LESSON OF THE MONTH

Shortness of breath in systemic lupus erythematosus: a diagnostic and therapeutic dilemma

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Series editor: Anthony D Woolf

Ann Rheum Dis 2002;**61**:588–590

CASE HISTORY

A 30 year old woman with systemic lupus erythematosus (SLE) was admitted to hospital complaining of shortness of breath, orthopnoea, swelling of ankles, and increased weight over the preceding eight days. She otherwise felt well, and reported that her lupus was inactive. She denied any associated chest pain, cough, or fever. A similar presentation had occurred three months previously, when she went to another hospital with the same symptoms, associated with a raised temperature (38.4°C). Investigations performed at that time included a complete blood picture, cardiac enzymes, and the measurement of antibodies against double stranded DNA (dsDNA). Blood and urine cultures were normal and a chest *x* ray examination was normal. All blood tests were normal with the exception of a raised troponin-t level of 0.62 μg/l (normal <0.1 μg/l). An echocardiogram and high resolution computed tomography (HRCT) chest scan were also done. She was discharged from hospital and given oral diuretics without a definite diagnosis being made. Two weeks later, her case was reviewed in our hospital and in view of the recent history, a repeat chest *x* ray examination, echocardiogram, and HRCT scan of the chest were performed. The only abnormality was seen on echocardiography, which showed a hypokinetic inferior, inferoposterior, and inferoapical left ventricle wall, with some mild to moderate left ventricular dilatation and systolic dysfunction. There was a small pericardial effusion with no valvular abnormalities and the ejection fraction of the left ventricle was estimated at 43%. Treatment was not altered and she remained stable until the current presentation.

The patient's SLE had been diagnosed 10 years previously, with initial symptoms including alopecia, Raynaud's syndrome, arthralgia, and a photosensitive skin rash. Six years after diagnosis she was diagnosed with WHO grade 4 lupus nephritis (diffuse proliferative and necrotising glomerulonephritis). Serum creatinine remained normal and she received no specific treatment for the glomerulonephritis. Two years before the current presentation she developed a vasculitic rash with painful leg ulcers, and treatment with pulse methylprednisolone (1 g) and intravenous cyclophosphamide (500 mg) monthly was started and continued for six months, then every three months for two years. Treatment was complicated by genital herpes requiring long term treatment with famciclovir. Other drugs included hydroxychloroquine 200 mg daily, prednisolone 5 mg daily, and calcitriol 0.25 μg twice daily. She was seen to have labile hypertension during this period, with blood pressure readings varying between 130/70 and 170/100 on repeated measurements.

On physical examination she was afebrile, hypertensive (blood pressure 180/100), with a 2 cm increase in the jugular venous pressure, a gallop rhythm 100/min, dual heart sounds with no murmurs, and mild pitting oedema of the ankles. Chest examination was clear without basal crepitations, there was no ascites, and there was no evidence of vasculitic rash or leg ulcers. Investigations showed urea 14.6 mmol/l (normal 3–8) and creatinine 0.145 mmol/l (normal 0.045–0.090), normal creatine kinase and troponin-t, albumin 18 g/l (normal 31–44), haemoglobin 98 g/l (normal 115–160), platelets 130×10^9/l (normal $150–450\times10^9$/l), white cell count 3.6×10^9/l (normal $4.0–11.0\times10^9$/l), C reactive protein 3 mg/l (normal 1–6), erythrocyte sedimentation rate 115 mm/1st h (normal 2–18), and 24 hour urine protein 4.2 g. She had a positive antinuclear antibody test (titre 1/2560) with extractable nuclear antigen specificity of anti-Ro/La/Sm/RNP autoantibodies, negative anticardiolipin antibodies, and dsDNA binding of 56 IU/ml (normal <7.0). An electrocardiogram demonstrated sinus rhythm 100/min and left ventricular hypertrophy by voltage criteria. Chest radiographs showed blunted costophrenic angles with no interstitial oedema. The echocardiogram demonstrated moderate to severe left ventricle (LV) global dysfunction, marked global hypokinesis, and septal/inferior wall akinesis, with an ejection fraction estimated at 28% and a left ventricular end diastolic diameter of 6.45 cm (normal <5.3).

A diagnosis of cardiac failure was made on the basis of clinical and investigative findings. A number of potential causes were considered including increased SLE disease activity complicated by myocarditis or coronary arteritis, hypertensive heart disease, drug related causes such as coronary atherosclerotic disease secondary to corticosteroid usage or cyclophosphamide cardiotoxicity and viral myocarditis.

Treatment was started with furosemide (frusemide) 120 mg daily, perindopril 4 mg daily, and digoxin 250 μg daily and proceeded to cardiac catheterisation, coronary angiography, and myocardial biopsy. The coronary angiogram was normal with no evidence of aneurysmal dilatation or atherosclerosis. The cardiac catheter showed raised arterial blood pressure, LV end diastolic pressures and right heart pressures. Six endomyocardial biopsy samples were taken from the right ventricle. The histopathology disclosed marked interstitial oedema, vacuolation, and variations in fibre size, but no haemorrhagic changes. Additionally, mild vascular inflammation was seen, mainly with polymorphonuclear cells with only occasional mononuclear cells. One of the six biopsies demonstrated a focus of myocyte necrosis with an associated mononuclear cell infiltrate (fig 1).

Three days after the treatment described above was started, the clinical signs had resolved and repeat echocardiography showed significant improvement in LV systolic function and global LV wall motion, with only mild residual septal hypokinesis. The ejection fraction had risen to 52% and the LV end diastolic diameter had reduced to 6.3 cm. The patient remains stable with an angiotensin converting enzyme inhibitor, furosemide, hydroxychloroquine, and prednisolone, with no symptoms of dyspnoea. Repeat echocardiography four months after discharge showed an LV ejection fraction of 67% and an end diastolic diameter of 5.8 cm.

Abbreviations: HRCT, high resolution computed tomography; LV, left ventricle; SLE, systemic lupus erythematosus

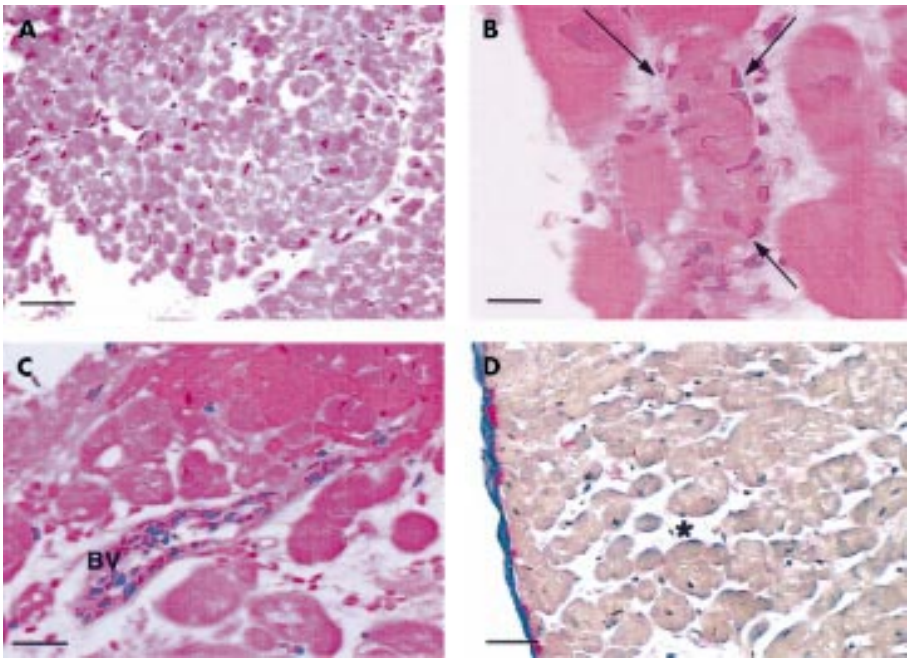

Figure 1 Endomyocardial biopsy specimen taken from the right ventricle. Stains used: haematoxylin and eosin (A–C) and van Gieson (D). (A) Non-specific features are seen suggestive of cardiomyopathy, including variation in fibre size with atrophied and hypertrophied fibres and vacuolation of myocytes (×20). (B) A focus of myocyte necrosis is seen with a moth eaten fibre (arrows) and associated mononuclear cell infiltrate (×40). (C) Mild vascular inflammation is seen, with polymorphonuclear and mononuclear inflammatory cells migrating through the vessel wall (BV) (×40). (D) Collagen stains pink and myocytes brown. There is no significant interstitial fibrosis. The separation between collagen and myocytes (*) is due to interstitial oedema in the ventricle wall. Of note there is no haemorrhage specifically suggesting cyclophosphamide toxicity (×20). (A, D) Scale bar = 50 μm; (B, C) scale bar = 25 μm.

DISCUSSION

Cardiac involvement is a well recognised manifestation of SLE, and includes pericarditis reported in 50–74% of patients, endocardial involvement in 50–63%, premature atherosclerosis and primary myocardial involvement (myocarditis) in 8–81%, depending on series and diagnostic criteria.[1] Necropsy studies suggest that myocardial involvement is common, affecting up to 40% of cases, with areas of myocardial inflammation, necrosis, and fibrosis seen.[2] An endomyocardial biopsy is required for a confident diagnosis before death of myocarditis secondary to active SLE. It has been known for some time that myocardial function is impaired in patients with SLE, in particular those with coexistent hypertension.[3] Abnormalities in systolic and diastolic LV function have been demonstrated on echocardiography[1] and cardiac catheter studies.[4] It is unclear from published reports how much of this impaired function is related to primary myocardial involvement with SLE and how much relates to drug toxicity from long term corticosteroid use, including hypertension and accelerated atherosclerosis affecting coronary arteries. Cyclophosphamide used in the treatment of vasculitic and renal complications of SLE is also a well known cause of cardiotoxicity and myocardial necrosis, usually presenting with acute pericarditis, acute cardiomyopathy, and congestive cardiac failure.[5] Cardiotoxicity is thought to be related to the dose of cyclophosphamide and has been infrequently reported at doses <200 mg/kg.[6]

It is against this background that we present this case of SLE complicated by cardiac disease, where the cause of the cardiac failure was unclear and potentially multifactorial. It was felt necessary to proceed to an endomyocardial biopsy to exclude cyclophosphamide cardiotoxicity and to obtain evidence of myocarditis secondary to active SLE, as these results would significantly affect future therapeutic decisions about this patient. The cumulative cyclophosphamide dose for this patient was 100–150 mg/kg, which together with the endomyocardial biopsy result, suggested that cyclophosphamide was not the cause of her cardiac failure. Based on laboratory evidence of active SLE and the histopathological evidence of myocarditis, it was decided cautiously to resume treatment with intravenous cyclophosphamide and corticosteroids.

THE LESSONS

- Cardiac involvement in SLE is common and often unsuspected.
- The cause of cardiac disease in patients with SLE is potentially multifactorial, including disease related, treatment related, and unrelated causes.
- Hypertension is commonly seen in SLE, but is rarely the sole cause for congestive cardiac failure in patients with SLE.
- Invasive procedures including cardiac catheterisation and endomyocardial biopsy may be necessary to investigate fully and make decisions about the treatment of patients with SLE presenting with shortness of breath.

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Accepted 17 January 2002

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UNUSUAL AND MEMORABLE

Case Number 24: Scalp necrosis in giant cell arteritis

Series editor: Gary D Wright

A 73 year old woman was referred with two weeks' history of temporal headaches, jaw claudication, and painful rash on both temples (fig 1). The jaw claudication was so intense that she could take fluids only and could not chew solid food. She had no visual symptoms. The erythrocyte sedimentation rate was 50 mm/1st h and C reactive protein 70 mg/l.

Diagnosis of scalp necrosis in giant cell arteritis (GCA) was made on clinical grounds. Biopsy was not undertaken as she had already been receiving oral corticosteroids and because of the risk (perhaps theoretical) of worsening the scalp necrosis. Treatment with corticosteroids led to a resolution of symptoms and complete healing of the scalp.

Scalp necrosis in GCA is a rare but recognised complication. It may represent a subset of severe disease. Of the 24 cases reported in English, 16 had visual loss, four gangrene of the tongue, and one nasal septal necrosis.[1]

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Figure 1 Scalp necrosis in giant cell arteritis. Reproduced with consent of the patient.

Reference

1 **Carry J**. Scalp necrosis in giant cell arteritis and review of the literature. Br J Rheumatol 1997;36:84–6.