Lupus nephropathy and vasculitis

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Abstract
Multi-system autoimmune diseases, including systemic lupus erythematosus (SLE) and vasculitis, are inflammatory conditions of unknown cause. Renal involvement can occur in a variety of forms and usually represents a severe disease manifestation. SLE is frequently complicated by renal involvement (lupus nephritis). The main renal manifestation of vasculitis is pauci-immune, necrotizing, crescentic glomerulonephritis. This is potentially reversible but, if left untreated, results in end-stage renal failure and death within days to weeks. Vasculitis is the most common cause of the syndrome of rapidly progressive glomerulonephritis (RPGN), but this can also be seen in SLE and anti-glomerular basement membrane disease. Other less frequent examples of renal involvement in multi-system autoimmune disease include vascular lesions in scleroderma, and interstitial nephritis or glomerular lesions in Sjögren's syndrome or rheumatoid arthritis. Lupus nephritis and renal vasculitis are the most frequent causes of renal failure in multi-system autoimmunity and are discussed in this contribution.

Keywords anti-neutrophil cytoplasmic antibody; immunosuppression; lupus nephritis; microscopic polyangiitis; rapidly progressive glomerulonephritis; systemic lupus erythematosus; systemic vasculitis; Wegener's granulomatosis

What's new?

- Despite immunosuppressive therapy, renal involvement remains a strong predictor of death in both anti-neutrophil cytoplasmic antibody-associated (ANCA-associated) vasculitis (AAV) and lupus
- Mycophenolate mofetil is an effective therapy in lupus nephritis, and is used both to control disease and prevent relapses
- Monoclonal antibody therapy targeted against B cells has shown efficacy in both systemic lupus erythematosus and AAV

Lupus nephritis

Epidemiology

Systemic lupus erythematosus (SLE) has a prevalence of 27 per 100,000 in the UK, predominantly affecting women under the age of 40 years. Overt renal disease occurs in at least one-third of SLE patients and is the most common severe manifestation. It is one of 11 diagnostic criteria proposed by the American College of Rheumatology, four of which are required to support a diagnosis. Development of nephritis is closely linked to survival and morbidity; 10–20% patients die and 10–25% reach end-stage renal disease (ESRD) within 10 years. However, there is considerable variation in presentation, pathology, course and outcome. Lupus nephritis responds to corticosteroid and immunosuppressive therapy, but the toxicity of drugs contributes to morbidity and mortality.

Pathology

Immune deposits in the glomeruli and mesangium are characteristic of SLE, and stain positive on immunofluorescence for immunoglobulin G (IgG), IgM, IgA and the complement components, C3, C1q and C4. Circulating autoantibodies to cellular antigens (particularly anti-dsDNA, anti-Ro and anti-C1q) and complement activation, with correspondingly reduced serum C3, C4 and C1q, are typical of lupus nephritis. Following the appearance of immune complexes, an inflammatory reaction develops, leading to mesangial cell proliferation, expansion of the mesangial matrix and infiltration of inflammatory leucocytes. Other pathogenic mechanisms include the infarction of glomerular segments, thrombotic microangiopathy, vasculitis and glomerular sclerosis. Extra-glomerular features of lupus nephritis include tubulo-interstitial nephritis (70% of patients), renal vein thrombosis and renal artery stenosis. Thrombotic manifestations are associated with autoantibodies to phospholipids, which are detectable as circulating anticardiolipin autoantibodies or the lupus anticoagulant.

Clinical features and investigations

Renal disease is the first manifestation of disease in only 25% of SLE patients. In 5% of cases renal abnormalities may occur up to several years before other diagnostic criteria or serological abnormalities become apparent. Lupus patients may present with asymptomatic urinary abnormalities on routine testing (microscopic haematuria or proteinuria), with hypertension or with a 'nephritic' syndrome (40%). Less commonly, lupus nephritis presents as acute renal failure, which may be accompanied by other severe manifestations, such as myocarditis or cerebritis.

The following factors influence the outcome, and should be considered in the evaluation of patients:

- demography (age, sex, socio-economic status, race, duration of SLE and nephritis)
- renal function (glomerular filtration rate, urinary abnormalities, blood pressure)
- serology (autoantibodies, complement, immunoglobulins, albumin)
- histopathology (light microscopy, immunofluorescence)
- extra-renal organ involvement and drug exposure.

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The histological appearance of glomerular disease has been classified according to the pattern and extent of immune deposition and inflammation (Figure 1, Table 1).[1] Transformation to a more severe or less severe histological class is well documented and may result from treatment or be part of the natural history of the disease. The activity and chronicity of lesions identified at renal biopsy are used to assess whether treatment should be intensified, and chronicity indices predict long-term renal outcomes. However, interpretation of renal biopsy is subject to observer bias and may be influenced by sample size.

Management

Treatment of lupus nephritis is governed by histological stage. Most data suggest that WHO class II lupus nephritis has a benign course, and treatment in the absence of other indications is usually not required. The outcome and treatment of class V disease are debated, reflecting differences in the interpretation of histological criteria. The decision to treat active WHO class III and IV lupus nephritis is less controversial. The first phase of treatment (known as induction) is aimed at inducing disease remission, achieved with a combination of corticosteroids and another immunosuppressive agent. Traditionally, pulsed intravenous, cyclophosphamide has been used. Long-term follow-up suggests that a regimen of six fortnightly intravenous pulses of 500 mg was as effective, but safer than using higher doses.[2]

Recent randomized controlled trials have shown that mycophenolate mofetil (MMF) is at least as effective as pulsed intravenous cyclophosphamide when used to induce remission in lupus nephritis classes III–V, with MMF superior in non-White patients.[3,4] Induction therapy generally lasts 3–6 months, although complete remission may take as long as 24 months.

Early withdrawal of immunosuppression increases relapse rate, hence MMF or azathioprine are commonly used following induction treatment to maintain remission. Recent evidence suggests that MMF is more effective at preventing relapse than azathioprine.[5] The optimum duration of therapy is debated; continuing treatment for a significant disease-free period, such as 2 years, is recommended. Ciclosporin and tacrolimus are alternative agents, particularly used in children.

Cyclophosphamide, MMF and azathioprine have severe adverse effects. Cyclophosphamide is associated with premature menopause in up to 50% of women, myelosuppression, an increased risk of severe infections and bladder malignancy. Azathioprine is associated with hypersensitivity reactions. With both azathioprine and MMF the risk of myelosuppression and infection are lower than with cyclophosphamide, but there is an increased risk of skin malignancy after prolonged exposure. Mycophenolate is teratogenic and should be avoided in pregnancy.

Treatment-related death and morbidity from infection are significant problems in SLE, and other less toxic agents should be sought. B lymphocytes play an important role in the pathogenesis of SLE, and recent studies have investigated the role of monoclonal antibodies in depleting or blocking stimulation of these cells. Although randomized trials have failed to convincingly demonstrate an additional benefit of rituximab (anti-CD20 chimeric monoclonal antibody) given in addition to MMF and glucocorticoids for remission induction in SLE and lupus

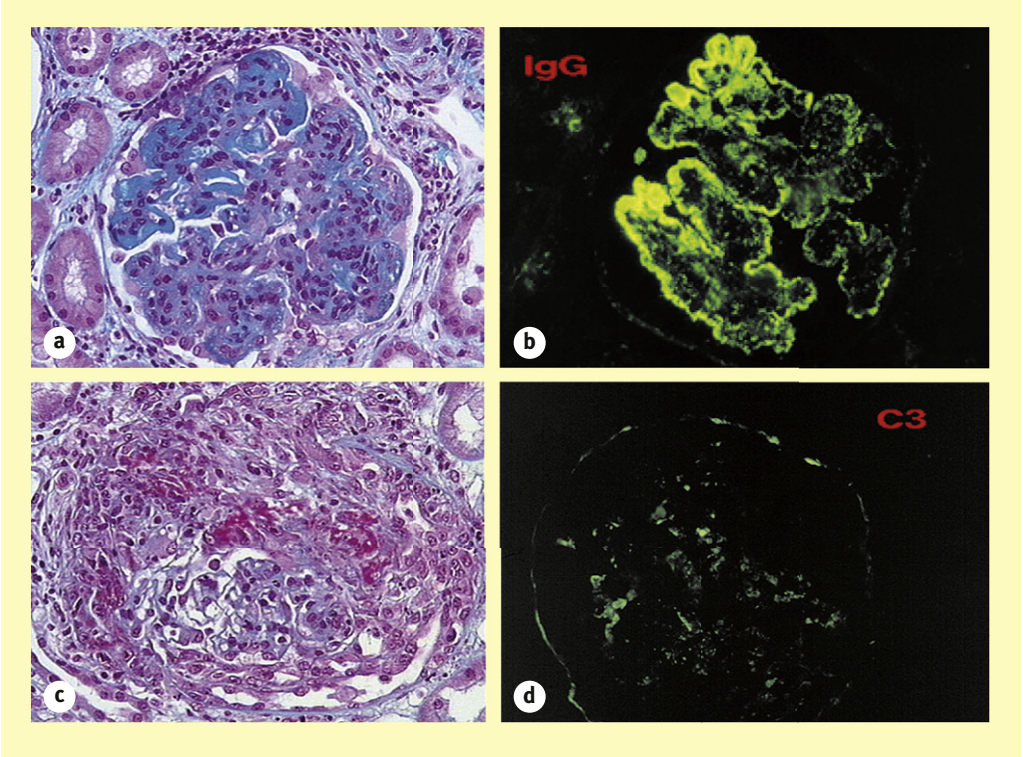

Figure 1 Renal histology in class IV lupus nephritis **a** light microscopy **b** immunofluorescence ANCA-associated 'pauci-immune' vasculitis **c** light microscopy and **d** immunofluorescence. Kindly provided by Dr Franco Ferrario, S. Carlo Borromeo Hospital, Milan, Italy.