Case 9.1 IgA nephropathy

A 14-year-old boy presented with an 18-month history of intermittent, painless haematuria, usually occurring after strenuous exercise, but without dysuria or increased frequency of micturition. He also had frequent colds and sore throats and believed that the haematuria also happened at these times. On examination, he appeared fit and healthy; his blood pressure was 120/75. Urine analysis showed microscopic haematuria (3+) and a trace of protein. Intravenous urography, a micturating cystogram and cystoscopy were normal. His haemoglobin, white cell count, blood urea and creatinine clearance were normal; the urinary protein excretion was 0.95 g/day. Immunoglobulin, CH_{50}, C4 and C3 levels were within normal limits. In view of the duration of haematuria, a renal biopsy was performed. Twelve glomeruli were present: all showed a diffuse increase in mesangial cells with thickening of the matrix. Immunofluorescent examination of the biopsy showed mesangial deposits of IgA and C3 (Fig. 9.5a). The appearances were characteristic of IgA nephropathy.

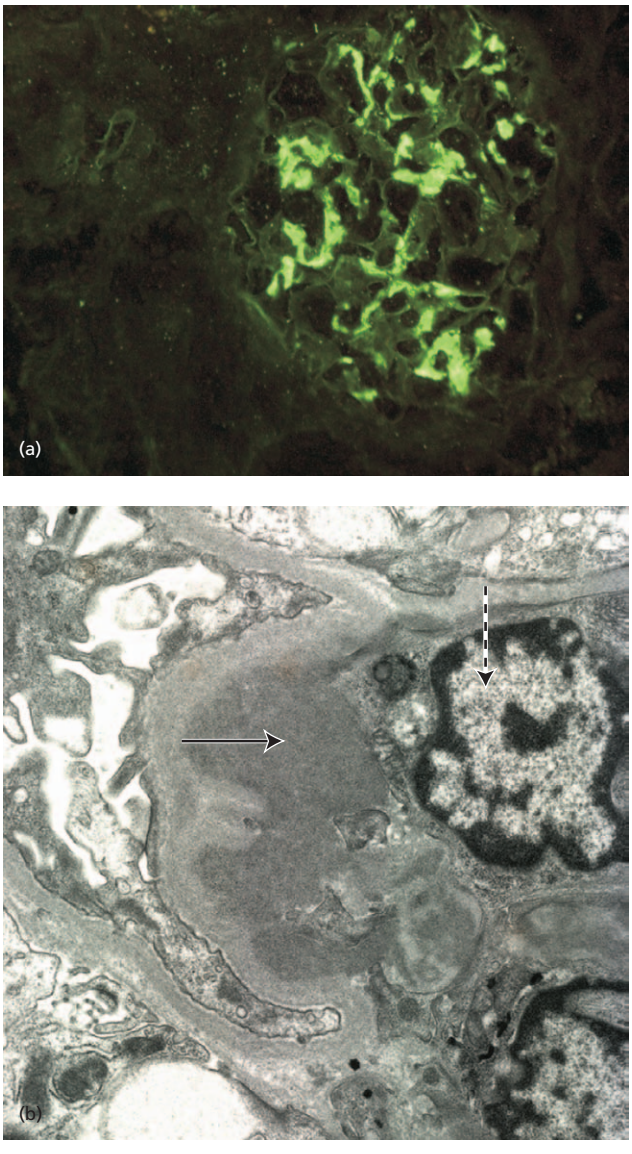


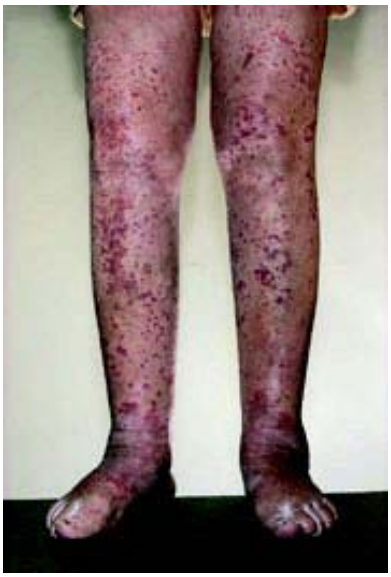
Fig. 9.5 (a) IgA nephropathy showing IgA deposits in the mesangium on immunofluorescence. (b) Electron micrograph of IgA nephropathy showing an IgA deposit (arrowed) and an adjacent mesangial cell (interrupted arrow).

Essentials of Clinical Immunology, Sixth Edition. Helen Chapel, Mansel Haeney, Siraj Misbah, and Neil Snowden.

Case 9.2 Henoch–Schönlein nephritis

A 12-year-old boy presented with a 1-week history of pain in the left loin. This was diagnosed as a urinary tract infection and treated with amoxicillin. One week later, he developed a purpuric rash around the ankles, accompanied by some blistering and superficial necrosis. Shortly afterwards, he developed pain in the left elbow joint. On admission to hospital, he was noted to have haematuria and proteinuria and a blood pressure of 130/90. Over the next month, he suffered further episodes of abdominal colic and purpura. His haemoglobin was 95 g/l with a normal white cell count. Antinuclear antibodies were negative and total haemolytic complement, C4 and C3 levels were normal. Although his blood urea was normal, his creatinine clearance was low at 31 ml/min per m^2 with proteinuria of 4.5 g/day.

A skin biopsy of a purpuric lesion showed vasculitic changes in the dermis, with IgA and C3 deposition in the blood-vessel walls. A renal biopsy, containing 21 glomeruli per section, showed epithelial crescents and diffuse mesangial hypercellularity in seven glomeruli. On immunofluorescence, granular deposits of IgA and C3 and, to a lesser extent, IgG and properdin were present in the mesangium. The clinical and histological features were those of Henoch–Schönlein nephritis (HSN). Because of the heavy proteinuria and diminished creatinine clearance, he was treated with a limited course of corticosteroids. Over a 9-month follow-up period, the purpura and episodes of abdominal colic subsided, his creatinine clearance increased to 47 ml/min, but he continued to have moderately heavy proteinuria (3.2 g/day). The prognosis is uncertain.



Case Figure 9.2 More extensive purpura in a middle-aged woman, also on the legs which is the commonest site (the dependent areas).

Case 9.3 Post-streptococcal glomerulonephritis

A 9-year-old boy was admitted as an emergency with puffiness of the face, eyes and trunk. A week previously he had complained of a sore throat. On examination, he was mildly pyrexial (temperature 37.5°C) and hypertensive (BP 170/110). There was periorbital and scrotal oedema. His urine showed proteinuria, haematuria and red cell casts. He was anaemic (Hb 107 g/l) with a normal white cell count and differential. A throat swab grew normal flora but antibodies to streptococcal antigens were present in high titre: antistreptolysin O titre 1600 IU/ml (normal <300 IU/ml). Serum complement studies done 3 days after admission showed a very low C3 (0.10 g/l; NR 0.8–1.40) and a normal C4 (0.23 g/l; NR 0.2–0.4). His creatinine clearance was 46 ml/min, serum albumin 29 g/l and urinary protein excretion 1.5 g/day.

These findings were typical of post-streptococcal glomerulonephritis and so renal biopsy was not performed. As anticipated, the serum complement returned to normal in 4 weeks, accompanied by disappearance of the proteinuria and hypertension, although a small amount of microscopic haematuria persisted. The prognosis is good. An unusual feature of this case was the degree of hypertension.

Case 9.4 Membranoproliferative glomerulonephritis – type II

A 13-year-old boy had been well until 4 weeks before admission, when he developed a cough, periorbital oedema, ankle swelling, headaches and upper abdominal discomfort. On admission, he was febrile with facial and ankle oedema; there was generalized, superficial lymphadenopathy, numerous adventitial sounds in the lungs and hypertension (BP 140/110). His haemoglobin was 72 g/l with a normal white cell count and an erythrocyte sedimentation rate (ESR) of 137 mm/h. His blood urea was high (27.5 mmol/l) with a low serum bicarbonate (13.6 mmol/l) and serum albumin (19 g/l). His creatinine clearance was 45 ml/min per m^2 with urinary protein loss of 6.7 g/day. His serum CH_{50} was low (14 U/ml; NR 25–45), as was his C3 level (0.20 g/l; NR 0.8–1.4); his C4 level was normal (0.30 g/l; NR 0.2–0.4). A chest X-ray showed several rounded opacities in both lungs. These were presumed to be infective and treated with amoxicillin and flucloxacillin with resolution of the radiological findings.

The association of a low C3 with acute glomerulonephritis suggested acute post-streptococcal disease as the most likely diagnosis (see Case 9.1), although no streptococci were isolated and streptococcal antibodies were not raised. Over the following 3 weeks, his blood urea fell but the proteinuria and hypertension persisted.

Three months later, he felt better but still had heavy proteinuria with a low serum albumin (22 g/l; NR 35–50). Surprisingly, the serum CH_{50} and C3 levels were still low at 18 U/ml and 0.4 g/l, respectively. This pattern was not consistent with the working diagnosis. It suggested continued complement activation via the alternate pathway, due either to some circulating activating factor or a regulatory defect caused by absence of the inhibitors I or H (see Chapter 1). However, serum levels of I and H were normal. Electrophoresis of fresh serum and plasma showed the presence of C3 breakdown products and his serum was able to break down C3 in normal serum due to the presence of C3 nephritic factor.

C3 nephritic factor shows a strong association with membranoproliferative glomerulonephritis (MPGN), but not with acute post-streptococcal glomerulonephritis. Since these conditions have different prognoses, a renal biopsy was performed at this late stage. This showed 11 glomeruli, all of which were swollen with proliferation of mesangial, endothelial and epithelial cells. On electron microscopy, the capillary loops showed basement membrane thickening with electron-dense deposits within the GBM (Fig. 9.13). On immunofluorescence, intense C3 deposition was present in the GBM without immunoglobulin staining. These appearances, together with the finding of circulating C3 nephritic factor, are characteristic of MPGN with dense intramembranous deposits (type II MPGN). Alternate-day prednisolone therapy was started; as this condition nearly always shows a slow progression to chronic renal failure, plasmapheresis was attempted with additional immunosuppression in the hope that progression could be avoided, since there were no crescents seen on histology.

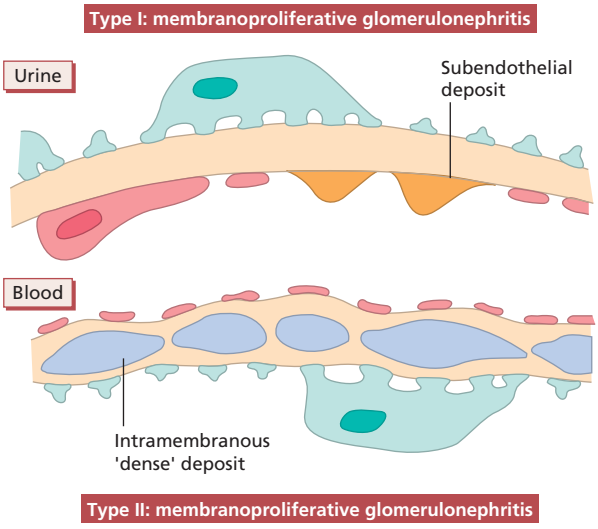


Fig. 9.13 Membranoproliferative glomerulonephritis. Two major types can be recognized, depending on whether the deposits are subendothelial (type I) or intramembranous (type II).

Case 9.5 Anti-glomerular basement membrane glomerulonephritis

A 55-year-old man presented with a 3-week history of malaise, nausea, fever and shivering. Although there were no urinary symptoms, analysis of a mid-stream urine specimen showed microscopic haematuria and proteinuria (2+). There was no cough or haemoptysis and no family history of renal disease or hypertension. On examination, he was mildly pyrexial but there were no vasculitic lesions, oedema or hypertension. Cystoscopy and renal ultrasound showed no cause for his haematuria. Over the next week, his blood urea rose steadily from 10 to 23 mmol/l (NR 2.5–7.5) and the serum creatinine from 164 to 515 μmol/l (NR 60–120). His haemoglobin was 89 g/l with a white cell count of 10.4×10^9/l and a normal differential. His urine contained red cell casts and he rapidly became oliguric. Antinuclear antibodies, including anti-DNA antibodies, were not detected and serum C3 and C4 levels were normal.

A renal biopsy specimen contained seven glomeruli: four showed focal necrotizing glomerulonephritis with epithelial crescents but the remaining three were normal. On immunofluorescence, linear staining with IgG was present along the glomerular capillary basement membrane (Fig. 9.15b). The patient's serum contained antibodies to GBM (see Chapter 19). The diagnosis was therefore rapidly progressive glomerulonephritis due to antibodies to GBM. Although oliguric, he was treated with high doses of prednisolone and cyclophosphamide, and underwent daily plasma exchanges for 2 weeks, until anti-GBM antibodies were no longer detectable. However, renal function failed to recover: cytotoxic therapy was stopped and regular haemodialysis started.

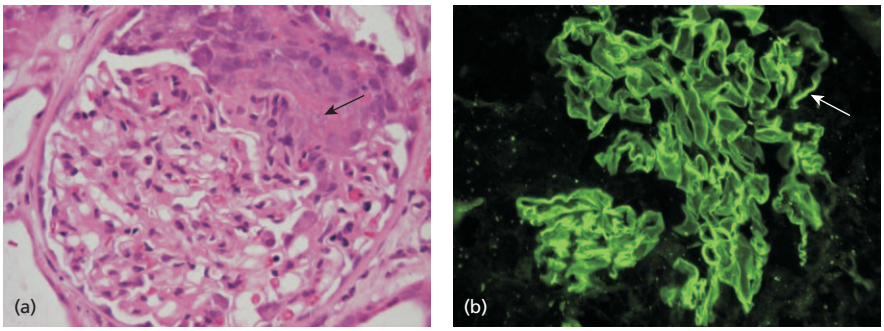
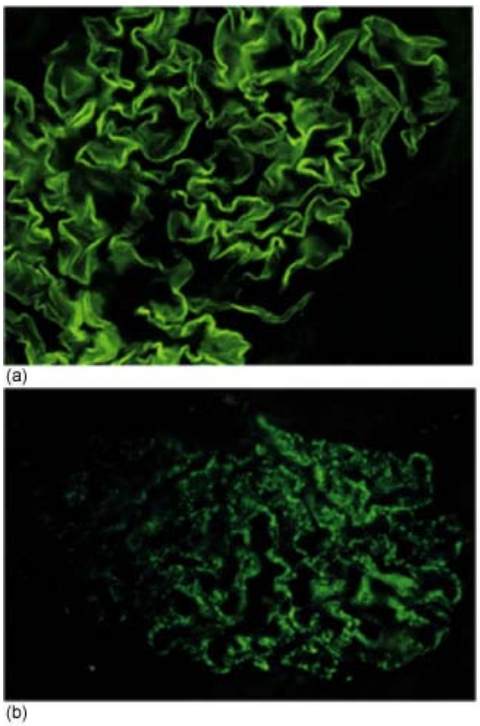


Fig. 9.15 Anti-glomerular basement membrane nephritis showing (a) a crescent with fibrin necrosis (arrowed) and (b) linear fluorescent staining along the basement membrane (arrowed).



Case Figure 9.5 A glomerulus stained with antibody to human IgG showing (a) a linear deposit along the basement membrane. (b) Contrast to immune complex deposits in SLE. Roitt & Rabson.

Case 9.6 Antineutrophil cytoplasmic antibody-associated necrotizing crescentic glomerulonephritis

A 64-year-old man presented with a 1-month history of nausea and malaise and a 1-week history of flu-like symptoms, rigors and vomiting. Eight weeks earlier, while on holiday, he developed infected insect bites around his left ankle and was treated with erythromycin. He had no urinary or joint symptoms and no family history of renal disease. On examination, he was pale with mild pitting oedema of both ankles and a blood pressure of 170/90. Analysis of a mid-stream urine specimen showed proteinuria (3+) with microscopic haematuria and granular casts. His haemoglobin was 92 g/l with a white cell count of 17.7×10^9/l and an ESR of 122 mm/h. His blood urea was 42.6 mmol/l (NR 2.5–7.5) and serum creatinine 1094 μmol/l (NR 60–120). Malarial parasites and hepatitis B surface antigen were not detected in his blood. Over the next 72 h, his urine output fell to 30 ml/day with further increases in his blood urea and serum creatinine.

Ultrasound examination showed bilaterally enlarged kidneys but no evidence of obstruction. Serum immunoglobulin levels were normal but C3 (1.56 g/l; NR 0.8–1.40) and C4 (0.46 g/l; NR 0.2–0.4) were raised. There was no paraproteinaemia and no free monoclonal light chains in his urine. Antinuclear, anti-dsDNA, and anti-GBM antibodies were negative. However, the patient's serum contained IgG antibodies which reacted strongly with cytoplasmic antigens of alcohol-fixed neutrophils, producing a granular pattern characteristic of classical antineutrophil cytoplasmic antibodies (cANCA). Further analysis showed antibodies to a neutrophil enzyme called serine proteinase 3 (PR3) by enzyme-linked immunosorbent assay (ELISA) (see Chapter 19).

A renal biopsy was performed to confirm the cause of his rapidly progressive glomerulonephritis. The biopsy specimen contained 30 glomeruli: one-third of these were totally sclerosed and all but one of the remainder showed necrotizing, crescentic glomerulonephritis. Cellular crescents, with extensive tuft necrosis (Fig. 9.16b), were seen in most glomeruli. Immunofluorescence showed no immune deposits in the glomeruli, so-called 'pauci-immune' disease. The diagnosis was that of ANCA-associated, necrotizing crescentic glomerulonephritis.

He was treated with pulse cyclophosphamide (500 mg/m^2) and pulse methylprednisolone (1 g daily for 3 days), followed by 60 mg of prednisolone daily. For the next 12 days he required peritoneal dialysis until his renal function improved. He was discharged on maintenance therapy of prednisolone 40 mg/day with pulse intravenous cyclophosphamide at monthly intervals. He continued on this regimen until his cANCA became negative; his treatment was then changed to oral prednisolone and azathioprine.

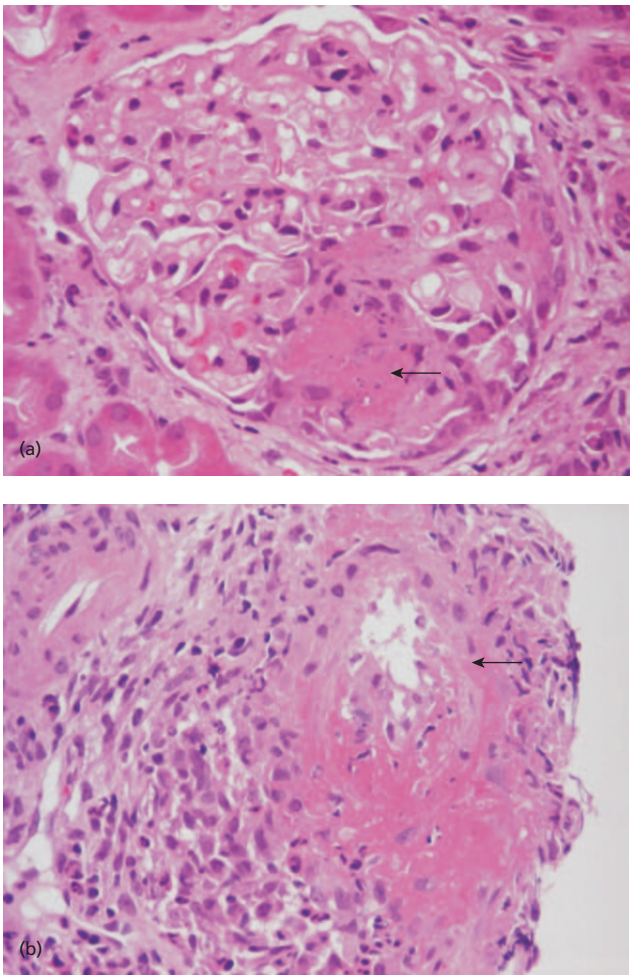
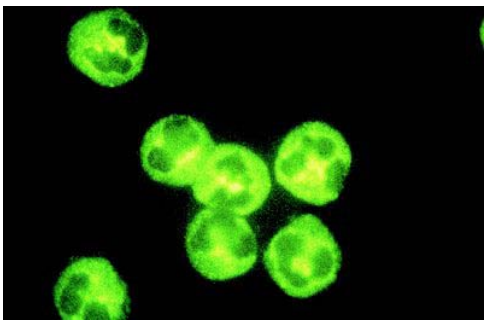
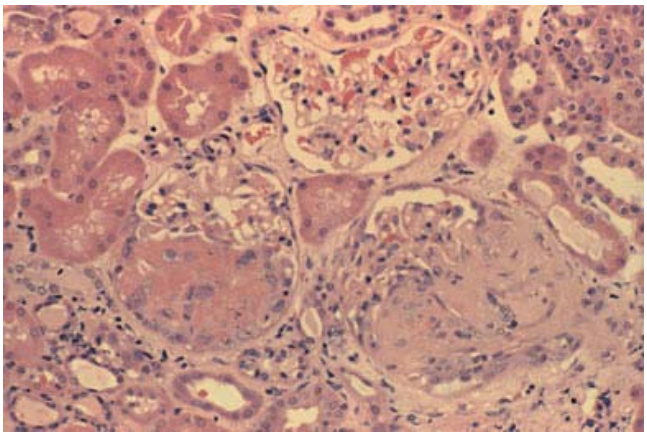


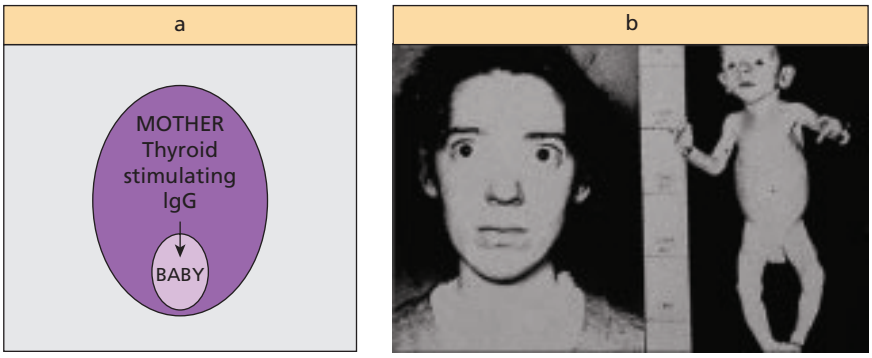
Fig. 9.16 ANCA-associated glomerulonephritis showing (a) a segmental area of tuft necrosis (arrowed) and (b) vasculitis of a renal arteriole (arrowed).



Case Figure 9.6a Strongly positive cytoplasmic anti-neutrophil cytoplasmic antibody detected in blood using indirect immunofluorescence in a patient with Wegener's granulomatosis.



Case Figure 9.6b Renal histological appearance focal segmental proliferative glomerulonephritis . Two of the 3 glomeruli show necrotizing, crescentic glomerulonephritis i.e. cellular crescents, with extensive tuft necrosis, typical of *ANCA-associated, necrotizing crescentic glomerulonephritis*.



Case Figure 9.6c To show the difference between a cANCA and pANCA. Antineutrophil cytoplasmic antibodies (ANCA). Both parts Roitt & Rabson 2000.

Case 9.7 Minimal-change nephropathy

An 8-year-old girl presented with a 3-day history of swelling of the legs and puffiness around the eyes following a cold 1 week earlier. She had some mild abdominal discomfort and a headache for 2 days. Examination revealed a generally oedematous girl with ascites and a blood pressure of 120/70. Her height was on the 50th centile but her weight was above the 90th centile. Urinalysis showed marked proteinuria without haematuria. Her haemoglobin, white cell count and urea and electrolytes were normal but there was marked hypoalbuminaemia (11 g/l) and proteinuria (26 g/day). The urinary clearance of IgG relative to that of transferrin was less than 0.1, indicating highly selective proteinuria. Creatinine clearance, CH_{50}, C4 and C3 levels were all normal. A throat swab grew commensal flora only and the antibody titre to streptococcal antigens was normal.

Highly selective proteinuria in a child with nephrotic syndrome is virtually diagnostic of minimal-change nephropathy. For this reason, renal biopsy was not performed but a trial of steroid therapy (prednisolone 60 mg/day) was started with dramatic effect. Over the next week, her serum albumin rose to 26 g/l and the proteinuria subsided. At discharge, only a trace of proteinuria was detectable but she continued to take 40 mg prednisolone on alternate days for a further 3 months. The nephrotic syndrome did not relapse when steroids were withdrawn.

Case 9.8 Membranous glomerulonephritis

A 48-year-old man presented with a 3-month history of intermittent swelling of his ankles and puffiness of his face. There were no urinary symptoms and no family history of renal disease. He was taking no medication. On examination, he was pale and thin with ankle oedema and a blood pressure of 130/80. Investigations showed a normal haemoglobin and white cell count and an ESR of 32 mm/h. His blood urea was 9.1 mmol/l (NR 2.5–7.5), serum albumin 26 g/l with a urinary protein loss of 7.8 g/day and a creatinine clearance of 106 ml/min. His serum immunoglobulin IgM and IgA, C3 and C4 levels were normal, but his IgG was low at 5.1 g/l (NR 7.2–19.0). Antinuclear antibodies, hepatitis B surface antigen and antibody, and hepatitis C antibody were not detected. There were no free light chains in his urine.

A renal biopsy was done to find the cause of his nephrotic syndrome; this showed no obvious increase in cellularity. However, the basement membrane of all glomeruli showed marked but uniform thickening with numerous subepithelial 'spikes'. Immunofluorescent examination showed granular deposits of IgG and C3 along all the glomerular capillary walls. The biopsy appearances were typical of membranous glomerulonephritis (Fig. 9.9). No specific treatment was given at this stage. One year later, he is asymptomatic but still has severe, non-selective proteinuria of 14 g/day.

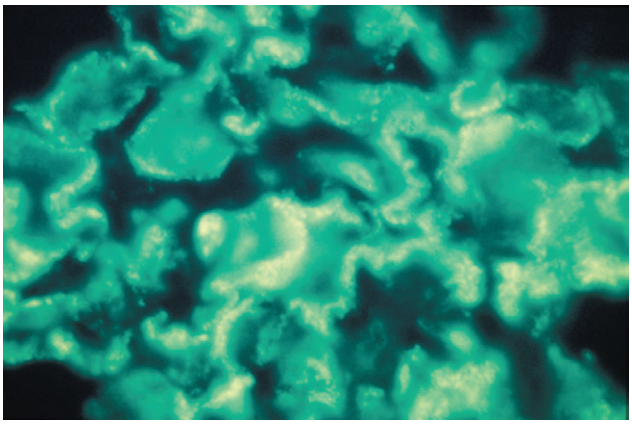
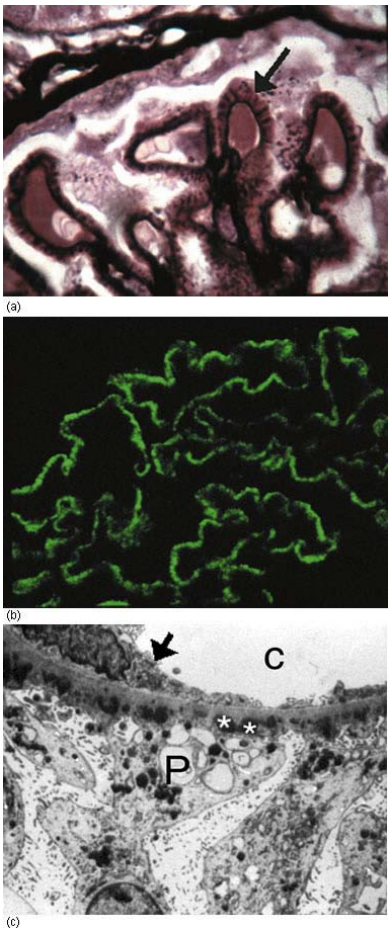
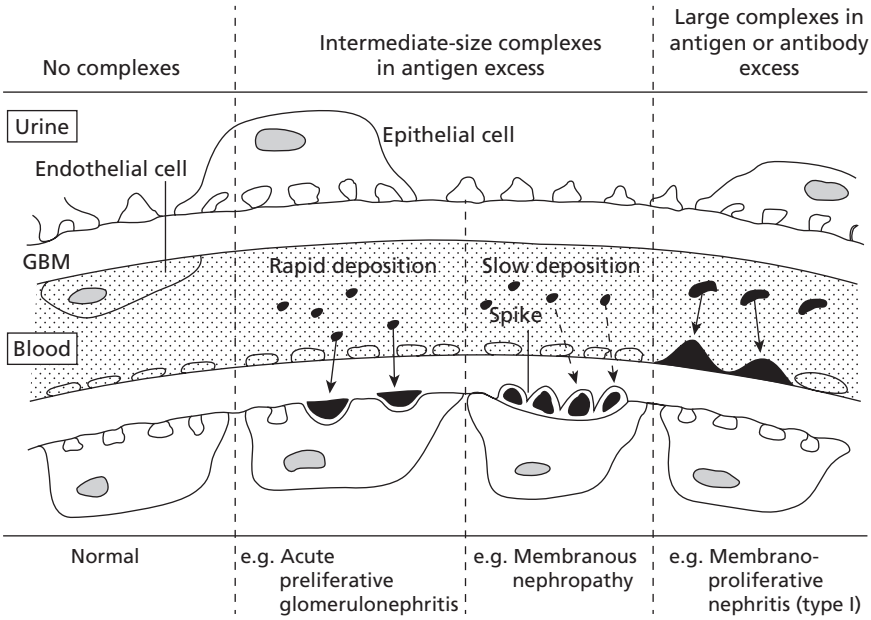


Fig. 9.9 Poststreptococcal glomerulonephritis showing 'lumpy-bumpy' deposits on immunofluorescence. Compare this with anti-glomerular basement membrane nephritis (Fig. 9.15b).



Case Figure 9.8a Characteristics of membranous nephropathy: (a) silver-stained section. The basement membrane is widened, with spikes (arrow). (b) Immunofluorescence for IgG (the same pattern for C3). Part of the glomerulus is shown. There is granular fluorescence along the basement membrane. (c) Electron micrograph of capillary loop. The basement membrane is seen adjacent to the capillary (C) lined by an endothelial cell (arrow). Within the basement membrane are electron-dense deposits (*). A podocyte (P) is also visible.



Case Figure 9.8b Sites of immune-complex deposition in humans. The size of the complexes and their rates of deposition influence the eventual renal morphology.

Case 9.9 Idiopathic AL amyloid

A 52-year-old woman presented with increasing swelling of both legs over a period of 3 months. Fourteen years earlier she had been treated for tuberculosis. On examination, she was pale, with gross bilateral leg oedema extending to the umbilicus and a large infected ulcer on the medial aspect of the right leg. Chest X-ray and electrocardiogram were normal but she had a microcytic anaemia (Hb 75 g/l) with an ESR of 140 mm/h. Her initial biochemical results showed a low serum albumin (14 g/l) and marked proteinuria (12 g/day) but a normal blood urea, serum creatinine and creatinine clearance. Serum electrophoresis showed no monoclonal band. Serum immunoglobulin levels were: IgG 2.2 g/l (NR 7.2–19.0); IgA 1.2 g/l (NR 0.8–5.0); and IgM 1.2 g/l (NR 0.5–2.0). Electrophoresis of a concentrated (×20) urine sample showed considerable amounts of albumin and gammaglobulin and an M band in the β region. Immunofixation of the serum and urine showed the presence of monoclonal free γ light chains in the urine only.

The presence of urinary monoclonal light chains suggested a possible diagnosis of light-chain myeloma or renal amyloid. A rectal biopsy was performed to look for amyloid deposits: this showed deposition of small amounts of amorphous material around blood vessels. This material stained strongly with Congo red and showed green birefringence when viewed under polarized light, an appearance which is characteristic of amyloid. A renal biopsy was also performed: striking deposits of amyloid were found in the GBM, in the tubular basement membrane and in the walls of several arterioles.

In view of her past medical history, the amyloid could have been associated with the previous tuberculosis or with the chronic infection of her leg ulcer; – acute-phase-associated AA amyloid (see Table 9.5). However, antisera to λ light chains stained the material in both biopsies, showing that the amyloid was light-chain-associated (Table 9.5) and thus idiopathic or due to multiple myeloma. The absence of suppression of IgA and IgM levels, the lack of plasma cell infiltration of the bone marrow and the absence of osteolytic lesions on X-ray excluded the diagnosis of multiple myeloma. Therefore, this was idiopathic AL amyloid. In view of her reasonable renal function, only supportive treatment was given; this consisted of a low-salt, high-protein diet and diuretics. To date, her proteinuria has persisted but has not worsened.

Table 9.5 Protein component of amyloid fibrils

Type of amyloid	Major protein of fibril	Chemically related protein (? precursor) in serum
Light-chain-associated amyloidosis		
Idiopathic	AL	Light chain
Myeloma	AL	Light chain
Other monoclonal gammopathies	AL	Light chain
Acute-phase-associated amyloidosis		
Chronic inflammation/ suppuration	AA	SAA
Senile systemic amyloid	ATTR (senile) amyloid	Transthyretin
Haemodialysis-associated amyloidosis	β_2M	β_2M
Transmissible spongiform encephalopathies	Prion protein	?

AA, amyloid A protein; AL, light-chain amyloid protein; β_2M, β_2-microglobulin; SAA, serum amyloid A protein.

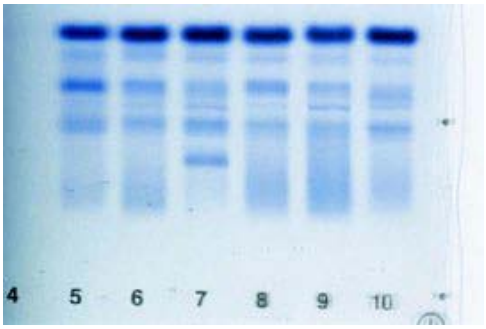
Case 9.10 Acute tubulointerstitial nephritis

A 37-year-old woman was admitted to hospital with a diagnosis of bacterial endocarditis. Blood cultures grew Streptococcus faecalis. She was treated with intravenous gentamicin and ampicillin with considerable improvement. However, on the 12th day of treatment, she developed a further fever and a macular rash on her trunk and limbs. Her white cell count was normal with an absolute eosinophil count of 0.32×10^9/l. Further blood cultures were negative but her serum creatinine rose from 140 μmol/l (NR 60–120) to 475 μmol/l over the next 3 days, with a rise in the eosinophil count to 0.92×10^9/l. Serum complement levels were normal. A renal biopsy showed marked interstitial oedema and infiltration of tubules by mononuclear cells, neutrophils and eosinophils. A diagnosis of acute TIN, probably drug induced, was made; antibiotics were discontinued and prednisolone started instead. Her serum creatinine rose to a peak of 640 μmol/l but she never became oliguric and did not require dialysis. After 3 days of steroids, her renal function began to improve and the eosinophil count fell.

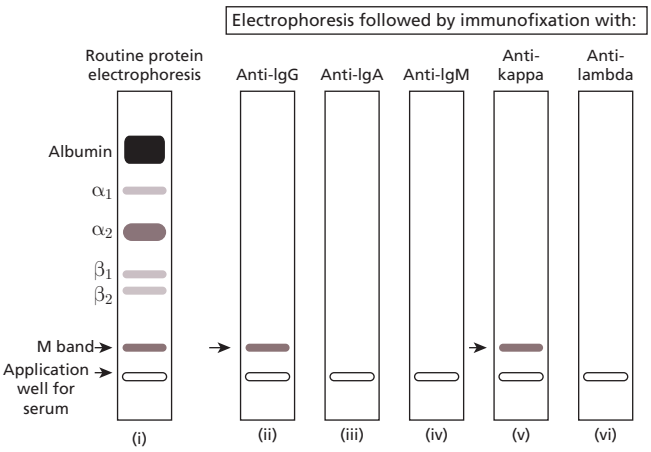
Case 9.11 Myeloma kidney

A 76-year-old man was admitted with a history of progressive weakness over a period of several months. On examination, he was unkempt, thin, pale and acidotic. His blood pressure was 110/60. He was markedly anaemic (Hb 64 g/l) with an ESR of 116 mm/h. His initial biochemical results showed a raised blood urea of 48 mmol/l (NR 2.5–7.5) and a grossly raised serum creatinine of 1910 μmol/l (NR 60–120) but a normal serum calcium. Urinary protein excretion was 2.8 g/day. A diagnosis of chronic renal failure of unknown cause was made. Peritoneal dialysis was started while other investigations were performed.

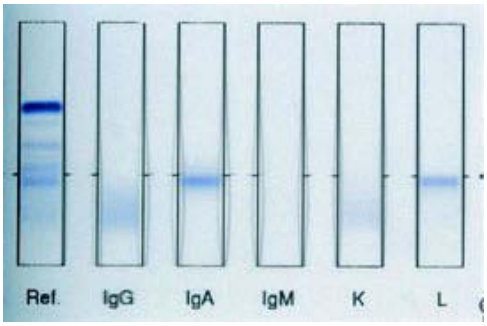
Serum electrophoresis showed a decreased γ fraction with a monoclonal band in the β region. Serum immunoglobulin levels were: IgG 1.4 g/l (NR 7.2–19.0); IgA 24.5 g/l (NR 0.8–5.0); and IgM 0.3 g/l (NR 0.5–2.0). Immunofixation of the serum and urine showed an IgA (λ type) paraprotein in the serum, with monoclonal free λ light chains in the urine. A bone marrow aspirate showed marked infiltration of atypical plasma cells. Radiology of the skeleton revealed osteolytic lesions in the pelvis and skull. A diagnosis of myeloma kidney was therefore made. Despite symptomatic treatment of his renal failure and therapy for myelomatosis, he died from renal failure 5 weeks after admission.



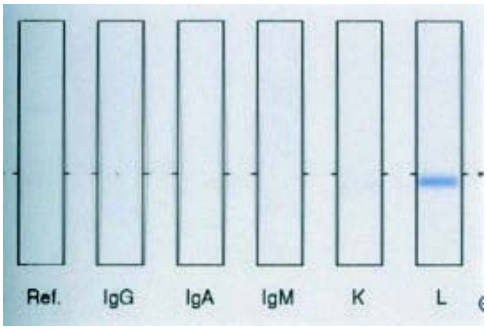
Case Figure 9.11a Electrophoresis of serum – track 7 shows monoclonal band between gamma and beta regions. This band is smaller than the one in Case Figure 9.11 which at 24.5 g/l would be much thicker.



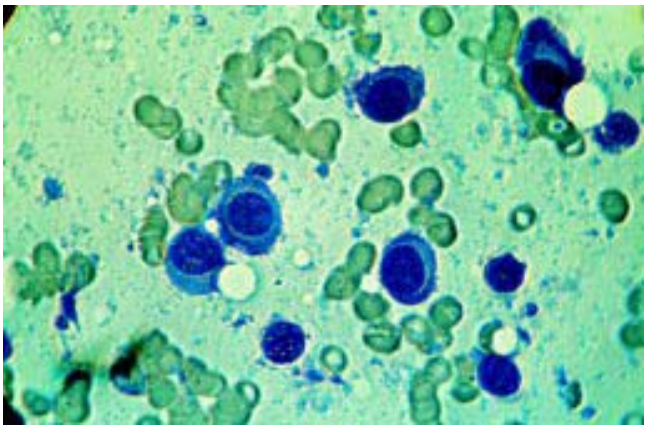
Case Figure 9.11b Typing an M band by immunofixation. In this example, the M band found on electrophoresis (i) is identified as an IgG (type K).



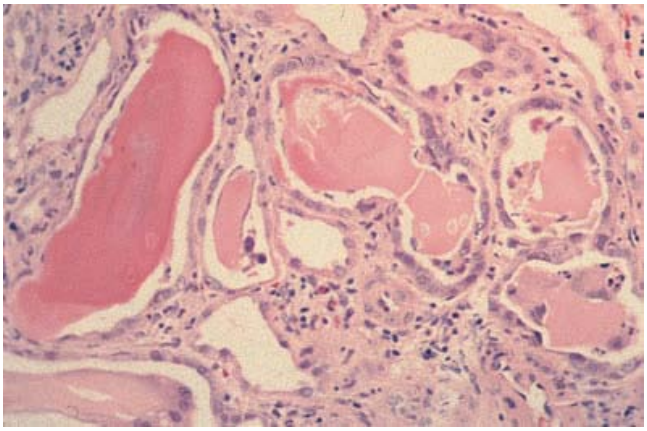
Case Figure 9.11c Immunofixation of the IgA band. (Ref track is stained for protein and shows albumin in fastest position (thickest band) and M band – between gamma and beta regions as before. This is the band stained by precipitating antibodies to IgA and lambda light chains. In myeloma kidney, the M band is much larger than the one shown here.



Case Figure 9.11d Monoclonal lambda: Immunofixation of urine shows free monoclonal lamba band.



Case Figure 9.11e A plain skull X-ray in Case Figure 9.11 shows multiple osteolytic lesions in the skull. Similar 'punched-out' lesions were found elsewhere in the skeleton.



Case Figure 9.11f Myeloma kidney. Dense intratubular casts are shown, with accompanying tubular cell atrophy (H&E ×200).