artery aneurysms is associated with an increased mortality, 26% over 5 years.[80] These findings warrant more aggressive evaluation and therapy with closer follow-up. The use of angiotensin converting enzyme (ACE) inhibitors in the management of the hypertension is controversial.[81,82]

2.5 Hypersensitivity Vasculitis

Hypersensitivity vasculitis (HV) is a heterogeneous group of clinical syndromes characterised by immune complex deposition in capillaries, venules and occasionally arterioles. The histology is described as leucocytoclastic vasculitis (fig. 5). The source of antigens for the complexes is varied

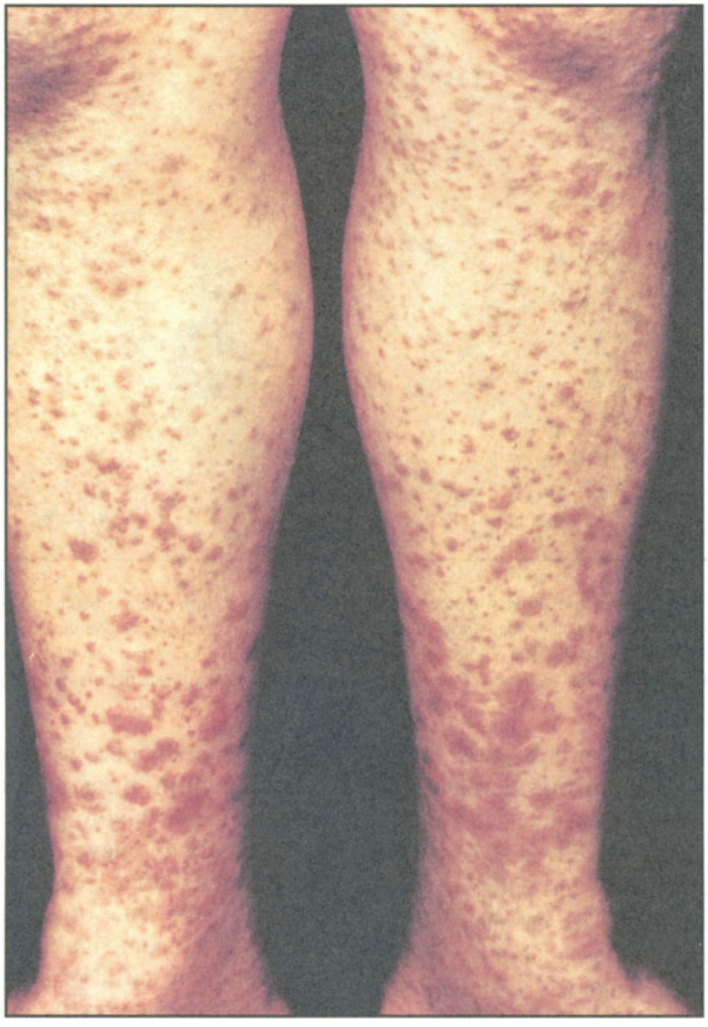

Fig. 6. Palpable purpura in a patient with hypersensitivity vasculitis. The lesions tend to occur in a symmetrical distribution in dependent areas. The fresh lesions are slightly raised due to the inflammatory infiltrates with oedema. The older lesions demonstrate hyperpigmentation due to the haemoglobin pigment products in the dermis.

and includes both exogenous (drugs, foreign proteins, food, bacteria and viruses) and endogenous (immunoglobulins, DNA and tumour antigens) substances.

HV is the most common type of vasculitis, representing 17 to 29% of cases in the American College of Rheumatology vasculitis study.[49] HV is usually not life threatening. The typical manifestations are dermatological, with more than 95% of patients exhibiting palpable purpura (fig. 6). Other manifestations include urticaria, erythema multiforme and livedo reticularis. The lesions tend to be in the same stage of development, with a symmetrical distribution usually in dependent areas of the body. Visceral involvement is infrequent and usually of mild severity.

Laboratory tests, other than biopsy, are not particularly helpful in making a diagnosis. The ESR

and levels of other acute phase reactants are typically increased, circulating immune complexes and cryoglobulins may be present and serum complement may be slightly decreased.

Specific syndromes within the HV group are numerous.[83] Serum sickness reactions are rare, since heterologous serum therapy is seldom used. A similar syndrome can occur with high-dosage antibiotic therapy in which immune complexes develop from antibodies to the circulating drug. Henoch-Schönlein purpura usually occurs in children after a viral or streptococcal illness and is associated with arthralgias or arthritis, abdominal pain, gastrointestinal tract haemorrhage, and mild nephritis with deposition of immune complexes containing IgA. Mixed cryoglobulinaemia is characterised by immune complexes containing IgM rheumatoid factor that aggregates IgG. Essential mixed cryoglobulinaemia, cryoglobulinaemia not associated with malignancy or connective tissue disease, is characterised by generalised weakness, peripheral neuropathy, and a 50% incidence of significant renal disease. Hepatosplenomegaly, mononeuritis multiplex and diffuse glomerulonephritis distinguish essential mixed cryoglobulinaemia as having a greater morbidity and mortality than other forms of HV.[84]

The prognosis of HV is generally good. Removal of an offending exogenous antigen, antihistamines for urticarial manifestations, or benign neglect may be all that is needed. Recurrent or persistent vasculitis may be resistant even to aggressive immunosuppressive therapy, plasma exchange or intravenous immunoglobulin administration,[85] which are reserved for those rare cases of HV with progressive renal disease or neuropathy.

Interferon-α therapy for mixed cryoglobulinaemia may be useful.[56] In this study, within 4 weeks of initiating therapy, 16 of 21 treated patients experienced clinical improvement, reduction or resolution of cutaneous vasculitis, improvement in renal function and decrease in levels of circulating cryoglobulin. Long term remission or suppression of disease was noted in 9 patients. Antibodies specific to exogenous interferon may limit the effectiveness of this treatment. It is unknown whether the improvement in the cryoglobulinaemia is a result of an antiviral effect of the interferon therapy.

2.6 Kawasaki Disease

Kawasaki disease is an acute vasculitis that primarily affects infants and young children. It occurs in both an endemic and epidemic form worldwide, but is most prevalent in Japan. In Japan, the annual endemic incidence is 67 per 100 000 children younger than 5 years of age. The incidence during an epidemic, which usually occurs in the autumn or late winter, is 200 per 100 000 children. Occurrence data are incomplete in the US, but 2126 cases were reported to the Centers for Disease Control between July 1976 and December 1985. The incidence seems to be increasing worldwide, and Kawasaki disease is a leading cause of acquired heart disease in children. The aetiology is unknown, with the most widely held aetiological theory being that an infectious agent is responsible.[86,87]

Kawasaki disease typically has 4 phases. Stage 1, 1 to 10 days after disease onset, is characterised by high fever (often >40°C), nonexudative conjunctival injection, erythematous and fissured lips, erythema of the pharynx and oedema of the tongue (strawberry tongue), cervical adenopathy, oedema and erythema of hands and feet, an exanthem and elevation of acute phase reactants.

Immune activation is a striking feature of this acute phase of the illness. The documented immunoregulatory abnormalities during Stage 1 include:

- T cell lymphopenia
- deficiency of CD8 suppressor/cytotoxic T cells
- increase in activated CD4 T helper cells
- polyclonal B cell activation
- ANCA
- antibodies specific for endothelial cell antigens
- increase in serum levels of cytokines such as interferon-γ, IL-1, IL-6 and TNFα.[88]

The expression of endothelial cell antigens, such as endothelial-leucocyte adhesion molecule-1 (ELAM-1), ICAM-1 and MHC class II antigens, are stimulated or enhanced by IL-1, TNFα and interferon-γ. The expression of MHC class II antigens by endothelial cells enables them to serve as antigen-presenting cells to lymphocytes. IL-1 and TNFα may increase the susceptibility of endothelial cells to immunological injury from circulating antibody.[89] IL-1 and TNFα also induce endothelial procoagulant activity and decrease anticoagulant function via reduction of endothelial thrombomodulin/protein C anticoagulant.[90] These developments contribute to endothelial injury and thrombosis.

During Stage 2 (10 to 25 days after onset), the systemic manifestations resolve as vasculitis and myocarditis develop. The vasculitis resembles PAN, affects the coronary and other medium-sized muscular arteries, and is associated with the development of aneurysms with thrombosis in 15 to 25% of untreated patients. In Stage 3 (25 to 40 days after onset), the vasculitis regresses with fibrosis of affected vessels. In Stage 4 (40 days to 4 years after onset), scar formation and organisation of thrombi of affected vessels leads to stenosis. Mortality secondary to untreated Kawasaki disease is 0.5 to 1%. Approximately 80% of the deaths are due to myocardial infarction secondary to thrombosis or rupture of a proximal coronary artery aneurysm. Other contributing causes of death are arrhythmia and heart failure. The peak time of death is 3 to 4 weeks after onset of the acute illness, but death can occur as early as 1 week or as late as 14 years.

The diagnosis is based upon recognition of the clinical features in the appropriate age group. Two-dimensional echocardiography is the mainstay of clinical assessment, utilised to assess myocardial function and dilatation of the coronary arteries. Coronary aneurysms may be detected as early as 7 days after the onset of fever, and the incidence of aneurysm peaks 3 to 4 weeks into the illness.

High dosage intravenous immunoglobulin reduces the occurrence of coronary artery aneurysms, the cause of the major morbidity and mortality. A single dose of 2 g/kg should be infused over 10 hours. This schedule of administration is more effective than giving 400 to 500 mg/kg/per day for 4 to 5 consecutive days.[91] The mechanism of action of intravenous immunoglobulin is unknown, but possibilities include: (a) immunomodulation, with a rapid decrease in the acute phase response after administration; (b) neutralisation of an unidentified infectious agent; and (c) blockade of Fc receptors. Low dosage aspirin (5 mg/kg/day) may be useful for antithrombotic therapy after resolution of the acute illness.

2.7 Other Forms of Vasculitis

The spectrum of vasculitis is diverse, and numerous entities do not fit into the above broad categories. Examples of these include: Buerger's disease, vaso-occlusive vasculitis of the lower extremities associated with cigarette smoking; Behçet's disease, prevalent in the Orient and Middle East and characterised by recurrent aphthous stomatitis, genital ulcerations, uveitis, meningoencephalitis and phlebitis; and isolated central nervous system vasculitis, a rare disease with a poor prognosis which primarily affects intracranial arteries without a systemic acute phase response.[92]

3. Conclusions

The immunological cardiovascular diseases are a heterogenous group of conditions. Many of these entities are associated with serious morbidity and mortality due to cardiac impairment, ischaemic complications or organ dysfunction, particularly of the kidneys, lung and nervous system. The systemic nature of these conditions, coupled with vague symptoms and nonspecific initial physical findings makes the differential diagnosis complicated. All physicians need to have an awareness of these illnesses, as affected individuals may be of any age and could present to a generalist or specialist.

Several of the immunological cardiovascular diseases occur following specific infections, and treatment of these infections ameliorates or mitigates these diseases. Other immunological cardio-

vascular diseases may result from a preceding infection, but the aetiological agent has not been identified. In this latter situation, the clinician must resort to symptomatic or immunosuppressive treatment.

Immunosuppressive therapy, despite the potential complications, has improved the prognosis of some of the more serious immunological cardiovascular diseases. The possibilities of active untreated infection, malignancy and collagen vascular disease should be excluded prior to the initiation of immunosuppressive anti-inflammatory treatment, as such therapy may mask and potentially complicate these conditions.

Improvement in the treatment of the immunological cardiovascular diseases awaits identification of additional aetiological agents, improved definition of host factors that predispose an individual to develop these conditions, and better understanding of the immune dysregulation responsible for the pathology.

Acknowledgements

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