Autoimmune rheumatic diseases and the heart

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Involvement of the heart is a common finding in autoimmune rheumatic diseases. Although clinically silent changes are common, potentially life-threatening manifestations are well known but early recognition is important if appropriate therapy is to be instituted.

The term autoimmune rheumatic disease encompasses systemic lupus erythematosus (SLE), primary antiphospholipid syndrome (PAPS), systemic sclerosis (SS), rheumatoid arthritis (RA), primary Sjögren's syndrome (PSs), dermatomyositis (DM) and polymyositis (PM). These conditions are diagnosed on the basis of groups of symptoms, signs and serological abnormalities. However, there is considerable overlap between these features and individual diagnostic tests are exceptional (e.g. immunoglobulin (Ig) G anti-double stranded DNA antibodies in SLE).

This article will review the frequency of cardiac manifestations in these autoimmune diseases. These are systemic diseases and are associated with potentially serious complications contributing to both mortality and morbidity. Acute vasculitis may mimic obstructive atherosclerotic disease presenting as unstable angina, myocardial infarction (MI), congestive cardiac failure (CCF) or sudden death from arrhythmia. Pericarditis, coronary artery disease, myocardial disease, conduction abnormalities and valvular heart disease can occur in up to 50% of patients.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a great mimicker of many conditions. It is characterized by inflammation and the involvement of most systems. Osler first recognized involvement of the heart in 1895 when he described pancarditis in patients with SLE.

Coronary artery disease

Premature atherosclerosis is a well-recognized problem in patients with SLE. It has been long considered a complication of corticosteroid therapy, which can alter the lipid profile to 'encourage' atherosclerosis. Acute vasculitis of the large epicardial arteries is uncommon but has been reported (Doherty and Siegel, 1985; Mandell, 1987). In addition to causing true vasculitis, SLE (and PAPS) have been associated with the development of accelerated atherosclerosis, even in the absence of standard risk factors (Doherty and Siegel, 1985). Patients with SLE or PAPS have increased levels of antibodies to oxidized low-density lipoprotein, a subgroup of antiphospholipid antibodies associated with the progression of atherosclerosis and the risk of atherosclerotic thrombosis (Amengual et al, 1996).

In a patient with SLE presenting with unstable angina or MI, the clinical and angiographic differentiation between pure vasculitis and atherosclerosis is difficult, but may be of considerable importance because of the conflicting indications for and against the use of steroids. Steroids are generally considered contraindicated in patients with acute MI, based on experimental data in which high dose steroids led to delayed healing of the infarct and thinning of the scar and even a short course may impair scar formation.

Management of unstable angina with a strong suspicion of coronary vasculitis using a short course of high-dose prednisolone may be appropriate in conjunction with standard treatment. The initial management of acute MI is the same regardless of the underlying pathology. Steroids probably should not be used if there is clear evidence of evolving MI, unless there is vasculitis involving other organs, in which case doses and duration should be minimal.

Pericardial disease

Acute pericarditis, with or without effusions, is the most common form of cardiac involve-

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ment in SLE. Mandell (1987) reviewed 22 studies of pericardial involvement in SLE and demonstrated that whereas 29% of the patients had clinical symptoms, transthoracic echocardiography (TTE) revealed abnormalities in 37% of patients (showing pericardial thickening rather than pleural effusions), and autopsy studies showed that 66% of patients had pericardial involvement. Other studies have showed TTE evidence of pericarditis in up to 75% of patients (Doherty and Siegel, 1985). The progression to tamponade or constrictive pericarditis is rare but has been reported.

The differentiation between rheumatic pericarditis and other causes of pericarditis is difficult on the basis of clinical findings. Pericarditis in these conditions usually occurs in the setting of an obvious flare, however, pericarditis is occasionally the sole or presenting finding, especially in SLE.

TTE may be helpful in SLE and the other autoimmune rheumatic diseases as they are commonly associated with findings other than effusion, for example pericardial thickening, valvular insufficiency and sterile vegetations. Sterile vegetations are present in 30–50% of patients and are usually associated with antiphospholipid antibodies (Doherty and Siegel, 1985).

Leung et al (1990) showed a correlation between antiphospholipid antibodies, valvular abnormalities and left ventricular dysfunction. Pericardial fluid glucose is usually low in SLE (Doherty and Siegel, 1985) and in RA (Pizzarello and Goldberg, 1985), but is usually normal in viral pericarditis. The presence of antinuclear antibodies or low complement levels in the pericardial effusion may not provide any significant information over and above that obtained from testing the blood. Other intercurrent problems such as uraemia, viral or bacterial infections may contribute to pericardial effusions.

Histological examination shows fibrinoid degeneration and inflammatory infiltrates. Immune complex components have been found throughout the pericardial tissue. There is no diagnostic pathological finding for lupus pericarditis, with the possible exception of haematoxylin bodies (Mandell, 1987).

Treatment depends upon coexistent extracardiac disease and haemodynamic sequelae. Often uncomplicated cases can be treated with non-steroidal anti-inflammatory drugs. Corticosteroids may be added for symptomatic relief. Tamponade necessitates corticosteroid therapy as well as drainage.

Myocardial disease

This is less common than pericardial disease and necropsy studies show that it is more frequent than suspected clinically. Doherty and Siegel (1985) reported it in up to 40% of cases of SLE. Acute myocarditis can occur up to 15% of patients and may present with unexplained tachycardia, CCF, arrhythmia and conduction abnormalities. Echocardiographic studies have suggested that myocardial function can deteriorate in parallel with flares of generalized lupus activity. This probably reflects transient myocarditis or increased local ischaemia secondary to small vessel obstruction caused by vasculitis.

Treatment includes use of pharmacological support with positive ionotropic agents, diuretic and systemic anticoagulation. There is anecdotal evidence supporting the use of high-dose steroids but few data on the use of immunosuppressive agents. It has also been suggested that steroids may be deleterious in the acute stages of viral myocarditis.

Conduction defects

These may occur in up to 10% of patients. Mobitz II or complete heart block (CHB) imply advanced disease and are a strong indication for a prophylactic permanent pacemaker.

Neonatal lupus is a disease of the newborn caused by the transplacental passage of maternal immunoglobulin (Ig) G autoantibodies. The major clinical manifestations are a transient skin rash and CHB which may be permanent. The presence of anti-La antibodies (in association with anti-Ro antibodies) is a more specific disease marker in patients with congenital heart block. As well as CHB, fibrosis of the chordae tendinae and ventricular septum have been reported. The incidence is 10% of mothers with SLE with the above autoantibodies. The current recommendation is to monitor the fetus using fetal echocardiography. If CHB or fetal hydrops develops during gestation, treatment of the mother with dexamethasone and plasmapharesis may reverse the CCF but not the CHB.

Valvular disease

Systolic murmurs have been recorded in up to a third of patients but in the majority this probably represents a hyperdynamic circulation secondary to chronic anaemia. The classic endocarditis described by Libman and Sachs in 1924, although identified in up to 50% of cases at autopsy, rarely causes clinically significant lesions which comprise proliferating and degenerating valve tissue with fibrin and thrombi.

Khamashta et al (1990) and Leung et al (1990) demonstrated valvular lesions in 23% of their patients. These lesions were associated with antiphospholipid antibodies. Roldan et al (1992) performed transoesophageal echocardiograms (TOE) in 69 patients, with a second TOE at least 18 months later. Valvular abnormalities were detected in up to 61% of patients *vs* 9% of controls. Vegetations were observed in 43% of patients. At the second TOE it was noted that lesions did regress or persisted unchanged.

TOE is too expensive to use routinely and physical examination cannot detect mild valvular disease. Thus all patients with SLE should probably receive antibiotic prophylaxis for dental and other non-sterile surgery (Crawford, 1997).

Bacterial endocarditis has also been reported on a number of occasions. As most lesions of the Libman–Sachs endocarditis are too small to be assessed accurately by TTE, any vegetations in patients with SLE who are febrile should raise the possibility of bacterial endocarditis.

PRIMARY ANTIPHOSPHOLIPID SYNDROME

PAPS is a thrombophilic disorder in which patients may develop both venous and arterial occlusions, recurrent fetal loss, or thrombocytopenia associated with persistently positive tests for anticardiolipin antibodies of the IgG or IgM type or lupus anticoagulant. Tests for the antibodies are essential to a diagnosis of PAPS.

Heart valve disease, particularly mitral valve involvement, is strikingly associated with PAPS (Khamashta et al, 1990). This may be due to a combination of valvular thrombosis and degeneration. Most patients are asymptomatic, but cases requiring replacement have been reported. Emboli from sterile vegetations can cause multiple cerebral thrombi. Valvular abnormalities occur in 36% of PAPS, 35% of lupus patients, and 48% of patients with SLE and antiphospholipid antibodies. Valvular dysfunction causing CCF occurs in up to 6% of patients (Nesher et al, 1997). Dramatic response to treatment with prednisolone, when symptomatic measures fail, is described.

RHEUMATOID ARTHRITIS

RA is a systemic disease involving many organ systems and is frequently accompanied by cardiac manifestations. Pericarditis is a common finding at autopsy but causes relatively few symptoms in patients. Manifestations range from friction rub to severe exudative pericarditis with cardiac tamponade (Doherty and Siegel, 1985; Hara et al, 1990), but most cases are benign and self-limiting. Clinically silent disease may be present in up to 50% of patients (Corrao et al, 1995).

Acute vasculitis involving the large epicardial coronary arteries is uncommon but has been reported (Pizzarello and Goldberg, 1985). Management is as for patients with SLE.

Rheumatoid nodules may deform the mitral leaflets and result in mitral insufficiency (Pizzarello and Goldberg, 1985). Aortic valve disease has also been reported in up to 25% of patients but overt aortic regurgitation occurs in only 2% of patients (Corrao et al, 1995).

Conduction disturbances may be caused by infiltration by rheumatoid nodules and may cause varying degrees of atrioventricular block — including CHB in a minority of patients.

SYSTEMIC SCLEROSIS

Atherosclerosis

No definite predisposition to coronary atherosclerosis has been demonstrated, although diffuse narrowing of intramural coronary arteries secondary to intimal thickening and periadventitial sclerosis is occasionally found. This may be associated with myocardial infarction and sudden death (Owens and Follansbee, 1987).

Pericardial disease

SS is more commonly associated with chronic effusions (35%) than pericarditis (10–15%). Pericardial tamponade is rare but has been reported. Management is as for patients with SLE.

Myocardial fibrosis

This occurs randomly throughout both ventricles, affecting the entire thickness of the ventricular wall. It occurs in up to 30–50% of patients and may cause CCF. Vasoconstriction of the small intramyocardial coronary arteries may be responsible for the diffuse myocardial fibrosis out of proportion to frankly obstructive coronary disease that is observed (Follansbee et al, 1990). Myocardial fibrosis is responsible for conduction abnormalities (Owens and Follansbee, 1987).

Pulmonary hypertension

With the improvement in the management of renal disease this is now the major cause of death in scleroderma. A median survival of 78 months with 60% dead at 5 years has been found in those patients with diffuse skin disease. Pulmonary hypertension should be suspected if there is an isolated marked decrease in diffusing capacity for carbon monoxide (<50% of predicted normal) in the absence of significant

restrictive ventilatory abnormality. Pathologically the arteries show intimal and medial hyperplasia and is usually more common in the limited cutaneous type (Follansbee et al, 1990). A subset of patients have severe pulmonary hypertension and a very poor prognosis. Death is caused by severe respiratory insufficiency and right ventricular failure. Treatment is with prostacyclin infusion, oral anticoagulation and long-term oxygen.

POLYMYOSITIS AND DERMATOMYOSITIS

These are the most common form of the idiopathic inflammatory myopathies. DM is distinguished from PM by the characteristic skin rash and both are characterized by progressive proximal muscle weakness. Cardiac involvement has been found in up to 70% of patients on echocardiography (Taylor et al, 1993) but only present clinically in only 10–15% of patients. The activity of the cardiac disease may be independent of the myositis (Rechavia et al, 1985).

Myositis in children is invariably DM. The electrocardiogram is abnormal in over half of the children, representing asymptomatic conduction abnormalities. Vascular occlusions in the absence of an inflammatory infiltrate in adults with early lesions of dermatomyositis have been well described.

Pericardial disease

This is seen in 5–25% of patients but is usually asymptomatic (Tami and Bhasin, 1993). Significant pericarditis without SLE overlap is rare.

Myocardial disease

CCF from myocarditis is found in up to 3% of patients (Bohan et al, 1977) and may be present in 25% at autopsy (Haupt and Hutchins, 1982). Epicardial arteries are rarely abnormal despite ischaemic electrocardiogram changes.

Histological changes consist of non-specific inflammatory cell infiltrate identical to that occurring in the skeletal muscle. Myocyte necrosis and fibrosis involving the cardiac conduction tissue have also been described, as has mitral valve prolapse.

Conduction disturbance

Taylor et al (1993) found electrocardiogram abnormalities in 81% of patients but 58% of these were non-specific ST and T wave changes. Varying types of atrioventricular block including bundle–branch block may also be present.

PRIMARY SJÖGREN'S SYNDROME

Cardiac manifestations in PSs are described infrequently. Rantapaa-Dahlqvist et al (1993) and Gÿongyösi et al (1996) conducted echocardiographic examination in patients with PSs. An echogenic pericardium was demonstrated in 33% of patients in the absence of clinical signs and radiographic changes. No such changes were found in control subjects. They concluded that this was a consequence of a symptom-free pericarditis associated with the basic autoimmune disease. Left ventricular function was also abnormal in spite of the fact that patients with a condition that is known to cause left ventricular dysfunction (e.g. diabetes and hypertension) were excluded.

The cardiac manifestations in PSs need further evaluation.

CONCLUSIONS

The multisystem nature of the autoimmune diseases is reflected in the frequency of major organ involvement (*Table 1*). Cardiac involvement may cause significant mortality and morbidity. In a study by Ward et al (1995), cardiovascular disease was the third most common cause of death in a group of 144 patients with SLE after death attributable to the disease itself (49%) and infection (22%). Early recognition may improve the outcome in these patients. Cardiac involvement is often clinically

TABLE 1.
Major organ involvement in autoimmune diseases

Condition	Coronary disease	Pericardial disease	Myocardial disease	Conduction system disease	Valvular disease
Rheumatoid arthritis	+	+	+	+	+
Systemic lupus erythematosus	+	++	+	++	+
Primary antiphospholipid syndrome	++	–	++	–	++
Sjögren's syndrome	–	–	–	–	–
Systemic sclerosis	+	++	++	++	+
Myositis	+	+	++	++	–

++ occurs in 5–50% of patients; + occurs in <5% of patients; – occurs rarely if ever. From Maddison et al (1998)

silent and probably does not exert serious influence on the disease outcome in most cases. In some cases, especially in patients with scleroderma, cardiac involvement is most important in determining outcome. For this reason, further studies of their prognostic significance may be indicated. HM

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KEY POINTS

- Cardiac disease is the third most common cause of death in patients with systemic lupus erythematosus.
- Atherosclerosis in patients with systemic lupus erythematosus is probably a complication of steroid therapy.
- Accelerated atherosclerosis is also a feature even in the absence of standard risk factors and is probably related to disease activity.
- Valvular abnormalities are common on transoesophageal echocardiography, therefore all patients with systemic lupus erythematosus should probably receive prophylactic antibiotics for dental and other non-sterile surgery.
- Pulmonary hypertension is a major cause of death in patients with scleroderma.
- Clinically silent disease is a common feature of the autoimmune rheumatic diseases and further studies of their prognostic significance are indicated.