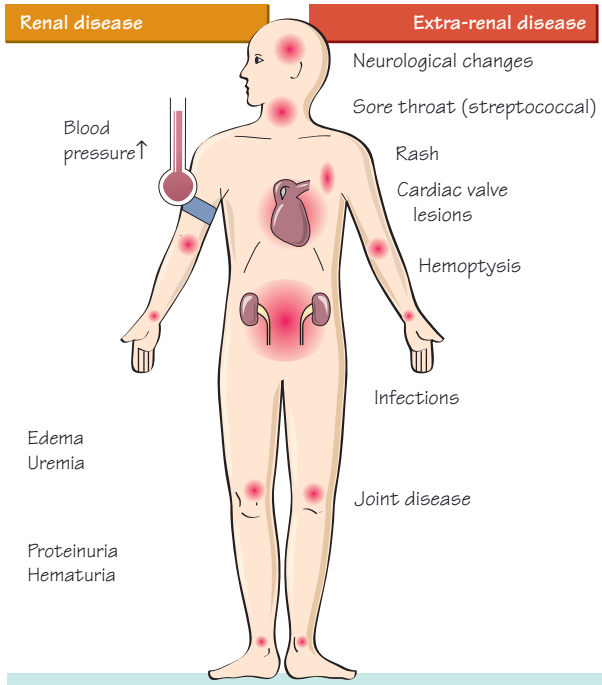
29 Glomerular disease: an overview



Clinical syndromes

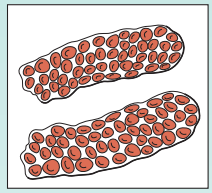
Asymptomatic Hematuria or Proteinuria		Hematuria Proteinuria
Acute Glomerulonephritis	BP↑ Edema GFR↓	Hematuria Proteinuria
Chronic Glomerulonephritis	BP↑ GFR↓	Hematuria Proteinuria
Rapidly progressive Glomerulonephritis	GFR↓	Hematuria Proteinuria
Nephrotic syndrome	Albumin↓ Edema	Proteinuria ± Hematuria

Investigating glomerular disease syndromes

Urine

- Dipstick analysis → Blood, Protein
- Biochemical → Protein-creatinine ratio; Albumin-creatinine ratio; Creatinine clearances; Protein excretion (24hr)

Microscopy

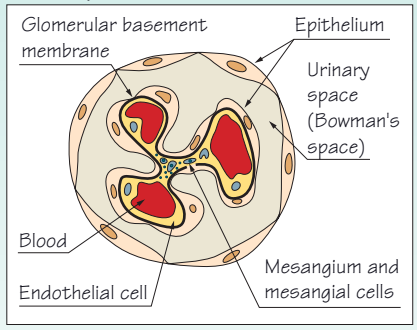


Red cell casts

Blood

- Biochemical
  - Electrolytes
  - Urea, creatinine
  - Glucose → Exclude diabetes mellitus
  - Immunoglobulins → Exclude dysproteinemias
- Microbiology
  - Culture → Exclude infection
  - Serology → Exclude infection
  - ASOT (streptococcal) → Exclude infection
- Immunology
  - Anti glomerular basement membrane Ab (AGBM) → Goodpasture's
  - Anti neutrophil cytoplasmic antibody (ANCA) → Vasculitis
  - Anti nuclear antibody → Lupus
  - Anti dsDNA → Lupus
  - Cryoglobulins → Cryoglobulinemia

Renal biopsy



 The Renal System at a Glance, 3e. By Chris O'Callaghan. Published 2009 by Blackwell Publishing. ISBN 978-1-4051-8472-4.

Although many different diseases act on the glomeruli, the effects of glomerular damage are relatively similar whatever the cause.

- **Reduced glomerular filtration** rate resulting from damage to glomerular components.
- **Proteinuria** caused by protein leakage through the glomerular basement membrane.
- **Hematuria** resulting from active glomerular injury, causing glomerular bleeding.
- **Hypertension** caused by sodium and water retention, often with excess renin secretion.
- **Edema** also resulting from sodium and water retention, often with excess renin secretion.

Classification of glomerular disease

Glomerular disease is primary if only the kidney is affected and secondary if the disease process also affects other tissues. Glomerular disease produces the different clinical syndromes discussed below, such as asymptomatic hematuria or the nephrotic syndrome. Glomerular disease can be classified according to the clinical syndrome produced, the histopathological appearance, or the underlying disease. Only the last is a diagnosis, but the clinical syndrome and histopathological appearances guide the diagnosis. If the etiology is unknown, the histopathological description, such as minimal change disease, also serves as the diagnosis, which is really idiopathic minimal change disease.

Pathological classification

In **proliferative** disease, there is abnormal proliferation of cells within the glomerulus. In severe cases, proliferation of cells, especially macrophages within Bowman's capsule, causes an appearance known as a crescent. In **mesangial** disease, there is excess production of mesangial matrix. In **membranous** disease, the glomerular basement membrane is damaged and thickened. **Membranoproliferative** disease causes both thickening of the glomerular basement membrane and cellular proliferation, usually of mesangial cells. **Vasculitis** is inflammation of the blood vessels. Usually, renal biopsies are interpreted with light microscopy, immunostaining studies and, if necessary, electron microscopy.

- **Focal** disease affects only some glomeruli.
- **Diffuse** disease affects all the glomeruli.
- **Segmental** disease affects only part of the glomerulus.
- **Global** disease affects the whole glomerulus.

Clinical syndromes

Glomerular disease produces five major clinical syndromes. These result from different combinations of the possible effects of glomerular injury. **Asymptomatic proteinuria or hematuria** can result from mild glomerular damage. **Acute glomerulonephritis** is the same as **acute nephritic syndrome** and consists of hematuria, an acute fall in glomerular filtration rate (GFR), sodium and water retention, and hypertension. **Chronic glomerulonephritis** consists of slow progressive glomerular damage, often with proteinuria, hematuria, and hypertension. **Rapidly progressive glomerulonephritis** is a syndrome of very rapid renal failure. There is oliguria and often hematuria and proteinuria, usually without the other features of the nephritic syndrome. **Nephrotic syndrome** consists of heavy proteinuria, leading to hypoalbuminemia and edema (see Chapter 33).

Diagnosing glomerular disease

Clinical assessment

A history of recurrent frank hematuria 1–2 days after an upper respiratory infection suggests IgA nephropathy. Nephritic syndrome occurring 1–3 weeks after an infection suggests post-infective glomerulonephritis, typically post-streptococcal. Hemoptysis with rapidly progressive glomerulonephritis suggests Goodpasture's syndrome. Other features such as skin or joint involvement suggest an underlying condition such as systemic lupus erythematosus or vasculitis. Examination may reveal hypertension, edema, or signs of uremia. It is important to examine for skin, joint, lung, and heart lesions, as well as for neurological disturbances which can indicate systemic lupus erythematosus, vasculitis, or even infection. Both systemic lupus erythematosus and infective endocarditis can cause cardiac valve lesions and glomerular disease. Obesity is associated with focal segmental glomerulosclerosis.

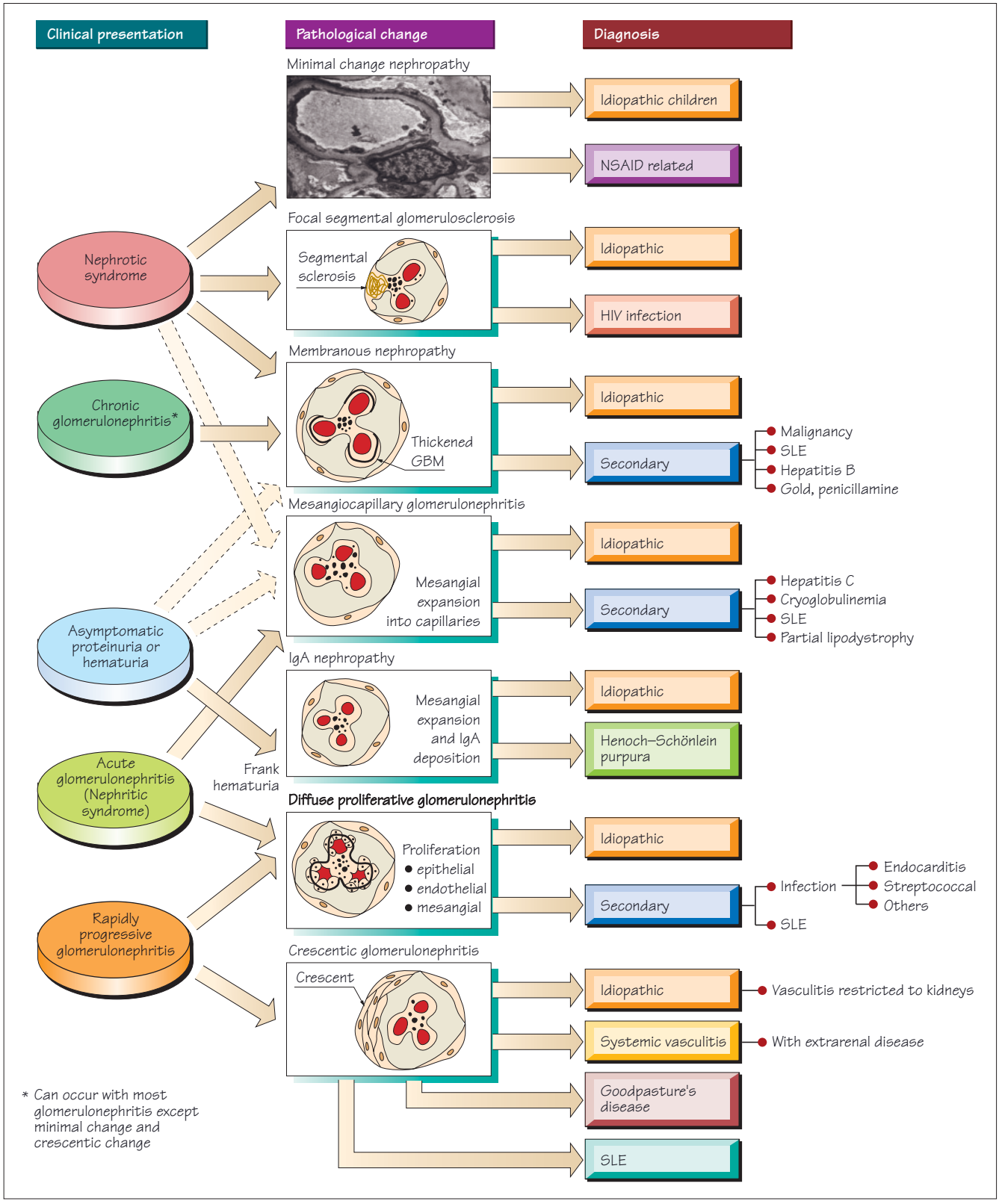
Investigations

Analyze urine for blood and protein, and examine it with a microscope. Red cell casts indicate active glomerular injury causing glomerular bleeding. Measure serum albumin and quantify any proteinuria with a 24-h urine collection or spot urine protein/creatinine ratio or spot albumin/creatinine ratio. Assess GFR from serum urea and creatinine and, if necessary, creatinine clearance. Selected blood tests may indicate a specific diagnosis.

- Blood glucose, immunoglobulins, and blood cultures may indicate diabetes mellitus, myeloma, or other tumors and infection.
- Significant plasma levels of antiglomerular basement membrane antibody indicate antiglomerular basement membrane (Goodpasture's) disease.
- Significant levels of antineutrophil cytoplasmic antibodies (ANCA) suggest systemic vasculitis. If ANCA antibodies are present, these can be checked for specificity against myeloperoxidase (MPO) or protease 3 (PR3).
- Antinuclear antibodies with specificity for double-stranded DNA and low complement levels indicate systemic lupus erythematosus.
- Cryoglobulins are present in cryoglobulinemia.
- Lung function tests may be abnormal if there is pulmonary hemorrhage (Goodpasture's syndrome) because blood in the alveoli absorbs the carbon monoxide used to measure gas transfer, which spuriously raises the gas transfer coefficient.

Unless the diagnosis is clinically obvious, a renal biopsy is usually performed.

30 Glomerular pathologies and their associated diseases



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Diseases of the glomerular basement membrane

Minimal change nephropathy

Minimal change nephropathy accounts for 90% of the nephrotic syndrome in children and 20% in adults. In children, it is associated with atopy (asthma, eczema, and hay fever), and it often follows an upper respiratory tract infection. The disease is termed 'minimal change nephropathy', because light microscopy and immunostaining are normal. However, electron microscopy shows fusion of the podocyte foot processes. The condition responds to steroids and, if it relapses, ciclosporin is useful. Renal impairment does not occur. Non-steroidal anti-inflammatory drugs can cause minimal change disease.

Focal segmental glomerulosclerosis

This accounts for 15% of the adult nephrotic syndrome and can also cause hematuria and hypertension. Focal and segmental scarring is seen, and the scars contain immunoglobulins and complement. Electron microscopy shows podocyte foot process fusion as in minimal change nephropathy. The two conditions may be different results of an essentially similar disease process. Some patients respond to steroids, which are often given for 4–6 months and relapse may be reduced by ciclosporin or cyclophosphamide. Many patients eventually develop end-stage renal failure and the disease can recur after renal transplantation. A variant is associated with HIV infection. Obesity is now a recognised cause of focal segmental glomerulosclerosis. Defects in the CD2AP slit pore protein have been associated with focal segmental sclerosis in some black patients.

Membranous nephropathy

Membranous nephropathy is the most common cause of the nephrotic syndrome in older patients. There is proteinuria and often renal impairment. Histologically, there is thickening of the glomerular basement membrane and **subepithelial deposits**. It is usually idiopathic, but can be secondary to malignancy, hepatitis B, systemic lupus erythematosus, or use of gold or penicillamine drugs. Some patients respond to steroids and chlorambucil or cyclophosphamide, but a minority develop end-stage renal disease.

Proliferative glomerulopathy

Mesangiocapillary glomerulonephritis

This is also known as membranoproliferative glomerulonephritis. It is uncommon and occurs mainly in young adults and children. The presentation varies from asymptomatic hematuria or proteinuria to the usual presentation with combined nephrotic and nephritic syndromes. Most patients develop end-stage renal failure and there is no useful treatment. There is mesangial cell proliferation, excess mesangial matrix, and thickening of the glomerular basement membrane. Most cases are of type 1 with **subendothelial and mesangial immune deposits**. In the more rare type 2 disease, there are immune deposits in the membrane. Type 1 disease is usually associated with systemic lupus erythematosus, infection, or cryoglobulinemia. Patients have low levels of C3 and C4 as a result of complement depletion. Type 2 disease is associated with antibodies that activate and deplete complement, and some patients have the rare disorder partial lipodystrophy.

Immunoglobulin A (IgA) nephropathy (Berger's disease)

Worldwide, this is the most common primary glomerular disease. The typical presentation is in a young man who develops macroscopic hematuria 1–2 days after an upper respiratory tract infection. It can also present with asymptomatic microscopic hematuria, proteinuria, and renal impairment. There is mesangial cell proliferation, increased mesangial matrix, and IgA deposition in the mesangium. Patients often have raised serum IgA levels. Treatment is usually unsuccessful. Nearly a third of patients eventually develop end-stage renal disease and recurrence can occur after renal transplantation.

Henoch–Schönlein purpura

This disease mainly affects children aged under 10. Typically, there is a purpuric rash on the ankles, buttocks, and elbows, abdominal pain, and renal disease. There is usually hematuria, proteinuria, hypertension, fluid retention, and renal impairment, sometimes with the nephrotic syndrome. The histology looks the same as IgA nephropathy. Most children recover fully without treatment.

Diffuse proliferative glomerulonephritis (diffuse endocapillary proliferative glomerulonephritis)

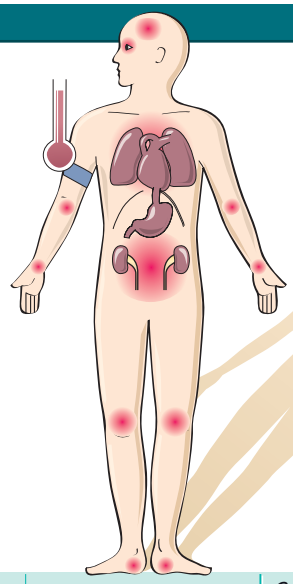
This pathological appearance is typical of **post-infective glomerulonephritis**, which often follows streptococcal infection but can follow other infections, especially infective endocarditis. The classic presentation is nephritic syndrome occurring several weeks after infection. Most patients have low complement levels. There is endothelial and mesangial cell proliferation and glomerular infiltration by neutrophils and monocytes. There is deposition of complement, IgM and IgG on the basement membrane and in the mesangium. Electron microscopy shows **subepithelial deposits**. Antibiotics are given to eradicate any lingering infection and only a few percent of patients develop end-stage renal disease.

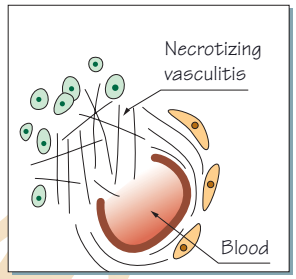
Crescentic glomerulonephritis

Crescents are accumulations of macrophages within Bowman's capsule and indicate severe glomerular injury. There are many causes, especially antiglomerular basement membrane disease (Goodpasture's syndrome), systemic vasculitis, and systemic lupus erythematosus, IgA nephropathy, Henoch–Schönlein disease, vasculitis, and cryoglobulinemia. 'Idiopathic rapidly progressive glomerulonephritis' may be a form of limited vasculitis.

31 Specific diseases affecting the glomeruli

Vasculitis





Vessel size	No granulomata	Granulomata present	May have granulomata
Small Medium Large	Microscopic polyangiitis Polyarteritis nodosa	Wegener's Churg–Strauss	Giant cell arteritis Takayasu's arteritis

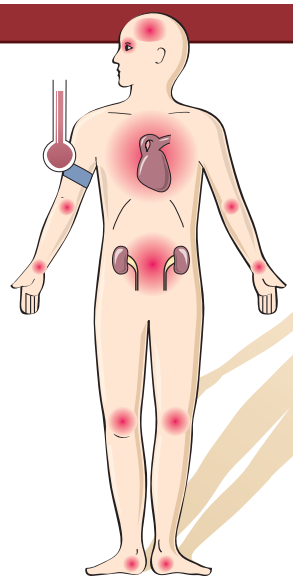
General features

Neurological change → CNS vasculitis → ischemia
Neurological change → Peripheral
Eyes – uveitis
Skin – rash
Joint inflammation
Cardiac vasculitis → ischemia
Gut vasculitis → ischemia
Hypertension
Pulmonary disease
ENT problems
Ix
ANCA
MPO, PR3

Characteristics of vasculitic disease

Wegener's disease	ENT, lung, renal disease
Microscopic polyarteritis	Skin, renal, joint, lung disease
Polyarteritis nodosa	Hypertension, mononeuritis, multiplex, gut, kidney, cerebral ischemia
Churg–Strauss	Asthma, eosinophilia

SLE



Types
1. minimal change
2. mesangial proliferative
3. focal proliferative
4. diffuse proliferative
5. membranous
6. advanced sclerosing

General features.

Female>Male
Skin – butterfly rash
Eyes – uveitis
Joint inflammation
Heart – valve lesions
Neurological/psychiatric disease
Anemia
Thrombosis
Ix ANA
dsDNA
C3↓ C4↓
ESR↑ CRP →
Antiphospholipid antibodies

Antiglomerular basement membrane disease (Goodpasture's syndrome)

This disease is caused by antibodies against the C-terminal end of the α_3 chain of type 4 collagen in the glomerular basement membrane and the alveolar basement membrane in the lung. The antibody binds to these membranes, triggering inflammation. This causes rapidly progressive crescentic glomerulonephritis with acute renal failure and lung hemorrhage. Patients are usually male with the tissue type HLA-DRB1*1501 (usually abbreviated to HLA-DR15). If untreated, patients die from pulmonary hemorrhage or renal failure. Treatment involves plasma exchange to remove the antibodies and immunosuppression with steroids and cyclophosphamide to inhibit glomerular inflammation and reduce antibody pro-

duction. If treated early, most patients recover and relapse is uncommon.

Primary systemic vasculitis

The primary vasculitic diseases produce necrotizing inflammation of vessels and often affect the kidneys, respiratory tract, joints, skin, and nervous system. They are classified according to the size of the smallest vessels affected and the presence or absence of granulomata (see figure). The two small vessel diseases (and less commonly, Churg–Strauss syndrome) can cause a focal segmental proliferative glomerulonephritis with necrosis and crescent formation. Clinically, they often present as rapidly progressive glomerulonephritis. Histologically, there is infiltration of the glomeruli by neutrophils, but no complement or immunoglobulin deposition. Antineutrophil cytoplasmic antibodies (ANCA) against neutrophil granule contents are usually present. Patients with Wegener's granulomatosis have a cytoplasmic or **c-ANCA** reactivity against proteinase 3. Patients with microscopic polyangiitis have a perinuclear or **p-ANCA** reactivity against myeloperoxidase. Therapy is initially with steroids and cyclophosphamide. After several months, azathioprine is substituted for the cyclophosphamide. Plasma exchange is sometimes used in the acute phase. **Idiopathic rapidly progressive glomerulonephritis** is a small vessel vasculitis affecting only the kidney. There is no ANCA, but it is treated like the other small vessel disorders.

Systemic lupus erythematosus

This is a multisystem disease which can affect the nervous system, joints, skin, kidneys, and heart. The renal effects vary and have been classified by the World Health Organization and modified by the International Society of Nephrology as: type 1 — minimal change on light microscopy; type 2 — mesangial proliferative; type 3 — focal proliferative; type 4 — diffuse proliferative; type 5 — membranous; and type 6 — advanced sclerosing. The renal presentation depends on the histological lesion. It is typically nephrotic syndrome or renal impairment and can be acute. There are usually antinuclear antibodies to double-stranded DNA and low complement levels. Typically, the ESR (erythrocyte sedimentation rate) is raised. A raised CRP (C-reactive protein) indicates infection. Treatment for renal disease with steroids and cyclophosphamide or azathioprine is usually helpful. Plasma exchange is sometimes used.

Cryoglobulinemia

Cryoglobulins are immunoglobulins that precipitate in the cold. They occur in inflammatory or neoplastic diseases, including myeloma, lymphoma, multisystem autoimmune diseases, and chronic infection. Plasma complement levels are usually low. Typically, cryoglobulins cause a type 1 mesangiocapillary glomerulonephritis. Mixed essential cryoglobulinemia is usually caused by hepatitis C infection. The clinical presentation is usually of a purpuric vasculitic rash, arthralgia, peripheral neuropathy, and glomerulonephritis. Cryoglobulins are removed by plasma exchange in severe disease.

Dysproteinemias

These disorders are characterized by excess antibody production by benign or malignant plasma cell activity. Malignant disease or myeloma can cause various renal problems, including glomerular deposition of amyloid fibrils, tubular toxicity from filtered light chains, which may form casts in the tubules (myeloma cast nephropathy), and mesangiocapillary glomerulonephritis resulting from glomerular deposition of light chains (light chain deposition disease). The presence of free immunoglobulin light chain (Bence Jones protein) in the urine or a monoclonal band in plasma raises the possibility of myeloma.

Rheumatoid arthritis and connective tissue diseases

Rheumatoid arthritis can cause renal amyloid deposition, mesangial proliferative glomerulonephritis, membranous nephropathy, or a focal segmental glomerulonephritis with vasculitis and necrosis. Systemic sclerosis or scleroderma is rarely associated with a crescentic glomerulonephritis. More commonly, there is hyperplasia of small renal arteries. Any additional vasospasm causes acute renal ischemia. This 'renal crisis' triggers renin release, which worsens the vasospasm and promotes severe hypertension.

Amyloidosis

Amyloid protein is usually a combination of amyloid P protein with either antibody light chains (AL amyloid) or the inflammatory amyloid A protein (AA amyloid). AL amyloid is typical of dysproteinemias, whereas AA amyloid is typical of chronic inflammatory diseases. Amyloid deposition can damage the kidney, liver, spleen, heart, tongue, and nervous system. Amyloidosis can cause proteinuria and nephrotic syndrome. Histologically, amyloid proteins can be visualized by Congo red or immunostaining in the glomeruli, the tubules, and the blood vessels. Treatment aims to reduce production of the amyloid proteins by treating any underlying dysproteinemia or inflammatory disease.

Drug causes of glomerular disease

Gold and penicillamine can both cause membranous nephropathy. Hydralazine causes a lupus-like disease. Non-steroidal anti-inflammatory drugs can cause minimal change glomerular disease, with nephrotic syndrome and sometimes with an interstitial nephritis.

Hereditary and other causes of glomerular disease

Thin basement membrane disease causes asymptomatic microscopic hematuria. The condition is inherited and does not normally cause renal deterioration. Alport's disease is usually an X-linked mutation in the α_5 chain of type 4 collagen, a component of the glomerular basement membrane. It causes proteinuria, hematuria, renal failure, and sensorineural deafness.