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 complicated by renal involvement (lupus nephritis) in over one-third of patients. Small vessel vasculitides, including anti-neutrophil cytoplasmic antibody-associated and anti-glomerular basement membrane disease, also frequently affect the kidneys causing a rapidly progressive glomerulonephritis (RPGN). Histologically, this manifests as a necrotizing, crescentic glomerulonephritis. This is potentially reversible but, if left untreated, would generally result in end-stage renal failure and death within days to weeks. A crescentic glomerulonephritis may also be seen in SLE, but this is not the typical pattern of lupus nephritis, which is usually characterized by immune complex deposition causing a diffuse, proliferative glomerulonephritis. Lupus nephritis and renal vasculitis are the most frequent causes of renal failure in multi-system autoimmunity.

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

What's new?

- Despite immunosuppressive therapy, renal involvement remains a strong predictor of death in both anti-neutrophil cytoplasmic antibody (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 targeting B cells has shown efficacy; belimumab is now licensed as additional therapy for non-renal systemic lupus erythematosus (SLE), and rituximab is also used as a second-line therapy for SLE
- Rituximab is licensed for the treatment of refractory and relapsing AAV. It can also be used as an effective maintenance agent, and may be more effective than standard treatment with azathioprine

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. In the 2012 Systemic Lupus International Collaborating Clinics (SLICC) diagnostic criteria, lupus nephritis in the presence of anti-nuclear antibodies or anti-double stranded DNA antibodies is sufficient to make a diagnosis of SLE.[1] Development of nephritis is closely linked to reduced survival and chronic morbidity; 10–20% of 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 drug toxicity 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 with nephritis), which involves lymphoid follicle formation and T-cell tubulitis; 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 prognosis

Nephritis is the first manifestation of disease in 25% of SLE patients. In 5% of cases renal abnormalities may occur 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.

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Poor prognostic factors that should be considered in the evaluation of patients with lupus nephritis include:

- demography (black or Hispanic race and ethnicity; delay in diagnosis or therapy commencement)
- impaired renal function (elevated serum creatinine, nephrotic range proteinuria, hypertension)
- anaemia with haematocrit less than 26%
- histopathology (severity of acute and chronic tubulo-interstitial disease and interstitial inflammation as well as the presence of cellular crescents)
- higher relapse rate and failure to achieve a partial or complete remission. Following treatment, normalization of proteinuria and the absence of relapse of nephritis are the best predictors of a good outcome.

The histological appearance of glomerular disease has been classified according to the pattern and extent of immune deposition and inflammation (Figure 1, Table 1).[2] Transformation to a more severe or less severe histological class is well documented; it 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.

The risk of cardiovascular disease is greatly increased in SLE and is a major cause of late mortality.

Management

Treatment of lupus nephritis is governed by histological stage. Most data suggest that ISN/RPS 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 ISN/RPS 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. Current guidelines regard intravenous cyclophosphamide or mycophenolate mofetil (MMF) as equivalent immunosuppressive agents and there is increasing use of lower dose cyclophosphamide regimens.[3,4] Whether ethnic or geographic factors should influence the selection of agent remains controversial. Induction therapy with higher dose corticosteroids aims for a response by 3–6 months, although complete remission may take more than 24 months to achieve.

A failure to reach complete remission or early withdrawal of immunosuppression increases relapse rates, hence MMF or azathioprine with low-dose corticosteroid are commonly used over the longer term to maintain remission, MMF being probably 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 2–5 years, is recommended. Ciclosporin and tacrolimus are alternative agents, particularly for children and in Class V, membranous, nephropathy.

Cyclophosphamide, MMF and azathioprine have severe adverse effects. Cyclophosphamide is associated with infertility and premature menopause, myelosuppression, an increased risk of severe infections and (with total cumulative doses >20 g) bladder malignancy. The risk of infection during treatment with

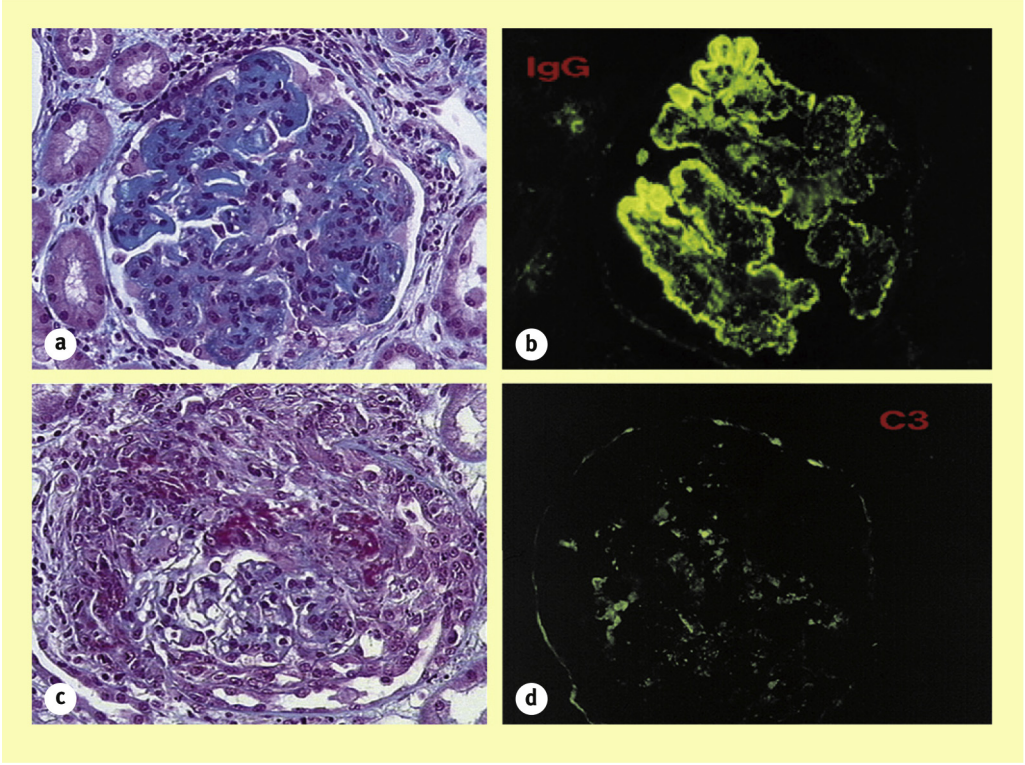

Figure 1 Renal histology in class IV lupus nephritis **(a)** light microscopy **(b)** immunofluorescence anti-neutrophil cytoplasmic antibody-associated 'pauci-immune' vasculitis **(c)** light microscopy and **(d)** immunofluorescence. Kindly provided by Dr Franco Ferrario, S. Carlo Borromeo Hospital,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