Cardiac involvement in mixed connective tissue disease

A fatal case of scleroderma combined with systemic lupus erythematosus

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Summary

A 27-year-old black woman with cardiac failure, angina pectoris and Raynaud's syndrome is presented. Skin biopsy and barium studies established the diagnosis of scleroderma (progressive systemic sclerosis (PSS)). Systemic lupus erythematosus (SLE) was strongly suggested by the results of immunological studies and increasing severity of renal failure. Because of the possibility of a cardiomyopathy, cardiac catheterization, selective coronary angiography and right ventricular endomyocardial biopsy were carried out but failed to show any histological features of either SLE or PSS. The patient went into progressive renal failure despite immunosuppressive therapy and plasmapheresis and died; consent for autopsy was refused. A final diagnosis of mixed connective tissue disease (MCTD) was made. The salient features of cardiac involvement in SLE, PSS and MCTD are outlined.

Case presentation

A 27-year-old black woman was admitted to Tygerberg Hospital on 12 July 1983 from a country hospital. She claimed to have been perfectly well until 1 year previously when she noticed the onset of swelling of and pain in her small and large joints. Some 4 months before admission to Tygerberg Hospital she also experienced swelling of the face and lower limbs, weight loss, generalized malaise, a dry cough and grade II-III effort intolerance. A most striking feature in her history was the
presence of Raynaud's syndrome and angina pectoris. She had no difficulty in swallowing and denied having any alopecia.

Of significance in the past history was chronic lower-limb ulceration during the years 1979 - 1981 with spontaneous healing. Pulmonary tuberculosis had been treated during childhood. A persistently elevated erythrocyte sedimentation rate (ESR) of about 80 mm/1st h (Westergren) was recorded during the year preceding admission; tests for antinuclear factor (ANF), rheumatoid factor (RF), lupus erythematosus (LE) cells and C-reactive protein (CRP) had all been negative. Nevertheless, the antistreptolysin O titre was elevated. The Mantoux reaction was strongly positive on repeated testing but the sputum was persistently negative for acid-fast bacilli despite some reported changes on the pulmonary radiograph.

On examination at admission to Tygerberg Hospital she looked ill and had a few areas of depigmentation paranasally and at the base of the neck. Arthritis of the interphalangeal joints and ankles was confirmed. Some of the fingertips exhibited small, dry, prugangrenous changes. Her pulse rate was 120/min and her blood pressure 110/70 mmHg, and there was a heaving apex beat in the 6th intercostal space outside the midclavicular line, and loud 3rd and 4th heart sounds. There was no pericardial friction rub or pericardial effusion. There were no further abnormal clinical signs.

Side-room investigations demonstrated a hypochromic, microcytic anaemia, with normal white blood cell and differential counts but a raised ESR of 90 mm/1st h. Biochemical screening and microscopic examination of the urine revealed no abnormality. A resting ECG demonstrated sinus tachycardia of 110/min, a P-R interval of 0.13 second, and a mean frontal axis of +55°. The QRS voltage was markedly reduced in the bipolar standard limb leads, and asymmetrical T-wave inversion was evident anterolaterally. The ECG features were rather nonspecific, although they could have been interpreted as in keeping with a myopericarditis with or without a pericardial effusion (Fig. 1). The chest radiograph showed features of left ventricular (LV) cardiomegaly with associated moderate pulmonary congestion (Fig. 2A). The ANF test (speckled pattern) was positive to a titre of 1:80 and there were anti-DNA (double-stranded (ds)) antibodies. Tests for RF, LE cells and CRP and the Wassermann reaction were all negative. The C3 and C4 components of serum complement were both normal. Blood urea, serum creatinine and creatinine clearance values were within normal limits, but liver function tests demonstrated a markedly reduced albumin/globulin ratio of 31/69. Serum electrophoresis delineated raised α₂- and gamma globulin fractions, whereas serum immunophoresis identified the IgG fraction as being approximately twice normal with an additional small rise in the IgA component. The serum aspartate transaminase level was slightly elevated, the lactate dehydrogenase and creatinine kinase values were 1½ times normal, the serum aldolase level was moderately elevated, and the alanine transaminase value was within the normal range. Radiographs of the hands were unremarkable. The blood gases were essentially normal, with pulmonary function test results in keeping with the predominant restrictive pattern, as seen in scleroderma; the forced expiratory volume in 1 second/forced vital capacity was 83%, the total lung capacity 66%, and the vital capacity 50%. Results of a barium swallow study were normal. A skin biopsy specimen showed the histological characteristics of scleroderma in that the epidermis was...
normal while thick collagen bundles extended from the deep dermis into the subcutaneous fat in the absence of any inflammatory cells (Fig. 3). Despite the raised muscle enzyme values, a skeletal muscle biopsy specimen and the results of electromyography were normal. Serum ferritin values were high, and a bone marrow biopsy specimen demonstrated normal iron stores. M-mode echocardiography delineated features of mild LV decomposition with some left atrial and ventricular dilatation. The ejection fraction was borderline at 52% and there was no evidence of pericardial effusion.

A clinical diagnosis of scleroderma (progressive systemic sclerosis (PSS)) was fairly confidently made, with the possibility of additional systemic lupus erythematosus (SLE) — the entity of "mixed connective tissue disease" (MCTD). At this stage there was no evidence of renal failure. The presence of significant clinical left-sided cardiac failure despite standard medical therapy suggested the possibility of a cardiomyopathy due to one or other component of the MCTD. In view of this cardiac catheterization and right ventricular (RV) endomyocardial biopsies were performed.

Cardiac catheterization
This procedure was undertaken employing the Seldinger technique via the right femoral artery and vein. All the intracardiac pressures and indices were normal. However, LV cine angiography in the right anterior oblique projection delineated marked segmental inferior hypokinesia with slight hypokinesia of the remainder of the LV (Fig. 4), and a mild degree of mitral insufficiency. Aortic cine angiography in the left anterior oblique view demonstrated a normal aortic valve and arch. Selective coronary cine angiography in multiple projections, using 7F Judkins catheters, revealed that both the right and left coronary arteries were free of disease. The rate of coronary blood flow appeared to be normal, tending to exclude 'small-vessel disease' (intramural). An Olympus FB-2 Biopomte was then utilized to take multiple RV endomyocardial biopsy specimens from various sites so as to exclude a possible underlying cardiomyopathy. The procedure was completed without complication.

RV endomyocardial biopsy
This failed to show the classic features of scleroderma previously noted in the skin biopsy specimen. The light microscopic appearances were within normal limits (Fig. 5). Immunological studies were not carried out on the biopsy material.

Further clinical course
The normal haemodynamic parameters demonstrated by cardiac catheterization were somewhat incongruous with the clinical picture of left heart failure, although the heart was undoubtedly enlarged and contractility was abnormal. In view of this and possible collagen disease involvement of the
myocardium (despite normal RV endomyocardial biopsies, which might well have been due to a sampling error), a rather conservative dose of prednisone 40 mg/d was commenced in addition to digoxin and diuretic therapy. Within the following week the patient’s condition deteriorated further and dysphagia appeared. A barium swallow now clearly demonstrated loss of peristaltic movements within the oesophagus distal to the level of the carina, with a strong suspicion of a small ulcer at the oesophagogastric junction.

In an attempt to elucidate the possible coexistence of SLE with PSS, repeat serological screening was carried out. This showed an increased ANF (speckled) titre of 1:160, lowered serum complement titres, and positive extractable nuclear antigens for both RNA and DNA-treated fractions, detected on two separate occasions. At this stage the test for anti-DNA (ds) became negative and that for CRP positive to a concentration of 88 μg/ml.

The patient’s condition then deteriorated rapidly – particularly the severity of the cardiac failure, clearly demonstrated by the cutaneous changes on radiographs (Fig. 2B). Maximum anti-cardiac failure therapy was employed, in addition to moderate doses of steroids and four successive 3-litre plasma exchanges. At this juncture cyclophosphamide 100 mg/d was added to the therapeutic regimen. Despite this the patient developed haematuria and proteinuria, and in rapidly progressive renal failure. She died a few days later, on 11 August 1983, almost 1 month after admission. Unfortunately, consent for autopsy was refused. A final diagnosis of the syndrome of mixed scleroderma and SLE was proposed – scleroderma because of the clinical and histologically typical skin changes with concomitant abnormalities on barium swallow examination, and SLE because of the positive test for anti-DNA (ds) antibodies and the terminal, rapidly progressive glomerulonephritis.

Discussion

Scleroderma, a chronic connective tissue disorder of unknown aetiology and pathogenesis, may be self-limiting, but prognosis is mostly related to the type and extent of visceral involvement (mainly cardiac, renal and pulmonary). The condition is classified as the form without systemic involvement (morpha), and the form associated with systemic involvement, for example, systemic sclerosis. The latter can be subdivided into the CREST syndrome (calcinosis, Raynaud’s phenomenon, sclerodactyly and telangiectasia) and PSS. This classification, although often overlapping, can give some indication of prognosis, which usually worsens with increasing age and is also less favourable in males. Scleroderma has a peak onset in the 3rd - 5th decades, with a 3:1 predominance in females. It is widely distributed geographically as well as racially. Raynaud’s phenomenon occurs in 80 - 90% of patients and stratifies the cutaneous changes by 5 - 30 years in females. Oedema of the skin early on in the disease is followed by fibrosis and atrophy, clinically evident as finger-pulp atrophy which may progress to acro-osteolysis. Calcinosis and telangiectasia are usually late manifestations.

The CREST syndrome, with its relatively benign, slowly progressive course, may be associated with limited internal involvement, mostly oesophageal dysfunction. Although this is not related to an adverse prognosis, isolated cases with fatal pulmonary hypertension due to oblitative pulmonary vascular disease have been described. Associations of CREST syndrome with primary biliary cirrhosis and of systemic sclerosis with Sjögren’s syndrome are well known.

The risk of life-threatening visceral involvement is greatest in the initial 5 years. Apart from excessive collagen deposition and vascular changes in these organs, cold-induced vasospasm not only gives rise to Raynaud’s phenomenon, but renal and pulmonary function is also decreased in the winter months. High plasma renin levels observed in scleroderma may further contribute to renal vasospasm. There is no way of predicting which patient is at risk of developing severe renal disease; heavy proteinuria, hypertension, azotaemia and micro-angio-pathic haemolytic anaemia progress to oliguric renal failure. Conventional treatment is ineffective, but the newer anti-hypertensive agents such as minoxidil and captopril should be tried before nephrectomy or transplantation is considered. Early lung involvement at a stage before dyspnoea or radiological involvement becomes apparent can be revealed by lung function tests sensitive to small-airways disease, for example, maximal mid-expiratory flow and closing volume determination. Lung biopsy specimens show perivascular infiltration around small arteries, but no fibrosis. When dyspnoea sets in lung function tests reveal a restrictive pattern with interstitial fibrosis on biopsy. No effective therapy is available for progressive pulmonary disease.

Gastro-intestinal involvement as such is not associated with decreased survival but, apart from the more common dysphagia and oesophagitis leading to fibrosis and stricture formation, small-bowel involvement may lead to ileus, bacterial overgrowth, malabsorption and diarrhoea. The colon may be affected and this may produce no symptoms but ulceration, bleeding, perforation and obstruction may occur. In the musculoskeletal system, polyarthralgia or polyarthritis with radiological absorption of terminal phalanges, tendon contractions and wasting and weakness of limb-girdle muscles may be associated with the typical skin changes.

Diagnostic aspects

The various collagen disorders can be differentiated by clinical involvement patterns, serological and other laboratory investigations and histological changes, but there is often a certain degree of overlap. Regarding the differential value of auto-antibodies, one must take into consideration the fact that auto-immunity can be explained as B-cell overactivity with excessive auto-antibody production as a result of a defect in the ‘suppressor’ T-cell population, whether this is due to environmental agents (for example, viruses), genetic factors or lymphocytotoxic antibodies against this subset of modulating T cells, or even a combination of these factors.

A positive RF test, although sensitive, is not specific and may indicate any of the conditions listed in Table 1. It is positive in 70% of patients with rheumatoid arthritis, and this positivity (if unqualified) only indicates the presence of IgM RF; the 30% of patients with seronegative rheumatoid arthritis may still have a positive IgA or IgG RF which may not be detected by routine tests. RF tests are considered positive at a minimal titre of 1 : 20; the higher the titre, the more severe the disease, while most people with a low titre do not have rheumatoid arthritis. The Rose-Waaler test (regarded as positive at a minimal titre of 1:16) is highly specific for rheumatoid arthritis, although not as sensitive as the RF test.

ANF tests 2-3 are considered positive at minimal titres of 1:10; like RF, they represent a wide variety of antibodies (though against nuclear antigens). The test may also occasionally be positive in normal people (especially the elderly, and usually at a low titre), and although less specific it is generally used as a screening test for SLE, which is then confirmed by the more specific anti-DNA (ds) antibody. A high antibody titre to ds DNA is strongly suggestive of SLE; while lower levels do not exclude it, they may indicate the drug-induced syndrome.

Apart from the significance of the ANF titre, the nuclear staining pattern, although not diagnostic, may also help to establish a diagnosis: (i) homogeneous staining indicates antibodies to histones like deoxyribonucleoprotein, as in drug-induced
SLE; (ii) rim or peripheral staining correlates with antibodies to native DNA and deoxyribonucleoprotein, particularly found in SLE; (iii) speckled staining occurs with antibodies to non-histone proteins such as n-RNP (nuclear-) (see below), systemic sclerosis B and Sm antigen (see below), seen in MCTD, PSS, SLE and other conditions; (iv) nuclear staining indicates antibodies to nucleolar ribonucleic acid, and is a particular feature of PSS and Sjögren's syndrome.

ANF tests are positive in 100% of patients with active SLE, 95 - 100% of patients with MCTD, 50 - 90% with PSS, 20 - 40% with rheumatoid arthritis and 60 - 80% with Sjögren’s syndrome.

Extractable nuclear antigen contains two major antigenic components — n-RNP and Sm antigen — distinguished by enzyme (ribonuclease) sensitivity of the n-RNP antigen, as opposed to the resistance of the Sm antigen. Antibody to the Sm antigen is specific for SLE (but only positive in 30% of cases), and although antibodies to n-RNP also occur in SLE, it is particularly a marker of MCTD, which is distinguished from SLE by the lack of antibodies against Sm antigen and ds DNA. Clinically, MCTD is relatively benign, with a mixed picture of scleroderma, polymyositis and SLE but no cerebral or renal involvement. The ANF test (speckled pattern) is strongly positive, but complement titres are not decreased as in SLE. Extractable nuclear antigen may therefore be present in MCTD or SLE, or in an overlap syndrome, but not in a typical case of PSS.

As in MCTD, serum complement titres are usually normal or high in rheumatoid arthritis, except when concurrent vasculitis is present. In SLE low serum complement titles are a useful guide to disease activity and correlate well with the degree of renal involvement; C4 is usually first to fall and last to rise. When it is not clear whether fever is due to concurrent infection or to the disease itself, such as SLE and scleroderma (also diabetes, leukaemia and ulcerative colitis), a positive CRP test favours coexistent infection.

**Management**

Treatment is aimed at symptomatic relief, since no lasting effective therapy for the underlying lesion or the vasoconstrictive changes is presently available. The only clear indication for steroids is progressive myositis, although smaller dosages are also used in the early oedematous phase and for persistent arthritis. Addition of drugs capable of blocking collagen biosynthesis, such as D-penicillamine and colchicine, may contribute to softening of affected skin (for example, D-penicillamine in doses from 250 to 1 500 mg), but no consistent favourable response of either vascular disease or visceral involvement has been reported.

Immunosuppressive agents are also ineffective and chromosomal abnormalities are found in patients treated with cyclophosphamide. Sympathectomy only gives temporary improvement in peripheral capillary blood flow in Raynaud’s syndrome. Although the initial response of Raynaud’s syndrome to plasmapheresis is dramatic, improvement could not be sustained over a 6-month period.

Thus, treatment consists of anti-inflammatory drugs and physiotherapy for symptomatic relief and in order to maintain mobility and muscle power and prevent contractures. Oesophagitis is managed with antacids, conduction defects by relevant drugs and sometimes a permanent pacemaker, and stagnant-bowel syndrome with antibiotics to prevent bacterial overgrowth.

In our patient manifestations such as Raynaud’s phenomenon, finger ulceration, abnormal cine oesophagography and other visceral and muscle involvement, a positive ANF test and elevated gammaglobulin levels could fit in with the diagnosis of either SLE or scleroderma. Although the skin involvement was typical of scleroderma, lesions suggestive of coexistent disease and unusual in scleroderma included discoid LE, arthralgia and arthritis, and anaemia. This was supported by the special investigations: the positive test for extractable nuclear antigen (treated), i.e. Sm antigen, as well as the positive test for anti-DNA (ds), which confirmed additional SLE. The final diagnosis reached was that of an overlap syndrome of scleroderma and SLE.

**Cardiac involvement in scleroderma (PSS)**

Characteristically, the microvasculature is involved in the disease process of PSS, which need not necessarily be ‘progressive’ in nature — hence the synonym ‘systemic sclerosis’. The pathological hallmark of ‘contraction–band necrosis’, as evidenced by myocyte necrosis (‘myofibrillar degeneration’) accompanied by dense eosinophilic bands, has been considered an important feature in the acute phase. Difficulties remain in differentiating ‘primary’ involvement of the heart from ‘secondary’ involvement when renal and pulmonary disease coexist. Weiss et al. as early as 1943 clearly established primary cardiac involvement in this disease; an estimated 50% of patients dying from PSS have primary cardiac involvement. Renal involvement is the most common reason for a poor prognosis and death, being followed in importance by primary cardiac PSS. Cor pulmonale and hypertensive heart disease due to pulmonary and renal PSS respectively often cause difficulty in assessing primary cardiac PSS, which is said to occur in some 12% of cases. Congestive or dilated cardiomyopathy may result from the disease process affecting the intramural or small coronary arteries and giving rise to myocardial ischaemia and replacement fibrosis. Thus, patients with PSS can present with angina pectoris, acute myocardial infarction (AMI), and invariable angiographically normal epicardial coronary arteries and giving rise to myocardial ischaemia and replacement fibrosis. Thus, patients with PSS can present with angina pectoris, acute myocardial infarction (AMI), and invariable angiographically normal epicardial coronary arteries and giving rise to myocardial ischaemia and replacement fibrosis.

Conduction disturbances, such as varying degrees of atrioventricular block and bundle-branch blocks are well-known complications of the disease. Some reports have established the occurrence of progressive heart block over varying periods. All forms of arrhythmia have also been reported. Asymptomatic acute and chronic pericarditis is classic in this disease.

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**TABLE I. CONDITIONS IN WHICH A POSITIVE RF TEST MAY BE FOUND**

<table>
<thead>
<tr>
<th>Connective tissue diseases</th>
<th>Rheumatoid arthritis (70%)</th>
<th>Sjögren’s syndrome (100%)</th>
<th>SLE</th>
<th>PSS</th>
<th>MCTD</th>
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<tbody>
<tr>
<td>Other diseases with immunological factors</td>
<td>Chronic active hepatitis and other chronic liver diseases</td>
<td>Fibrosing alveolitis</td>
<td>Paraproteinaemias</td>
<td>Cryoproteinaemias</td>
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<tr>
<td>Chronic infections</td>
<td>Subacute bacterial endocarditis</td>
<td>Pulmonary tuberculosis</td>
<td>Syphilis</td>
<td>Leprosy</td>
<td></td>
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<tr>
<td>Infective mononucleosis</td>
<td>Others</td>
<td>Normal individuals (5%), especially the elderly</td>
<td>Relatives of patients with rheumatoid arthritis</td>
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</table>
Cardiac involvement in SLE

Most often this is asymptomatic and it is not until the patient presents with symptoms secondary to involvement of the other organs, especially the kidneys, that the heart is noticeably affected. This experience is not unlike that encountered in scleroderma. Some studies have shown a frequency of clinical cardiac abnormality of 50 - 60%,7,28 despite the fact that the microvascular abnormalities are usually first detected only at autopsy.26 Probably pericarditis is the commonest manifestation, occurring in some 70% of patients coming to autopsy.7,25,26

The pericardial fluid often contains autoantibodies, reduced complement, and immune complexes. Very rarely, pericardial effusions may be large enough to give rise to cardiac tamponade and constrictive pericarditis,25 particularly in procainamide-induced cases.36,37

The classic lesion in SLE is the verrucous endocardial involvement termed Libman-Sacks endocarditis.38 Valvular involvement, although rare, more commonly involves the mitral valve,45,46 and less often the aortic valve.47,48 Dajee et al.,4 in their review of cardiac valve replacement in this disease, could find a total of only 12 cases; they were quite emphatic that valvuloplasty was ineffective on account of the destructive process. Mitral or aortic valvular incompetence and subsequent cardiac failure is also known to be hastened by steroid therapy for systemic involvement, whereas mitral stenosis is rare. Such complications as acute rupture of the chordae tendineae45,46 and perforation of the mitral valve48 have been documented, but papillary muscle dysfunction secondary to AMI has rarely been reported.47 AMI due to epicardial coronary arteries is most unusual1,49 and steroid therapy has been claimed to accelerate atherosclerosis in these patients.25,45,46 The cardiomyopathy of SLE has been attributed to vasculitis of the mural coronary arteries resulting in focal necrosis, increased interstitial connective tissue and myocardial atrophy.50 However, congestive cardiac failure is most unusual unless there is hypertension due to renal involvement. Myocarditis is also rare, as are arrhythmias.52,53 Varying degrees of atrioventricular block54,55 including complete CHB56 have been reported, much interest has focused on the development of congenital CHB in infants born of mothers with SLE,56-60 suggesting the possible role of transplacental antibodies or small immune complexes.57,61

Cardiac involvement in MCTD

Alpert et al.63 reported on the cardiovascular abnormalities in 38 adult patients; 32 presented with cardiac symptoms such as dyspnoea, chest pain, presyncope and syncope, and 30 had abnormal cardiovascular signs, the majority (21 cases) exhibiting either systolic or diastolic murmurs. Other abnormal clinical signs were 3rd and 4th heart sounds, midsystolic and pulmonary ejection clicks, pericardial friction rubs, and RV enlargement. Alpert et al.63 were the first to document mitral valve prolapse in 10 of their cases (26%) of MCTD. Eleven (29%) had features of acute pericarditis sometimes accompanied by peri­cardial effusion; 11 of the 17 undergoing cardiac catheterization had varying grades of pulmonary hypertension in the absence of features of LV failure. Conduction disturbances (excluding AV block) were encountered in 5 patients, but the incidence of arrhythmias could not be reported since the patients did not undergo ambulatory ECG monitoring. In Alpert et al.63 series autopsies performed on 4 of 5 cases demonstrated severe intimal hyperplasia of both the epicardial and intramural coronary arteries, but no intimal plaques or intracoronary thrombi to suggest atherosclerosis. Furthermore, 2 exhibited prominent myocardial and perivascular leucocyte infiltration suggestive of a low-grade myocarditis. These workers concluded that cardiac abnormalities were common in MCTD.

Rakovec et al.64 reported conduction abnormalities in MCTD and produced autopsy proof of sinus node involvement.65 Clinical features of a dilated (congestive) cardiomyopathy were documented by Oetgen et al.66 and Whitlew et al.67 found evidence of myocarditis. However, widespread myocardial destruction is unusual in MCTD. A case of complete left bundle-branch block degenerating into CHB was reported by Emlen,68 and the likelihood of placentable antibody transfer was suggested by Nolan et al.69 to explain the occurrence of CHB in an infant born to a mother with undoubted evidence of MCTD.

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