MASTERCLASS

Deterioration of renal function in a patient with lupus

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Case history

A 38 year old woman of Pakistani-Hindu origin was diagnosed as having systemic lupus erythematosus (SLE) when she presented, aged 23, with fatigue, malaise, a photosensitive rash and arthralgia in 1977. Born in Sri Lanka, she lived in Japan from the age of nine months to 18 years. She then moved to England where the β -thalassaemia trait was diagnosed. Her father had insulin dependent diabetes and her sister also has SLE. Her sister lives in the USA, is currently well and is not available for comparative studies.

She was treated initially with prednisolone and azathioprine. Within the next 12 months she developed bilateral calf deep vein thromboses and was anticoagulated for three months. She was not taking the oral contraceptive pill.

In 1978 she presented with bilateral pleural effusions, right basal pulmonary consolidation, peripheral oedema and pericarditis. In addition, she had a vasculitic rash and cerebral lupus manifested by confusional episodes. Blood pressure was normal but she had a 24 hour urinary protein excretion of 2 g. Her plasma creatinine was 341 $\mu\text{mol/l}$ (normal range 50-125 $\mu\text{mol/l}$). She was treated with plasma exchange, blood transfusion, high dose steroids and azathioprine.

In 1980, azathioprine was stopped because she wanted to become pregnant. However, she had two spontaneous mid-trimester abortions in 1981 and 1982.

Her serology was documented as follows: anti-nuclear antibody positive (1:2560) with a homogeneous pattern, anti-DNA antibodies up to a titre of 207 U/ml ($N < 100$), with anti-cardiolipin antibodies (IgG 80 GPLU, $N < 5$; IgM negative), and the lupus anticoagulant as assessed by a prolonged partial thromboplastin time (80 s v control 32 s). Non-specific syphilis serology was negative, as were rheumatoid factor, extractable nuclear antigens, direct Coombs test and organ-specific autoantibodies.

In 1982 she developed hypertension (160/100) and thrombocytopenia. The latter did not respond to gammaglobulin infusions and she required intravenous steroids.

Renal biopsy was performed in 1984, when her creatinine was 195 $\mu\text{mol/l}$. This was reported as showing mesangial proliferation, some tufts showing striking peripheral capillary loop thickening, with 'wire loop' lesions (fig 1).

Occasional tufts showed segmental proliferation. There was a subcapsular scar but otherwise interstitial disease was mild. Immunohistochemistry showed coarsely granular deposits of immunoglobulin and complement.

In 1986, in spite of a series of plasma exchanges, her creatinine remained approximately 300 $\mu\text{mol/l}$. A trial of oral cyclophosphamide was not tolerated after only a few days because of nausea and malaise.

In 1987 she developed an acute abdomen. At laparotomy, free blood was found but no source identified. A second episode some weeks later was managed conservatively. Ultrasound showed an enlarged spleen containing areas of mixed echogenicity consistent with splenic infarcts.

In 1988, she developed end stage renal failure. Ultrasound of the abdomen showed small, non-obstructed kidneys. She was established on peritoneal dialysis following an episode of infective endocarditis associated with Permacath insertion. A murmur of mitral regurgitation had been noted first in 1982, and in 1992 she required mitral valve replacement. The excised valve showed myxoid degeneration with nodular expansion of the free margins. Small thrombotic vegetations were present on the surface of the valve cusps (fig 2). This is consistent with the heart valve disease associated with the presence of anti-phospholipid antibodies in SLE.

In October 1992 she presented with headaches, difficulty in finding words and a vasculitic rash on her left leg. In spite of intramuscular steroids, the headaches persisted, and cerebral lupus was suspected. MRI of the brain, however, showed an extensive subdural haematoma over the convexity of the left cerebral hemisphere. The patient had been involved in a minor road accident eight weeks previously, but there had been no apparent injury at that time. The clot was evacuated under local anaesthetic and she made a good recovery.

A review of the 1984 renal biopsy has shown in some glomeruli, in addition to proliferative lesions, hyaline thrombi in some of the peripheral capillary loops (fig 1). In the small muscular arteries there was oedematous thickening of the intima. These are the changes that have been associated with the presence of anticardiolipin antibodies.

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Figure 1 Lupus glomerulonephritis. The glomerular capillary loops are thickened (double arrow). A hyaline thrombus is seen in a capillary lumen (single arrow). H&E $\times 1000$ (original magnification).

Figure 2 Thrombotic endocarditis. A thrombotic vegetation (arrow) is being incorporated into the thickened, incompetent mitral valve. H&E $\times 100$ (original magnification).

Discussion

GENERAL COMMENTS

In addition to the issues relating to the causes of renal damage in SLE, this patient's history illustrates an important point in its management, that not every symptom or sign in a given patient is due to the disease. Thus the initial concern when the patient presented with a history of lethargy and a headache in October 1992 was that the disease was flaring – and not, as was later proved, that the patient had a subdural haematoma.

Although the original list of clinical features associated with the antiphospholipid variant of SLE did not include renal disease,¹ it has become apparent that patients with lupus may suffer ischaemic renal damage due to thrombi in small vessels in association with antiphospholipid antibodies.^{2–4} This patient represents an overlap of classic lupus nephritis and a more recently recognised variant.

Lupus nephritis used to be the major cause of death in patients with SLE. With the advent of immunosuppression, dialysis and renal transplantation, this is no longer the case. More recent analyses of deaths due to lupus have emphasised infection, usually secondary to immunosuppression, as an even more important factor than renal disease *per se*.^{5–7}

Lupus nephritis may present with any renal syndrome. It is, however, relatively unusual as the initial manifestation of SLE. Any component of the kidney may be involved. The light microscopic glomerular lesions can be classified according to the World Health Organisation system which is widely used in clinical trials (table). Some authors⁸ have extended the pathological classification in the form of 'activity' and 'chronicity' indices. Examples of 'active' lesions include glomerular crescents, diffuse glomerular proliferation and an interstitial mononuclear cell infiltrate, while 'chronic' lesions indicate scarring and consist mainly of glomerular sclerosis and interstitial fibrosis. Renal vessels may be involved as part of a hypertensive or vasculitic process. Recently,^{2–4} the association of microthrombi in small vessels with the presence of anticardiolipin antibodies has been described. These patients had renal impairment but no overt glomerular proliferation.

WHAT ARE THE INDICATIONS FOR RENAL BIOPSY IN SLE?

The renal biopsy in our patient was clearly important because the presence of diffuse proliferative glomerulonephritis meant that we had to persist with immunosuppressive therapy. Had the presence of glomerular thrombi been appreciated, anti-platelet therapy or formal anti-coagulation would have been considered. This patient is now fully anticoagulated because of her mechanical mitral valve replacement, but this occurred when she had already reached end stage renal failure.

A good general rule is that renal biopsy should be carried out when it may influence changes in management. The value of renal biopsy in SLE has been much debated. In a patient with no history of SLE who presents with acute renal failure, with normal sized kidneys, renal biopsy will form part of the diagnostic 'work-up'. In a patient known to have SLE, who has an acute deterioration in renal function, depending on the clinical setting, renal biopsy may be necessary to exclude other treatable causes of acute renal failure. In a patient with SLE, does a renal biopsy yield prognostic information which cannot be deduced from clinical or bio-

WHO morphological classification of lupus nephritis

1. Normal glomeruli.
2. Mesangiopathy, with mesangial widening +/- hypercellularity.
3. Focal proliferative glomerulonephritis.
4. Diffuse glomerulonephritis.
5. Diffuse membranous glomerulonephritis.
6. Glomerulosclerosis.

chemical markers? Studies which attempt to correlate histological, clinical and biochemical data with outcome are confounded by: (a) the nature of the disease whose activity fluctuates and affects a variety of organ systems and may affect the kidney focally; (b) the retrospective nature of these tests. To study the evolution of different forms of lupus nephritis in untreated patients is not ethically justifiable; (c) the variations in treatment of the patients, and (d) variations in time since disease onset.

Generally, patients with mesangial and membranous nephropathy have a better outcome than those with focal or diffuse proliferative glomerulonephritis⁹⁻¹¹ although this is not a universal finding. Clinical and biochemical markers have also been of prognostic value, including duration of renal disease¹² hypertension, serum creatinine and 24 hour urinary protein.⁹⁻¹² However, it is well documented that patients with mesangial disease may have significantly raised serum creatinine levels and patients with proliferative glomerulonephritis can have no overt evidence of kidney disease.¹³ Thus while there is little evidence that renal biopsy enhances the ability to predict outcome in an individual case,¹⁴ we have a low threshold for renal biopsy. Renal biopsy is imperative when there is either: (1) significant proteinuria (>1 g/day) or (2) renal insufficiency with an isotopic glomerular filtration rate below normal. This is because the biopsy has implications for treatment, as discussed below.

THERAPEUTIC INTERVENTION

Ideally, no patient with renal lupus should go into end stage renal failure. It is important to gain the patients' cooperation. Many of them, like our patient, are young women and they may have to take immunosuppressive and anti-hypertensive medication for years. These drugs have many potential side effects, while their benefits may not be immediately obvious.

INITIATION OF TREATMENT

Corticosteroids remain at the cornerstone of treatment in SLE. There is a distinction between using high doses of intravenous steroids for their profound anti-inflammatory effect and using steroids chronically as immunosuppressive agents.

Long term follow up of patients with lupus at the National Institutes of Health has suggested that the addition of intravenous cyclophosphamide to oral steroid treatment is beneficial in preserving renal function.¹⁵ The dose of steroid was 1 mg/kg of prednisone for four to eight weeks, which was then reduced as tolerated. Intravenous cyclophosphamide was given at a dose of 0.5–1.0 g/m² body surface, monthly for up to three months, then once every three months. However, these studies may be criticised as the patients had a wide range of duration of renal disease at the time of entry into the study (up to 49 months) and no information was provided about treatment before the study. The conclusions were based

on 20 patients who were randomised to intravenous cyclophosphamide treatment. Five of these patients had membranous disease, a category considered by many to be milder than proliferative disease and not requiring such aggressive treatment. This group was not analysed separately. The data for oral azathioprine and oral cyclophosphamide (in addition to oral prednisone) were almost as impressive as those for intravenous cyclophosphamide, and diffuse proliferative glomerulonephritis was well represented in this group. Our patient was unable to tolerate oral cyclophosphamide because of nausea, and stopped azathioprine when she wanted to become pregnant. We have now treated over a dozen patients with prednisolone and azathioprine during pregnancy without observing any adverse effects on the fetus or the mother.

Pulse methyl prednisolone therapy (1.0 g/m² over 30 minutes for three daily doses, then monthly doses for six months) and pulse intravenous cyclophosphamide (0.5–1.0 g/m² either monthly for six months or monthly for six months followed by three monthly doses for two years) have been compared in patients. Most of these patients had diffuse proliferative nephritis, and all were taking oral steroids.¹⁶ The outcome showed that intravenous steroid alone was associated with a higher probability of an exacerbation of nephritis and of a doubling of serum creatinine.

Thus a combination of a cytotoxic drug plus corticosteroid appears to be superior to corticosteroid alone in the treatment of lupus nephritis, and on balance we favour intravenous cyclophosphamide. These findings have major implications for the time and cost of treatment, plus potential toxicity, if it becomes standard clinical practice. Cyclophosphamide has potential ovarian toxicity in a population of patients with lupus who are mainly women of childbearing age.

Is there a group in which less aggressive treatment is justified? The Lupus Nephritis Collaborative Study Group identified certain patients with membranous and proliferative glomerulonephritis who had milder disease based on normal serum creatinine at the time of entry to the study and a response to therapy within 48 weeks (prednisolone and oral cyclophosphamide). They proposed that such patients would not require long-term cyclophosphamide therapy.¹⁷

On the basis of a renal biopsy showing lupus nephritis, the degree of glomerular proliferation will determine the initial dose of steroids given. We use intravenous methylprednisolone if there is a considerable degree of glomerular proliferation. The histological grade will determine whether a cytotoxic drug is required in addition to corticosteroids. In the presence of focal or diffuse proliferative glomerulonephritis, we often use intravenous cyclophosphamide in addition to corticosteroids to initiate treatment, the intravenous cyclophosphamide being given in monthly pulses for approximately three months.

Plasmapheresis has not been shown to improve outcome in patients who are already

taking oral prednisolone and oral cyclophosphamide.¹⁸

MAINTENANCE THERAPY

Inexperienced physicians tend to reduce therapy too soon. Once the patient is in remission, usually after two to three months of treatment with cytotoxic plus steroid, immunosuppression should be reduced gradually over a period of one to two years to a well-tolerated maintenance level: treatment should be held at this level for several years. For example, in a patient with diffuse proliferative glomerulonephritis, we switch from steroids-plus-cyclophosphamide to steroids-plus-azathioprine once the patient is in remission. Azathioprine is useful in this context, both as a steroid sparing agent and as an immunosuppressive. We use a dose of 2–3 mg/kg.

ANTICARDIOLIPIN ANTIBODIES AND MICROTHROMBI

The treatment of renal impairment in those patients with anticardiolipin antibodies in whom renal biopsy shows microthrombi is not well defined. Corticosteroids may suppress production of the circulating antibodies, but this is not necessarily followed by clinical improvement. Antiplatelet therapy with aspirin and/or dipyridamole or anticoagulation with warfarin may be appropriate. There are no clinical trials to confirm this, and treatment is empirical.

In our experience, patients who have glomerular thrombi alone have moderate degrees of renal impairment and, so far, we do not have any patients in this category with end-stage renal failure, though follow up times are short and this is not the universal experience.⁴ In our patient we do not know how much the glomerular thrombi contributed to her renal failure, compared to the diffuse proliferative glomerulonephritis.

It is possible that the glomerular hyaline thrombi were in fact emboli from mitral valve thrombus. However, in association with intimal thickening, they are likely to be thrombi and not emboli: thrombi and intimal thickening are well recognised in patients with anti-cardiolipin antibodies in the absence of valvular heart disease.

OTHER FACTORS

Renal biopsy in the patient with hypertension, proteinuria and a glomerular infiltration rate of <50% may show that the deterioration in renal function is non-immunologically mediated. This has implications for treatment in that angiotensin-converting enzyme inhibitors may be appropriate to reduce proteinuria and to slow the rate of loss of renal function. Increased immunosuppression would obviously be inappropriate in this context. As in all patients with renal disease, considerable attention must be paid to the treatment of coexistent hypertension, which may be

exacerbated by corticosteroid therapy. Ideally the blood pressure should be maintained below 140/80.

Occasionally, renal biopsy reveals other pathological processes, such as interstitial nephritis either secondary to SLE or to drugs such as non-steroidal anti-inflammatory drugs. In this case, high dose steroids and withdrawal of the drug will be appropriate.

POSSIBLE NEW TREATMENTS

As this patient's history confirms, we cannot always prevent end-stage renal failure. There remains a need to explore new agents and techniques. Other treatments which have been tried in lupus nephritis include intravenous gammaglobulin,¹⁹ cyclosporin A,²⁰ and monoclonal antibodies.²¹ As yet, these are not part of the standard treatment in lupus nephritis. Only small numbers of patients have been treated and larger trials are therefore needed.

Summary of key management points

- 1 Patients with SLE who have significant renal involvement should be managed jointly by a consultant rheumatologist and a consultant nephrologist in a specialised centre.
- 2 In the presence of proteinuria and/or renal impairment maintain a low threshold for renal biopsy, because the result has implications for a variety of treatment options designed to prevent a deterioration in renal function.
- 3 In the presence of diffuse proliferative glomerulonephritis, there is justification for using intravenous cyclophosphamide plus steroids to initiate treatment, and prednisolone plus azathioprine as maintenance therapy.
- 4 In patients with anticardiolipin antibodies and renal impairment associated with the presence of small vessel microthrombi, start treatment with aspirin, or aspirin plus dipyridamole. Warfarin is an alternative.
- 5 Patients with SLE and renal impairment require careful follow up, plus treatment of coexistent hypertension.

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