

## Fibrillary and immunotactoid glomerulopathy

### DEFINITION

Fibrillary glomerulonephritis is characterized by the appearance on electron microscopy in the mesangium of randomly arranged fibrils that are larger than those in amyloidosis (20–30 nm versus 10 nm in diameter) and do not stain with Congo red. Immunotactoid glomerulopathy is characterized by the formation of microtubules (30–40 nm in diameter).

### EPIDEMIOLOGY AND ETIOLOGY

It is controversial whether fibrillary glomerulonephritis and immunotactoid glomerulopathy are separate disorders. Fibrillary glomerulonephritis accounts for 85% of cases. It occurs principally in adults. In one centre's biopsy series it occurred in 1% of biopsies.

### PATHOGENESIS

Immunohistochemistry in cases of fibrillary glomerulonephritis is characterized by IgG4 subclass deposition, suggesting this may be key in fibril formation. Patients with immunotactoid glomerulopathy may have either a circulating paraprotein or monoclonal immunoglobulin deposition, and there is a disease association with B-cell lymphoma or chronic lymphocytic leukemia.

### CLINICAL HISTORY

Patients with these conditions may present with proteinuria usually with associated microscopic hematuria, hypertension, or progressive renal insufficiency. About 50% of patients develop end-stage renal failure within 2 years.

### HISTOLOGY

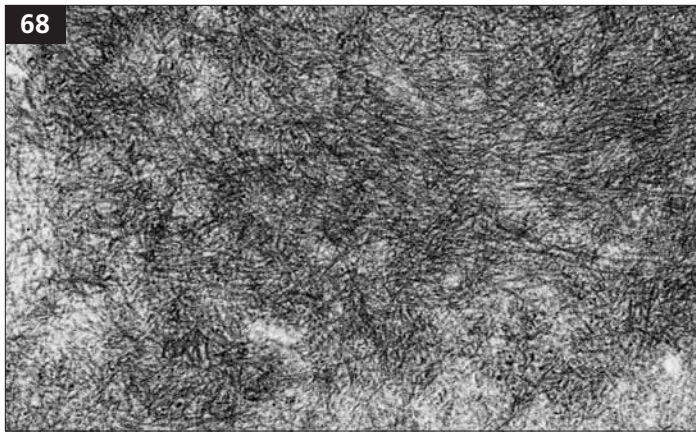
The light microscopic appearances are variable and include: mesangial hypercellularity, amorphous, eosinophilic, Congo red-negative expansion of the mesangium, sometimes showing a nodular pattern, mesangiocapillary pattern, or crescent formation. Immunohistochemistry in cases of fibrillary glomerulonephropathy may be positive for IgG, C3, and light chains. Electron microscopy (68) is required for definitive diagnosis and shows a fibrillar pattern, similar to amyloid, but usually the fibrils have a greater diameter, perhaps up to 20 nm.

### PROGNOSIS

About 50% of patients develop end-stage renal failure within 2 years.

### MANAGEMENT

There is no proven effective treatment. Although recurrent disease in the renal allograft is common, the rate of progression is slow, and transplantation has been successful.



68 Nonbranching fibers. Electron microscopy (×20,000).

## Systemic lupus erythematosus (SLE)

### DEFINITION

Systemic lupus erythematosus is an autoimmune disease characterized by autoantibody production in which renal involvement is common. According to the American Rheumatism Association classification, a diagnosis of SLE is made if four of the following 11 criteria are present:

- Malar rash.
- Discoid rash.
- Photosensitivity.
- Oral ulcers.
- Arthritis (two or more joints).
- Pleurisy–pericarditis.
- Renal abnormalities.
- Neurologic disorders (seizures, psychosis).
- Hematologic disorders (hemolytic anemia, leucopenia, lymphocytopenia, thrombocytopenia).
- Immunologic disorders (anti-DNA, anti-Sm, positive finding of anti-phospholipid antibodies).
- Anti-nuclear antibody.

### EPIDEMIOLOGY AND ETIOLOGY

SLE is about nine times more common in females than in males. The deleterious effect of estrogens on SLE explains the flares of disease activity with pregnancy or the use of oral contraception. All ages are affected but most cases occur between ages 16 and 55 years. There is a much higher incidence in black and Asian populations compared to Caucasians in the UK. There are certain HLA associations and some familial cases are associated with defects of the complement pathway. Exposure to sunlight or ultraviolet light can trigger a lupus flare.

### PATHOGENESIS

B-cell hyper-reactivity leads to the overproduction of auto-antibodies. The primary defect is not known, and there may be different abnormalities leading to loss of B-cell tolerance. One theory is that there is a genetic defect in apoptosis. Apoptotic cells express nuclear antigens on the cell surface where they trigger

auto-antibody formation. Auto-antibodies are formed to histones, DNA, RNA; anti-phospholipid antibodies are found in 30% cases. Immune complex deposition and complement activation leads to glomerular damage. The type of glomerular disease depends on the nature of the immune complex (specificity, size, affinity, charge, ability to activate complement) and the rate of its clearance by Fc receptors. Immune complexes cause damage by activating complement, leading to chemokine production and recruitment of inflammatory cells.

### CLINICAL HISTORY

Renal involvement usually appears after the initial presentation with SLE, and often follows a chronic remitting and relapsing course. Rarely patients may present with only renal disease and on renal biopsy have diagnostic features of lupus nephritis. Such patients may develop clinical symptoms or serologic tests of active lupus many years after the initial presentation.

Patients with World Health Organization (WHO) class I and II lupus nephritis normally have mild proteinuria and a normal GFR. Patients with WHO class III and IV nephritis typically have an active urinary sediment, heavier proteinuria, hypertension, and reduced GFR. Class V cases usually have nephrotic syndrome as the main presenting syndrome; renal vein thrombosis and pulmonary emboli are common. Over the course of the illness, the histologic pattern may transform from one class to another with associated changes in the clinical features of the renal disease. Rarely patients can present with oligoanuric acute renal failure, and the renal biopsy either shows extensive crescent formation or glomerular capillary thrombi usually associated with anti-phospholipid antibodies.

Lupus tends to flare during pregnancy and the puerperium. The risk is less in females with mild and well-controlled disease. Maternal flares are associated with increased prematurity and fetal mortality.

## Systemic lupus erythematosus (SLE) (continued)

### PHYSICAL EXAMINATION

Patients with lupus nephritis will often have obvious physical signs of SLE, i.e. alopecia, mouth ulcers, skin rash (69), Raynaud's phenomenon, non deforming arthritis, and retinal cotton wool spots (70).

### DIFFERENTIAL DIAGNOSIS

Mild forms of SLE may masquerade as other diseases for many years, especially the joint or neuropsychiatric presentations. Diseases which may be in the differential diagnosis include rheumatoid arthritis, subacute bacterial endocarditis, lymphoma, idiopathic thrombocytopenia, and HIV infection.

### INVESTIGATIONS

Anti-nuclear antibodies (ANA) are found in 99% of cases of SLE. They were discovered in the 1940s with the discovery of the LE cell (71). The initial screening test for ANAs is the immunofluorescence test; Hep2 cells are incubated with patient's serum and then fluorescein-tagged anti-human gamma globulin is added to produce an apple-green nuclear staining when viewed through the fluorescent microscope. The test is very sensitive, and the pattern of staining may be characteristic for specific antibodies (72–75). However, pattern recognition is now replaced with specific assays to identify precisely and quantitate antibody titers.

Anti-dsDNA antibodies are relatively specific (95%) for SLE and often fluctuate with disease activity. In some patients there is no correlation with disease activity. If a patient has been followed for several months and titers correlate with activity, it is likely that titers will continue to be useful for monitoring activity. Anti-dsDNA antibodies may be measured by the Farr assay (ammonium sulphate precipitation), *Crithidia lucillae* assay (76) or ELISA. Anti-Smith (anti-Sm) antibodies are directed against small ribonucleoproteins. They are insensitive but highly specific for SLE, and remain so when the disease is inactive and when anti-dsDNA antibodies have fallen into the normal range. They are found in 10–30% of Caucasians and 30–40% of Asians and Afro-Caribbeans with SLE. The presence of anti-Sm antibodies may be associated with milder renal involvement. Ro/SSA and La/SSB antibodies are detected in high frequency in the serum of patients with Sjögren's syndrome and subacute cutaneous lupus and neonatal lupus.



69 Discoid skin rash in a patient with systemic lupus erythematosus.

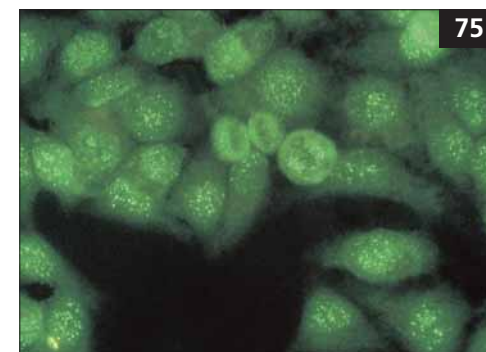
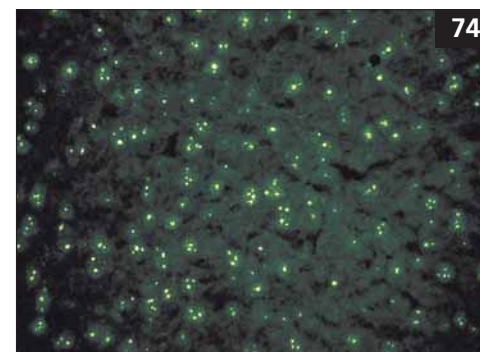
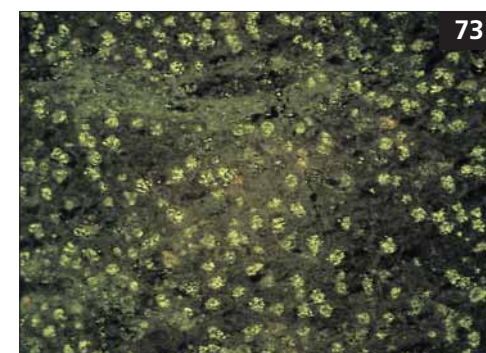
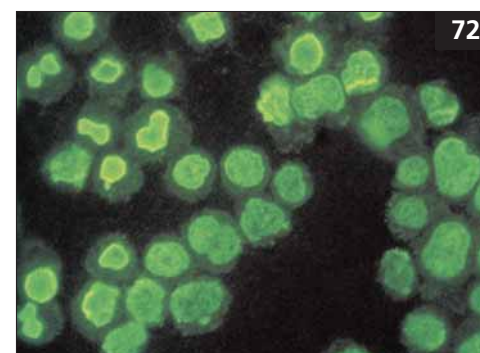
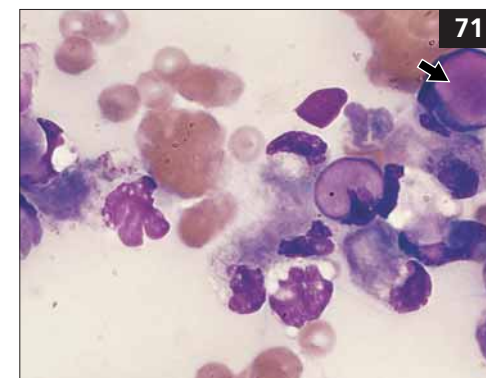


70 Retinal cotton wool spots in a patient with systemic lupus erythematosus.

Many patients with SLE have an activation of the classic complement cascade with consumption of the early complement components C1q, C4, and C3. C4 levels usually fall earlier and to a greater extent than C3 during a disease flare.

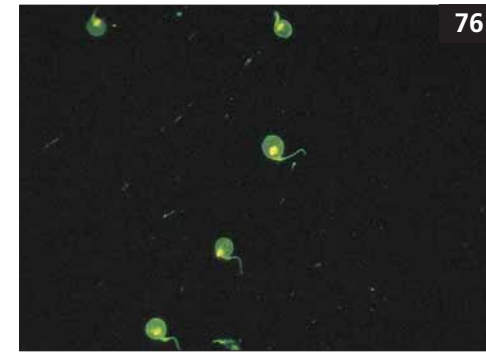
Renal biopsy in selected patients is necessary to decide which patients may or may not benefit from immunosuppression.

71 Buffy coat preparation from the peripheral blood of a patient with active lupus showing nuclear material phagocytosed by polymorphs (LE cells) (arrow). Light microscopy (MGG  $\times 1000$ ).



72–76 Different patterns of anti-nuclear antibody staining. Homogeneous staining on Hep2 cells ( $\times 1000$ ) (72). Speckled pattern on rat liver ( $\times 400$ ) (73). Nucleolar pattern on rat liver ( $\times 400$ ) (74). Centromere pattern ( $\times 1000$ ) (75).

76 Immunofluorescence staining of *Crithidia lucillae*. This trypanosome contains a kinetoplast circular DNA which is double stranded.



## Systemic lupus erythematosus (SLE) (continued)

### HISTOLOGY (77–84)

There is hypercellularity of the glomerular tuft, which can be segmental or global, focal or diffuse, and may include polymorphs. In active disease there may be foci of fibrinoid tuft necrosis, nuclear fragmentation, wire-loops, hyaline thrombi, and crescent formation. Hematoxylin bodies formed from digested nuclear material may be found in areas of necrosis.

Immune deposits are the hallmark of lupus nephritis. A 'full house' of staining for IgG, IgM, IgA, C3, C1q, and C4 is characteristic of lupus nephritis. Mesangial deposits are found even in patients without overt renal disease.

Capillary wall deposits, which are characteristically subendothelial when seen in electron microscopy, cause the thickened, rigid, and refractile capillary wall known as the classic 'wire-loop'. There will often also be subepithelial and intramembranous deposits, which may be an aid to diagnosis. The so-called 'hyaline thrombi' seen in light microscopy are in fact huge subendothelial electron-dense deposits that bulge out into the lumen, sometimes causing occlusion of the glomerular capillary lumen. True thrombi may be seen in the anti-phospholipid syndrome. Rarely, a fingerprint-like pattern or tubuloreticular inclusions may be seen in the electron-dense deposits.

The WHO classification is widely used by nephrologists and renal pathologists:

- Class I Normal
- Class IIA Mesangial deposits
- Class IIB Mesangial hypercellularity
- Class III Focal, segmental proliferative glomerulonephritis

- Class IV Diffuse proliferative glomerulonephritis
- Class V Membranous glomerulonephritis

Crescents are commonly found in classes III and IV lupus nephritis. Interstitial nephritis is common and rarely may occur without glomerular involvement. A thrombotic microangiopathy may occur in association with anti-phospholipid antibodies.

Activity indices based on the features mentioned above, and chronicity indices, based on features such as glomerular sclerosis, tubular atrophy, and interstitial fibrosis, are also useful in guiding treatment.

### PROGNOSIS

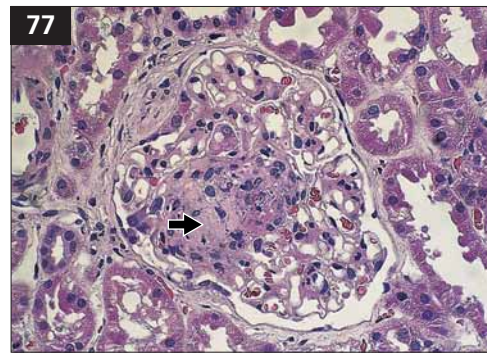
Patient survival has improved in lupus patients over the past few decades. The results from two prospective cohorts of 1000 European and 644 Canadian patients with lupus found 95% and 93% 5-year survival rates, respectively. Most deaths are caused by active SLE, thrombosis, or infection. Renal survival has also improved with the use of cytotoxic drugs.

### MANAGEMENT

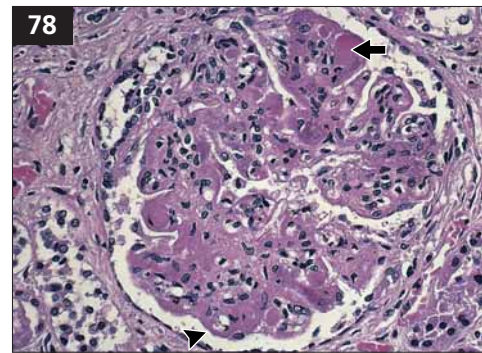
The management of lupus nephritis is complex. Corticosteroids and azathioprine are used for patients with mild renal involvement. For patients with severe lupus nephritis, intravenous methylprednisolone and cyclophosphamide are necessary but have undesirable side-effects. There is increasing experience with mycophenolate mofetil in the treatment of lupus

nephritis. Other drugs that have been trialled for lupus nephritis include cyclosporine (cyclosporin), tacrolimus, a thromboxane A2

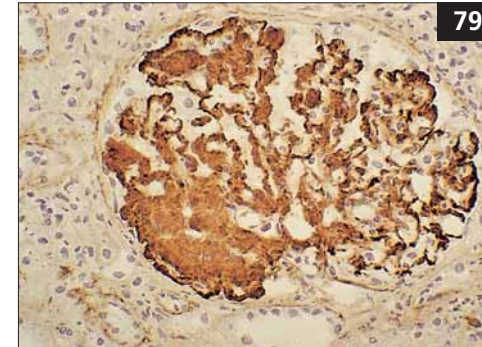
synthetase inhibitor, anti-CD40 ligand, and anti-interleukin-10. Lupus nephritis recurs infrequently after transplantation.



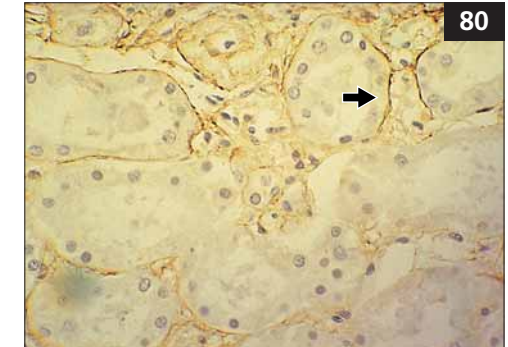
**77** Glomerulus from a case of focal proliferative lupus nephritis (WHO class III) showing a segmental area of consolidation and necrosis (arrow). Note the uninvolved tuft is normal. Light microscopy (H+E x350).



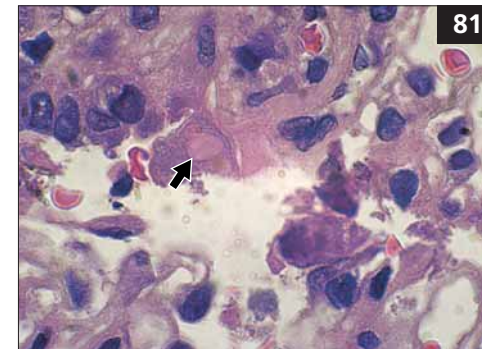
**78** Glomerulus from a case of diffuse proliferative lupus nephritis (WHO class IV) showing increased cellularity, wire-loop thickening of capillary walls (arrow head) and hyaline 'thrombi' (arrow). Light microscopy (H+E x400).



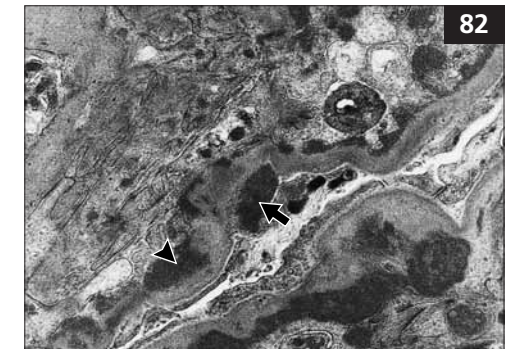
**79** Diffuse proliferative lupus nephritis showing IgG localizing on glomerular capillary walls and segmentally in mesangial areas (brown reaction product). Immunoperoxidase (anti-IgG antibody x400).



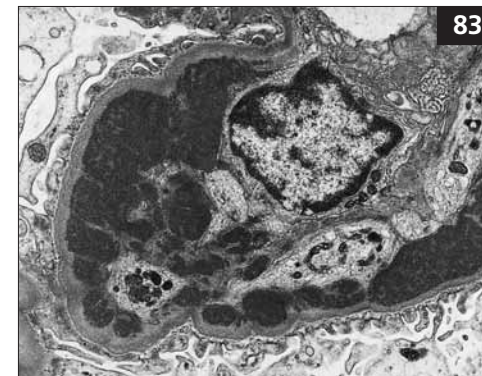
**80** Lupus nephritis showing focal IgG staining on tubular basement membranes (brown reaction product, arrow). Immunoperoxidase (anti-IgG antibody x400).



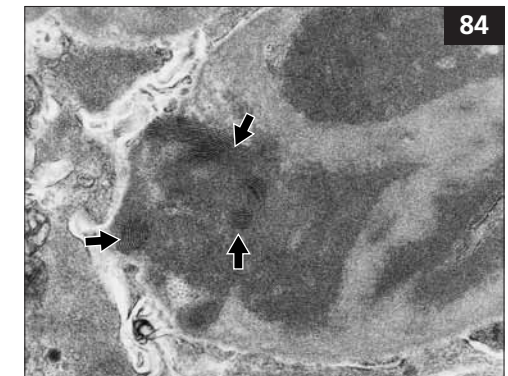
**81** Hematoxylin body (arrow). Light microscopy (H+E x1000).



**82** Subepithelial (arrow) and subendothelial deposits (arrow head). Electron microscopy (x4000).



**83** Very large subendothelial electron-dense deposits from the same case as **82**, that would equate to the hyaline thrombi seen in light microscopy. Electron microscopy (x5000).



**84** High magnification of deposits from the same case as **82**, showing the fingerprint pattern (arrows). Electron microscopy (x10,000).

## Primary anti-phospholipid antibody syndrome (PAPS)

### DEFINITION

Since the first description of the syndrome in 1981 its protean clinical and laboratory features have been defined. For a positive diagnosis there must be radiologic or histologic evidence of arterial or venous thrombosis, or recurrent miscarriages, and the presence of medium or high titers of IgM or IgG anti-cardiolipin antibodies or lupus anticoagulant on two occasions at least 6 weeks apart. This disorder is referred to as the primary APS when it occurs alone; however, it can also be found in association with SLE, or with certain infections and drugs.

### CLINICAL HISTORY

Patients usually have a history of a major thrombotic event such as a deep vein thrombosis or pulmonary emboli. There may be multiple miscarriages or severe pre-eclampsia due to small vessel thrombosis and placental insufficiency. There may be a history of arterial thromboses affecting the cerebral or coronary circulation. Other manifestations include livedo reticularis, hemolytic anemia, thrombocytopenia, neurologic dysfunction, pulmonary hypertension, avascular necrosis, and adrenal failure. Rarely, primary APS can cause multiorgan failure due to multiple small vessel occlusion. Renal involvement may present with hypertension, proteinuria, renal impairment, or acute renal failure. Renal arterial and venous thromboses have been reported. There is an association with renal artery stenosis.

### PHYSICAL EXAMINATION

A variety of cutaneous abnormalities may be seen, including livedo reticularis, digital gangrene, and Degos' disease (malignant atrophic papulosis). A major thrombotic event may cause obvious clinical signs.

### DIFFERENTIAL DIAGNOSIS

Systemic lupus erythematosus with associated anti-phospholipid antibodies is excluded by the clinical history and a negative ANA. Other thrombophilic conditions such as Protein C and S deficiency and factor V deficiency should be excluded.

### INVESTIGATIONS

The activated partial thromboplastin time is prolonged and is not normalized when the patient's plasma is diluted 1:1 with normal platelet-free plasma (lupus anticoagulant activity). IgG or IgM anti-cardiolipin antibody titers are measured by a standardized ELISA technique. In patients with neurologic involvement there may be multiple, small, high-density lesions on MRI (85).

### HISTOLOGY

The characteristic pathologic change is a thrombotic microangiopathy with minimal perivascular inflammation (86). Renal histological changes include small vessel vaso-occlusive lesions associated with fibrous intimal hyperplasia of interlobular arteries, and focal cortical atrophy.

### PROGNOSIS

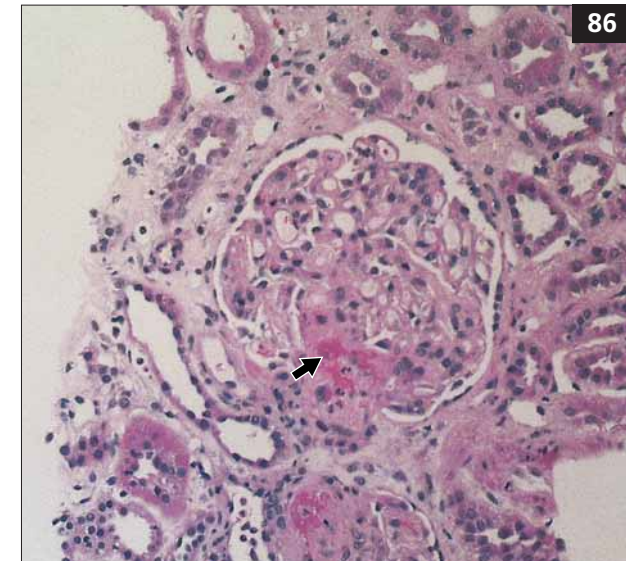
The renal prognosis is variable but generally the thrombotic microangiopathy leads to progressive renal destruction causing end-stage renal failure and can recur in renal allografts.

### MANAGEMENT

Patients with renal involvement must be anticoagulated to keep the INR >3. Selected patients with acute renal failure may respond to plasma exchange and/or immunosuppression.



85 MRI scan in a patient with primary anti-phospholipid antibody syndrome demonstrating periventricular white matter lesions.



86 Primary anti-phospholipid antibody syndrome. Thrombosis is present within the glomerular tuft and afferent vessels (arrow). Light microscopy (H+E x200).