Secondary glomerular disease

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Abstract

Secondary glomerular diseases are those with an identifiable underlying or systemic cause, in contrast to primary diseases, where a localized or intrinsic renal pathology is present. Diabetic and hypertensive glomerulopathies are the most common forms of secondary glomerular disease, although kidney biopsy is not usually required for their diagnosis or management. More commonly, biopsy is required in cases of suspected glomerulonephritis, where a variety of histological lesions can be seen, all of which — including podocytopathy, membranous nephropathy and various forms of proliferative glomerulonephritis — have established secondary causes or associations. These include: infections, the most common cause of secondary glomerulonephritis worldwide; autoimmune and rheumatic diseases, such as systemic lupus erythematosus and small vessel vasculitis; drugs, which can injure the glomerulus directly or via induction of autoimmune diseases; and cancers, including solid tumours and haematological malignancies. Where secondary causes are identified, the goals of treatment are generally to remove the offending trigger, with or without anti-inflammatory or immunosuppressive treatment directed at the renal pathology.

Keywords Focal segmental glomerulosclerosis; glomerulonephritis; HIV-associated nephropathy; membranous nephropathy; mesangiocapillary glomerulonephritis; MRCP; post-infectious glomerulonephritis

Key points

- Secondary focal segmental glomerulosclerosis (FSGS) can occur in response to viral or drug-induced podocyte injury, or more commonly as a maladaptive response to nephron-level hyperfiltration
- Glomerulonephritis (GN) associated with autoimmune diseases can be classified according to the pattern of immunostaining seen on biopsy: (1) GN with linear immunoglobulin G deposits; (2) immune complex GN; and (3) pauci-immune GN
- Infections of all types are associated with various patterns of glomerular injury, and these should be identified and treated prior to consideration of immunosuppression
- Drugs can directly injure the glomerulus, or induce systemic autoimmunity that can result in GN
- Solid tumours and haematological malignancies, as well as chemotherapeutic agents used in their treatment, can be associated with GN

Introduction

Secondary glomerulonephritis (GN) is a broad term used to describe glomerular disease associated with an identifiable underlying or systemic cause, whereas primary GN generally refers to localized or intrinsic renal pathology that drives glomerular injury. Most, if not all, glomerular histopathological lesions have identified secondary causes, and here therapy should be aimed at treating the underlying stimulus, with or without anti-inflammatory or immunosuppressive treatment directed at the renal pathology. It is thus essential that secondary diseases are considered in all patients presenting with glomerular disease to direct appropriate treatment.

The classification of GN as 'primary' or 'secondary' is, however, sometimes challenging, for several reasons. First, some terms are used interchangeably to describe either histopathological lesions or clinical diagnoses (e.g. focal segmental glomerulosclerosis (FSGS), discussed in more detail below). Second, as our understanding of disease pathogenesis improves, conditions previously regarded as 'idiopathic' or 'primary' are increasingly recognized to have an underlying systemic or 'secondary' cause. Thus, the spectrum of diseases that can be defined as 'secondary' GN is extensive and debatable; here, we focus on the glomerular abnormalities that encompass 'secondary FSGS' and those that can arise as a result of systemic autoimmune diseases, infections (the most common cause of secondary GN worldwide), drugs and malignancies. Other common and important causes of secondary glomerular disease, including diabetes mellitus, paraprotein-related GN and amyloidosis, are discussed elsewhere (see Identification and management of diabetic nephropathy, pp 654–660; Paraprotein-related renal disease, pp 666–671 of this issue).

Secondary FSGS

FSGS describes a histological lesion (in which there is sclerosis of a proportion of the glomerular tuft with only some glomeruli being affected) rather than a specific disease entity.[1] The finding of FSGS in the kidney biopsy does not provide a diagnosis, as it has a number of aetiologies. These can broadly be classified as primary, genetic or secondary, and in common they result in podocyte dysfunction, injury and loss, ultimately leading to glomerular scarring.

'Primary FSGS' is thought to be caused by an (as yet unidentified) circulating factor that is injurious to podocytes, and 'genetic FSGS' occurs in patients with spontaneous or inherited mutations in genes thought to regulate podocyte function.

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'Secondary FSGS' can arise after a diverse range of podocyte insults, including drugs and viral infections, as discussed further below. More commonly, it can arise as a maladaptive response to glomerular capillary hypertension, which may occur as a result of reduced nephron mass (e.g. prematurity, low birth weight, congenital abnormalities of the kidney and urinary tract, renal surgery, advanced renal disease of any cause) or as a result of nephron-level hyperfiltration (e.g. hypertension, obesity, androgen abuse). Interestingly, susceptibility to secondary forms of FSGS can be genetically determined, as there is an increased incidence of disease in individuals carrying apolipoprotein 1 (*APOL1*) variant risk alleles, common in African populations.

Abrupt-onset nephrotic syndrome is common in primary FSGS although less frequent in maladaptive FSGS; the latter typically presents insidiously with variable degrees of proteinuria (including nephrotic range proteinuria but without other features of nephrotic syndrome such as hypoalbuminaemia and oedema). Suggestive features on kidney biopsy include perihilar FSGS, compensatory glomerular hypertrophy, and segmental rather than diffuse podocyte changes. Primary FSGS can respond to immunosuppressive therapy, but this has no place in the treatment of secondary or maladaptive FSGS, where treatment should be directed at the underlying cause and at renin–angiotensin inhibition. FSGS is now the leading cause of end-stage renal disease (ESRD) in the USA, probably reflecting an increase in the incidence of hypertension, metabolic disorder and obesity in developed countries.

Glomerulonephritis secondary to systemic autoimmune diseases

A number of systemic autoimmune and rheumatic diseases can be complicated by the development of GN. The pathogenic mechanisms are generally immune-mediated and can be broadly classified according to the pattern of immunostaining observed in the kidney biopsy: (1) GN with linear immunoglobulin (Ig)G deposits; (2) immune complex GN; and (3) pauci-immune GN (Table 1). Many of the associated diseases are reviewed elsewhere in this issue, so they are discussed only briefly here (See Lupus nephropathy and vasculitis, pp 672–678 of this issue).

GN with linear IgG deposits

GN with linear deposition of IgG in capillary loops is the hallmark of antiglomerular basement membrane (GBM) disease, a rare small vessel vasculitis characterized by systemic autoimmunity to the non-collagenous 1 domain of the α3 subunit of type 4 collagen. This antigen is exclusively expressed in the glomerular and alveolar basement membranes; it therefore presents with rapidly progressive GN (RPGN) in nearly all cases, with concurrent pulmonary haemorrhage in about 50% (more commonly in current smokers). Treatment with immunosuppression and plasmapheresis must be initiated promptly to prevent irreversible loss of kidney function.

Immune complex GN

Immune complex GN is characterized by granular immunoglobulin and/or complement deposition in glomeruli, as seen by immunofluorescence or electron microscopy. These immune complexes can form *in situ* or in the circulation, and deposit in the glomerulus (subepithelial, subendothelial or mesangial areas); this results in glomerular injury via complement activation and recruitment of inflammatory leucocytes. Immune complex GN is commonly associated with systemic lupus erythematosus (SLE), IgA vasculitis (IgAV; formerly Henoch–Schönlein purpura) and cryoglobulinaemia. It can also be observed, although much less frequently, in other autoimmune rheumatic diseases such as mixed connective tissue disease, rheumatoid arthritis and inflammatory myopathies.

Lupus nephritis is a common manifestation of SLE, occurring in >80% of patients at some point in their disease course, with up to 10% of patients developing ESRD. IgAV is characterized by the dominance or co-dominance of IgA deposits in affected tissues, including the kidney; it is thought to occur after an exogenous stimulus (e.g. mucosal infection) that drives abnormal IgA synthesis. It is the most common systemic vasculitis to affect children, with adult patients having comparatively more severe disease with an associated poorer prognosis. Clinical presentation includes purpura, arthralgia, abdominal pain and GN. It frequently requires only supportive measures; immunosuppression can be used in patients presenting with severe renal involvement, with variable outcomes.

Cryoglobulins are immunoglobulins that precipitate below body temperature; they can be monoclonal (type 1; secondary to lymphoproliferative disorders) or mixed (types 2 and 3; most frequently associated with chronic infection and inflammatory diseases such as hepatitis C virus (HCV) and connective tissue disorders). Cryoglobulins are prone to formation of immune complexes, which can deposit in tissues, inducing an inflammatory response associated with hypocomplementaemia. Clinical features include purpura, arthralgia and lethargy, alongside features of local deposition. Renal involvement can present with nephrotic or nephritic syndrome, with or without renal impairment. Histologically, a mesangio-capillary GN is seen on light microscopy. Systemic autoimmune conditions, infections (particularly HCV) and neoplastic disorders should be considered as possible triggers, to which treatment should be directed. Immunosuppression or plasmapheresis can be required in severe or life-threatening cryoglobulinaemic manifestations.

Pauci-immune GN

The lack of antibody or complement deposition within the glomerulus on immunofluorescence and electron microscopy, despite significant glomerular injury as evidenced by the presence of focal necrosis or crescents, defines a pauci-immune GN. Most patients are, however, serologically positive for circulating antineutrophil cytoplasmic antibodies (ANCAs). Renal involvement is common and discussed in other chapters.

Glomerulonephritis associated with infection

Infections of all types are associated with various patterns of glomerular injury (Table 2). Glomerular injury can result from direct invasion of renal cells or, more commonly, from deposition of microbial antigen–antibody immune complexes; the latter are formed *in situ* or in circulation and deposited in the kidney, where they initiate inflammatory glomerular injury (e.g. post-streptococcal GN (PSGN)). Less frequently, glomerular damage arises as a complication of infection-related thrombotic microangiopathy (e.g. haemolytic–uraemic syndrome) or from the deposition of AA amyloid in glomeruli as a sequel of chronic or suppurative infections such as tuberculosis or schistosomiasis.

Glomerulonephritis in association with systemic autoimmune disease

Type	Immunofluorescence findings	Causes	Serological tests
I	Linear IgG ± C3 along GBM	• Anti-GBM disease (Goodpasture's disease)	Anti-GBM antibodies
II	Granular IgG and C′ components	• Systemic lupus erythematosus • Cryoglobulinaemia • IgA vasculitis	ANA Anti-dsDNA antibodies Complement C3 and C4 levels Serum immunoglobulins Rheumatoid factor Cryoglobulins
III	No or minimal staining for IgG or C′ ('pauci-immune')	• ANCA-associated vasculitis – Granulomatosis with polyangiitis – Microscopic polyangiitis – Eosinophilic granulomatosis with polyangiitis – Renal-limited vasculitis • ANCA-negative pauci-immune GN	Circulating ANCA detectable in 80–90% of cases

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; dsDNA, double-stranded DNA; GBM, glomerular basement membrane; GN, glomerulonephritis; Ig, immunoglobulin.

Table 1

The classical association of GN with infection is PSGN, usually developing 2–3 weeks after group A streptococcal pharyngitis or skin infection, most commonly in children. Clinical presentation ranges from asymptomatic urinary abnormalities through to RPGN. Laboratory features include hypocomplementaemia and raised titres of antibodies to extracellular streptococcal products (e.g. anti-streptolysin O antibodies). Renal biopsy shows a diffuse proliferative immune complex GN, with characteristic subepithelial deposits ('humps') on electron microscopy. PSGN is usually self-limiting, usually only requiring supportive care and antibiotics if there is evidence of active infection.

Examples of glomerular lesions associated with infection

Bacterial	Bacteria of all types	Diffuse proliferative GN Mesangiocapillary GN
	Escherichia coli and *Shigella* species	Thrombotic microangiopathy (haemolytic–uraemic syndrome)
	Syphilis	Membranous GN
Viral	Hepatitis B	Membranous GN Mesangiocapillary GN FSGS Vasculitis (polyarteritis nodosa)
	Hepatitis C	Mesangiocapillary GN Membranous GN FSGS
	HIV	Collapsing variant FSGS (HIVAN) Immune complex GN (HIVICK) IgA nephropathy
	Parvovirus (erythrovirus)	Collapsing variant FSGS
Parasitic	Malaria	Membranous GN Mesangiocapillary GN
	Schistosomiasis	AA amyloid

FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; Ig, immunoglobulin.

Table 2

Improved living standards, an increase in elderly and immunosuppressed populations, and more widespread use of antibiotic therapy has resulted in a change in the pattern of GN associated with bacterial infection in recent years. These infections can be chronic and continuing, so the term infection-related GN (IRGN) is a more accurate description than 'post-infectious'. Staphylococcal infections are the most common cause of IRGN, although a variety of Gram-positive and Gram-negative bacteria have been implicated.[2]

Staphylococcus-associated GN differs from PSGN in several ways, including sites of infection (e.g. soft tissue, heart, bones, indwelling vascular catheters), an association with cutaneous vasculitis that can mimic IgAV, and poorer renal prognosis. Histology is more variable than in PSGN; diffuse endocapillary proliferative GN remains the most common finding, although mesangiocapillary GN can be found (characteristic of 'shunt nephritis') as can extracapillary proliferation, particularly in GN associated with infectious endocarditis. Infectious endocarditis is a critical differential diagnosis in patients found to have a circulating ANCA, as up to 20% of patients with infectious endocarditis are ANCA-positive and crescentic GN can be found in both conditions. Thus, a thorough search for infection is essential to ensure that patients with positive ANCA serology are not given immunosuppression in error. Treatment for IRGN includes supportive care, and eradication of infection with antibiotics and source control.

As with bacterial infections, almost any acute viral infection can induce a transient immune complex proliferative GN. Chronic viral infections with recognized associations with GN include hepatitis B virus (HBV), HCV and HIV.

HBV-related GN most frequently presents with a membranous pattern (although mesangiocapillary GN, FSGS and IgA nephropathy can also be seen). Histologically, HBV-associated membranous GN is indistinguishable from 'primary'

membranous nephropathy; however, viral antigens have been demonstrated within the glomerular immune complexes in HBV-associated disease, suggesting a direct causal relationship. Anti-phospholipase A2 receptor autoantibodies, suggested to be a specific marker of primary membranous, have also been reported in a significant proportion of patients with HBV-associated disease; therefore the validity of this assay in differentiating primary and secondary membranous is unclear. Treatment of HBV-associated membranous GN is with antiviral therapy (interferon, oral antiviral agents) and is reported to be effective in 75–80% of individuals for inducing remission of GN.

The most common glomerular manifestation of HCV infection is mesangiocapillary GN secondary to type 2 mixed cryoglobulinaemia; this arises because of the lymphotrophic potential of the HCV virus, which can induce a polyclonal B cell response that includes the production of cryoglobulins. Eradication of viraemia is central to disease treatment, and the recent development of directly acting antiviral agents provides the opportunity for successful long-term clearance of HCV and elimination of cryoglobulins.

Renal disease in HIV is not uncommon and can occur from direct renal cell infection, immune complex-mediated disease or co-infections, as a complication of combined antiretroviral therapy (cART) or secondary to associated metabolic syndrome.[3] HIV-associated nephropathy (HIVAN) is a specific pathology that arises as a result of direct podocyte injury, histologically shown as collapsing FSGS. Clinically, abrupt-onset nephrotic syndrome with renal impairment is seen and is confined almost exclusively to patients of African descent who carry *APOL1* variant risk alleles. cART is the mainstay of treatment, along with renin–angiotensin blockade.

HIV immune complex disease of the kidney (HIVICK) is a separate entity, arising when active HIV infection causes glomerular immune complex deposition; this manifests with a variety of light microscopic findings, including membranous, mesangiocapillary and 'lupus-like' proliferative GN. As with HIVAN, treatment focuses on renin–angiotensin blockade and cART to halt further viral replication and immune complex generation. The renal prognosis of HIVICK tends to be better than that of HIVAN. Corticosteroids and immunosuppression are not advocated.

In addition to HIV, the collapsing variant of FSGS is seen in association with a number of other viral infections, including cytomegalovirus, Epstein–Barr virus and parvovirus (erythrovirus). In these, it has been suggested that the FSGS occurs either from direct viral infection of glomerular epithelial cells or as a response to high levels of circulating interferon present during viral infection.

Finally, parasitic infections have been reported in association with many patterns of glomerular injury. Malaria (membranous and mesangiocapillary GN), leishmaniasis (mesangiocapillary GN, FSGS; interstitial nephritis can also be seen) and schistosomiasis (mesangiocapillary and mesangial proliferative GN) are among those commonly seen and should be considered in individuals returning from endemic areas.

Drug-induced glomerulonephritis

Tubulo-interstitial injury is the most common drug-induced renal pathology (see Nephrotoxins and drugs in renal insufficiency. Medicine 2019; 47: 517–22.), although many drugs are capable of causing direct glomerular injury. This can occur at several sites: the epithelium (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), lithium and pamindronate causing podocytopathy presenting as minimal-change disease or FSGS); the endothelium (e.g. mitomycin C- and quinine-induced thrombotic microangiopathy); the GBM (e.g. gold-induced membranous GN); or the mesangium (e.g. tobacco-induced mesangial sclerosis).

In addition, numerous drugs have been associated with the formation of autoantibodies (including ANCA, antinuclear antibodies (ANA), anti-double-stranded (ds) DNA and anti-GBM antibodies); clinical manifestations of the associated diseases can subsequently develop.[4] In these cases, avoidance of the offending agent can be sufficient to allow renal recovery, although adjunctive corticosteroids or immunosuppressive treatment may be needed in cases of severe glomerular inflammation. Table 3 highlights some of the drugs commonly associated with various patterns of glomerular injury.

Malignancy-related glomerulonephritis

Membranous GN is the most common glomerular pathology associated with solid tumours (e.g. lung, gastrointestinal, prostate), and is thought to be related to tumour antigen-derived

Drugs associated with glomerulonephritis

ANCA-associated vasculitis	SLE	Anti-GBM disease	FSGS	Membranous GN	Minimal-change disease
Cocaine	Procainamide	Alemtuzumab	Bisphosphonates	Gold	NSAIDs
Levamisole	Quinidine		Interferon	Penicillamine	Lithium
Hydralazine	Hydralazine		Lithium	Captopril	Pamidronate
Propylthiouracil	Propylthiouracil		Pamidronate	NSAIDs	Interferon
	Isoniazid		Sirolimus	Anti-tumour necrosis factor	
	Methyldopa		Anabolic corticosteroids		
	Carbamazepine		Doxorubicin		

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; FSGS, focal segmental glomerulosclerosis; NSAID, non-steroidal anti-inflammatory drug; SLE, systemic lupus erythematosus.

Table 3

immune complexes depositing within the GBM. Secondary membranous GN should be considered in patients with known cancer presenting with proteinuria; conversely, malignancy should always be considered in patients newly diagnosed with membranous GN, particularly if risk factors are present (older age, smoker, immunocompromise, absence of serum anti-phospholipase A2 receptor (PLA2R) antibodies or negative glomerular PLA2R staining).[5] This will require thorough review of symptoms and clinical examination, with investigations directed to their findings, though there are currently no consensus guidelines on the routine use of radiological or endoscopic tests in screening asymptomatic patients for malignancy following a diagnosis of membranous GN.

Other tumour-associated glomerular diseases include minimal-change disease (lung, colorectal, renal cell), FSGS (renal cell) and mesangiocapillary (lung, renal cell, gastric) and thrombotic microangiopathy (gastric, lung, breast). It is sometimes unclear whether these associations are causal, although reports of glomerular disease resolving after treatment of the tumour, without specific therapy directed to the renal pathology, supports a causative link in some cases.

Haematological malignancies are likewise associated with glomerular injury. Hodgkin's lymphoma is typically associated with minimal-change disease, whereas chronic lymphocytic leukaemia has been associated with mesangiocapillary and membranous GN. Plasma cell dyscrasias can cause diverse renal lesions associated with circulating paraproteins; treatment is generally directed at the underlying plasma cell clone (see Paraprotein-related renal disease, pp 666–671 of this issue).

Finally, many chemotherapeutic agents used to treat malignancy can result in glomerular injury (see Table 3 and also Thrombotic microangiopathies and the kidney, pp 661–665 of this issue), and these causes should be considered in patients with known cancer found to have GN. ◆

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