Glomerulonephritis Associated with Other Bacterial Infections

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Introduction

Although *Streptococcus* and *Staphylococcus* are the most common pathogens associated with glomerulonephritis, several other bacteria (also viruses and parasites) can trigger similar immune-mediated kidney injury. It is estimated that approximately a quarter of infection-associated glomerulonephritis in adults is due to *Streptococcus* and another quarter due to *Staphylococcus* [1]. Other responsible bacterial infections include *Pneumococcus*, gram-negative rods, gram-positive rods, *Mycobacterium,* etc., although most are documented in either isolated case reports or small case series. Nonstreptococcal glomerulonephritis, especially in developed countries, is a disease of the elderly with comorbidities such as alcoholism, diabetes mellitus, malignancy, intravenous drug use, and HIV infection [1–3]. If often affects males, typically in the fifth decade of life. Caucasians and Asians appear to be more commonly affected in the nonpediatric age group, although all ethnic groups are at risk [4].

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Clinical Presentation

A clinical history of infection can be elicited in most patients, but more than a third lack evidence of infection [1, 2, 5]. The common sites of infections include upper respiratory tract infections, lung, skin, and heart valves with less-frequent reports of associated osteomyelitis, urinary tract infections, deep-seated abscesses, infected vascular Dacron prosthesis, and infected ventriculoperitoneal shunts [6, 7]. In typical cases, the acute infectious process usually comes to immediate clinical attention and the onset of renal manifestations range from 2 to 4 weeks. However, "postinfectious" glomerulonephritis may be unsuspected in the setting of insidious chronic infections with symptoms that range from none to mild and nonspecific. Quite often, the infection in an elderly person comes to light at the time of renal biopsy or only *after* a biopsy diagnosis of "postinfectious" glomerulonephritis prompts exhaustive investigation [7–9]. In this context, infection-associated GN appears to be a better terminology than postinfectious glomerulonephritis [4].

The usual clinical presentation of infection-associated glomerulonephritis involves mild proteinuria and hematuria, associated with new onset hypertension and sometimes oliguria [1, 2, 5, 7]. Although this acute nephritic syndrome presentation is more common, some patients have nephrotic range proteinuria or nephrotic syndrome. Low serum complement levels are seen in 35–80% of adults and 90% of

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children with postinfectious glomerulonephritis [1, 2, 5, 7]. Low C3 levels are more frequently encountered than low C4. However, normal complement levels should not deter a clinical or a pathological diagnosis of infection-associated glomerulonephritis. Circulating immune complexes have been detected in many infections. Their disappearance in the blood correlates with treatment of the corresponding infection, but these are not routinely investigated for clinical management. On occasion, rheumatoid factor is positive and serum cryoglobulins may be detected, especially in infective endocarditis and shunt nephritis [2, 7].

Light Microscopy

The renal biopsy findings are typically those of proliferative glomerulonephritis [1, 7] (Fig. 3.1). Diffuse proliferative glomerulonephritis is the most common pattern of glomerular injury with endocapillary proliferation and inflammatory cells occluding the capillary lumens (Table 3.1). The glomerular inflammatory infiltrate can be rich in neutrophils, leading to "exudative" glomerulonephritis [2, 10, 11] (Fig. 3.1a). Monocytes and macrophages may predominate in later phases, and are particularly prominent in infection-related cryoglobulinemic glomerulonephritis (type II or III) [12]. Scattered hump-shaped deposits can occasionally be seen on silver and trichrome stains. Depending on the severity of infection and the time internal between onset of symptoms and the kidney biopsy, milder glomerular changes such as focal proliferation and mesangioproliferative changes are encountered [2, 10, 11] (Fig. 3.1d). Crescents, when found, are often small and focal [1, 7]. However, rare cases of crescentic glomerulonephritis have also been reported. Chronic infections such as shunt nephritis result in membranoproliferative glomerulonephritis with lobular accentuation, mesangial proliferation, and basement membrane double contours [13–15] (Fig. 3.1g). Membranoproliferative glomerulonephritis has also been reported with pneumonia, deep-seated infections, and osteomyelitis. Visualization of deposits by light microscopy is usually a feature of cryoglobulinemic glomerulonephritis with large subendothelial deposits, intraluminal deposits, and intracellular deposits within macrophages [16, 17]. Variable degrees of focal segmental and global glomerulosclerosis are seen as a consequence of chronic glomerulonephritis (Fig. 3.1h), but in an elderly patient, chronic changes also represent underlying renal disease. The interstitial inflammation is predominantly localized to areas of tubular atrophy and interstitial fibrosis, but can be related to chronic infection or other causes. There are no specific infection-associated vascular changes, but underlying hypertensive arteriosclerosis may be evident. Transmural vasculitis and necrosis may be present in cryoglobulinemic glomerulonephritis [16, 17].

Immunofluorescence Microscopy

As with streptococcal infections, C3-dominant deposits are the defining feature of all postinfectious glomerulonephritis (Fig. 3.1b). Immunofluorescence with IgG is also positive in infection-associated glomerulonephritis and isolated C3 is seen in less than a third of the patients, especially in the resolving phase [7, 18]. In most cases, IgM and IgA staining is minimal or absent; however, in the cases of cryoglobulinemic glomerulonephritis and IgA-dominant postinfectious glomerulonephritis, respectively, these immunoglobulins are abundant. Underlying diabetic nephropathy manifests as linear glomerular and tubular basement membrane staining with IgG and albumin. Staining for kappa and lambda light chains is usually absent in infection-associated glomerulonephritis. A renal biopsy performed early in the course of disease has a "starry sky" pattern with C3 and IgG capillary wall deposits, while a late biopsy in an acute self-limited infection with resolving glomerulonephritis reveals mesangial deposits with mostly C3 staining (Fig. 3.1e). Bulky capillary wall deposits manifest as "garland" pattern on immunofluorescence [2, 11].

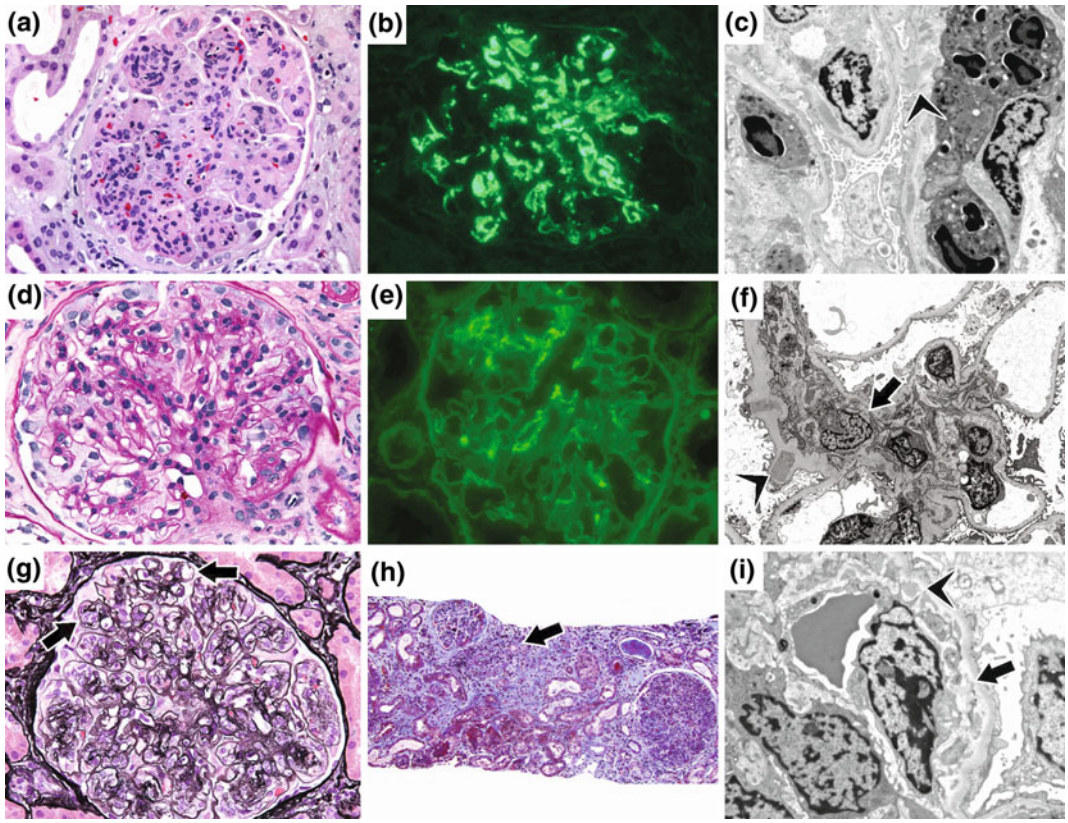

Fig. 3.1 Histological spectrum in infection-associated glomerulonephritis. **a–c** Infection-associated exudative glomerulonephritis with numerous infiltrating neutrophils is usually associated with acute presentation of nephritic syndrome (**a** H&E, ×400). The glomerular deposits are C3-dominant and are often bulky, involving the mesangium and capillary walls (**b** C3, ×400). Ultrastructural examination confirms the presence of small subepithelial deposits (*arrow head*) in addition to mesangial and subendothelial deposits (**c** ×7500). **d–f** Resolving phase of postinfectious glomerulonephritis is often associated with mild clinical disease and histological changes. Segmental mesangial hypercellularity is seen (**d** PAS, ×400) and the C3 deposits are weak and segmental (**e** C3, ×400). Electron microscopy shows mesangial deposits (*arrow*) along with occasional subepithelial humps (*arrow head*) (**f** ×3000). **g–i** Membranoproliferative glomerulonephritis is often a feature of chronic infection-associated immunological injury to the kidney. Lobular accentuation of glomeruli is present along with basement membrane double contours (*arrow*) (**g** JMS, ×400). The renal cortical tissue shows patchy tubular atrophy and interstitial fibrosis (*arrow*) in a young patient without preexisting disease, reflective of chronic injury (**h** trichrome, ×100). Electron microscopy confirms the presence of basement membrane reduplication (*arrow*) along with subendothelial deposits (*arrow head*) (**i** ×5000).

Electron Microscopy

Ultrastructural examination characteristically shows large subepithelial deposits that are fewer per capillary loop than membranous nephropathy and have a special predilection for mesangial "notch" (glomerular basement membrane reflection over the mesangium) (Fig. 3.1c, f). These "humps" or "bell shaped" deposits also lack associated glomerular basement membrane remodeling and are overlaid by podocyte basement membrane. Mesangial and subendothelial deposits are typically small and few [1, 2, 5, 7, 18] (Fig. 3.1c, f). However, mesangial deposits may predominate in chronic infections and

Table 3.1 Nonstreptococcal and nonstaphyloccocal infection-associated glomerulonephritis: histological patterns

	Diffuse proliferative GN	Focal proliferative GN	Mesangioproliferative GN	Membranoproliferative GN	Cryoglobulinemic GN	Membranous nephropathy
Common renal presentation	Acute nephritic syndrome	Mild hematuria and proteinuria	Mild hematuria and proteinuria	Nephrotic range proteinuria, nephrotic syndrome, hematuria	Nephrotic range proteinuria, nephrotic syndrome, hematuria, skin purpura	Nephrotic range proteinuria or nephrotic syndrome
Clinicopathological correlation	Acute infections	Early or resolving infection	Early or resolving infection	Chronic infections	Acute or chronic infections	Acute or chronic infections
Laboratory investigations	Low C3 ±	Low C3 ±	Low C3 ±	Low C3 ±	Low C3, normal C4, cryoglobulins +, rheumatoid factor +	Normal C3, C4
Light microscopy	variable neutrophils (if ≫ exudative GN); visible subepithelial deposits	Focal and segmental endocapillary proliferation	Mesangial proliferation	Mesangial proliferation, lobular accentuation, GBM double contours	> monocyte/macrophage infiltration, bulky subendothelial and intraluminal deposits	Thick GBMs, mesangial proliferation ±
Immunofluorescence microscopy	C3 dominant, IgG +; starry sky or garland pattern	C3 dominant, IgG (starry sky pattern)	C3, IgG ± (mesangial pattern)	C3 dominant, IgM or IgG +	C3 dominant, IgM or IgG +	C3, IgG ±
Electron microscopy: deposits	Subepithelial humps, mesangial, subendothelial ±	Subepithelial humps, mesangial, subendothelial ±	Mesangial, subepithelial and intramembranous ±	Mesangial, subendothelial, subepithelial/intramembranous ±	Mesangial, subendothelial, intraluminal deposits	Subepithelial deposits, mesangial ±

(continued)

Table 3.1 (continued)

	Diffuse proliferative GN	Focal proliferative GN	Mesangioproliferative GN	Membranoproliferative GN	Cryoglobulinemic GN	Membranous nephropathy
Common associated infections	*S. epidermidis, Pseudomonas aeruginosa, Hemophilus influenzae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter cloacae, Mycobacterium leprae, Mycoplasma pneumoniae, Treponema pallidum, Bartonella henselae, Coxiella burnetii, Rickettsia rickettsii, Borrelia burgdorferi, Chlamydia pneumoniae*			*S. epidermidis* (*shunt nephritis*), *Mycoplasma pneumoniae, Mycobacterium leprae, Propionibacterium acnes, Neisseria meningitidis, Borrelia burgdorferi, Nocardia, Coxiella burnetii*	*S. epidermidis* (*Shunt Nephritis*)	*Yersinia enterocolitica, Treponema pallidum*
Comments				ANA frequently + in shunt nephritis		

glomerular basement membrane duplication with mesangial cell interposition is often present (Fig. 3.1i).

Pathophysiology

Infection-associated glomerulonephritis is an immune complex-mediated process, triggered by the host response to an extrarenal infection [19]. Circulating immune complexes have been detected in several infections and microbial antigens have been detected within glomerular immune deposits [20–22]. The physiochemical properties of antigen and/or antibody such as size and charge play a role in localization of the deposits. A cationic antigen traverses the anionic glomerular basement membrane resulting in subepithelial localization with subsequent binding of circulating antibody, while bulkier immune complexes are entrapped in the subendothelium [19, 23]. Activation of innate and adaptive immune system, coagulation, and complement pathways triggers the cascade of tissue injury [24, 25]. Classical, alternative, and lectin-binding complement pathways are likely involved in a variety of infections. In addition, the host factors such as underlying diseases causing immunodeficiency and possibly defective alternative complement pathway are likely needed for development of clinically recognized glomerulonephritis [25]. These mechanisms are well characterized in streptococcal infections [9], but data suggests that similar pathogenic mechanisms could account for other infection-related glomerulonephritis.

Treatment and Prognosis

Treatment of underlying infection is the mainstay of therapy in infection-associated glomerulonephritis. It includes surgical drainage of abscesses and antibiotic therapy. Successful therapy leads to resolution of GN and the serum complements normalize within a few weeks [5]. There may be a role for immunosuppressive therapy in unresponsive severe proliferative or crescentic glomerulonephritis once the infection is cleared. In general, the renal survival of infection-associated glomerulonephritis in elderly individuals is significantly worse than in pediatric poststreptococcal glomerulonephritis. The underlying comorbidities influence the outcome adversely. Despite successful therapy, a third to two-thirds of patients have either persistent renal dysfunction or progress to end-stage renal disease [1, 4, 7].

Related Diagnoses

C3 Glomerulopathy: Postinfectious glomerulonephritis and C3 glomerulopathy fall within a spectrum of glomerulonephritis with overlapping clinical and pathological features [26]. C3 glomerulopathy is related to dysregulation of alternative complement pathway and is characterized by isolated/predominant C3 stain, intramembranous or transmembranous deposits and less-frequent subepithelial hump-like deposits [27]. Patients with C3 glomerulopathy have progressive renal disease despite milder disease at presentation [26]. Persistent low C3 levels and proteinuria in the setting of treated infection should suggest a diagnosis of C3 glomerulopathy. Such atypical postinfectious glomerulonephritis patients have an underlying defect in alternative pathway of complement [28]. To further complicate the diagnostic challenges, infections can precipitate C3 glomerulopathy in a predisposed individual [29, 30].

Autoimmunity, ANCA, and Pauci-immune Glomerulonephritis: Many chronic infections are known to trigger autoantibodies such as cryoglobulins (IgM antibodies directed against IgG), rheumatoid factors, antinuclear antibodies, and antineutrophil cytoplasmic antibodies (ANCA) [12, 25, 31]. The mechanisms by which pathogens can trigger autoimmunity include dysregulated host immune system, molecular mimicry, epitope conformational change, epitope spreading, and anti-idiotypic antibodies [25]. Polymorphisms of various genes involved in immunological processes can modulate the regulator T cell function and predispose an

individual to develop infection-triggered autoimmunity. Some bacterial antigens share amino-acid sequences with self-antigens and the antibodies that develop in the host can target the self [32]. It has been shown that such molecular mimicry by clostridial antigens of glomerular basement membrane can result in anti-GBM disease [33]. Similarly, *Staphylococcus aureus* has sequences similar to complementary proteinase 3 (PR3) peptide resulting in anti-idiotype antibodies (ANCA) directed against PR3 antigen [34]. ANCA serology has been documented with suppurative lung disease, gram-negative bacterial infections (*Pseudomonas, Klebiella, Escherichia coli*), and subacute bacterial endocarditis [35, 36]. Antibodies to lysosomal membrane protein-2 (LAMP-2) were identified in some, but not all, patients with pauci-immune glomerulonephritis [37, 38]. Their pathogenic role has been demonstrated by some investigators [37, 38]. LAMP-2 antigen is expressed on the surface of neutrophils and endothelial cells and has homology to fimbrial adhesin of *E. coli* and *Klebsiella.* The antibody response to fimbrial adhesin in urosepsis can trigger anti-LAMP-2 antibodies and precipitate pauci-immune glomerulonephritis [37, 39].

Positive ANCA serology has been documented in association with subacute bacterial endocarditis due to *Streptococcus, Staphylococcus, Enterococcus, Bartonella, and Brucella* [40, 41]. A recent study indicated that up to 28% of patients with endocarditis have serum pANCA or cANCA with most having either positive MPO or PR3 or both [35]. In such a clinical setting, renal biopsy findings are critical in distinguishing between immune-mediated endocarditis-associated glomerulonephritis and pauci-immune ANCA-mediated glomerulonephritis as both are associated with prominent glomerular crescents [35] (Fig. 3.2). The dominant C3 ± immunoglobulin staining with electron-dense deposits favor endocarditis-associated glomerulonephritis, while paucity of staining and lack of deposits on electron microscopy suggests ANCA-mediated glomerulonephritis. The possibility of pauci-immune glomerulonephritis superimposed on endocarditis-associated GN adds to the diagnostic challenge [41]. Treatment of infection is critical in both and the role/effectiveness of immunosuppression is not well established due to limited data [35].

Specific Bacterial Infections

Pneumococcal Infections

Streptococcus pneumoniae can trigger a postinfectious glomerulonephritis similar to *S. pyogenes*. It typically causes pneumonia and bacteremia and the data related to acute nephritis is limited to a few case reports [21, 42–44]). The renal manifestations are hematuria, proteinuria, edema, and renal insufficiency, which typically develop 2–3 weeks after pneumococcal infection. The immune mechanisms triggered by pneumococcal antigen result in acute proliferative glomerulonephritis or pure mesangial proliferative glomerulonephritis. The serum complement C3 levels can be either reduced or normal depending on the stage of the disease at the time of testing [20]. Antistreptolysin (ASO) titers are often elevated and cryoglobulinemia has also been reported. In addition to dominant C3 staining in the mesangium and capillary walls, IgG, C1q, and properdin have also been found, compatible with activation of both classical and alternative complement pathways [20, 21]. The pathogenic mechanism involves glomerular deposition of pneumococcal polysaccharide capsular antigen that triggers the complement activation. The pneumococcal antigen has been detected by immunofluorescence in glomeruli as well as alveoli [20, 21]. Ultrastructural evidence of subepithelial humps helps render a diagnosis of postinfectious glomerulonephritis. Treatment of the infection with antibiotics and supportive therapy result in complete resolution of glomerulonephritis.

Meningococcal Infections

Caused by *Neisseria meningitidis*, meningococcal infections can result in immune complex-mediated glomerulonephritis [45]. Clinically overt renal disease is rare, but biopsy triggered by laboratory

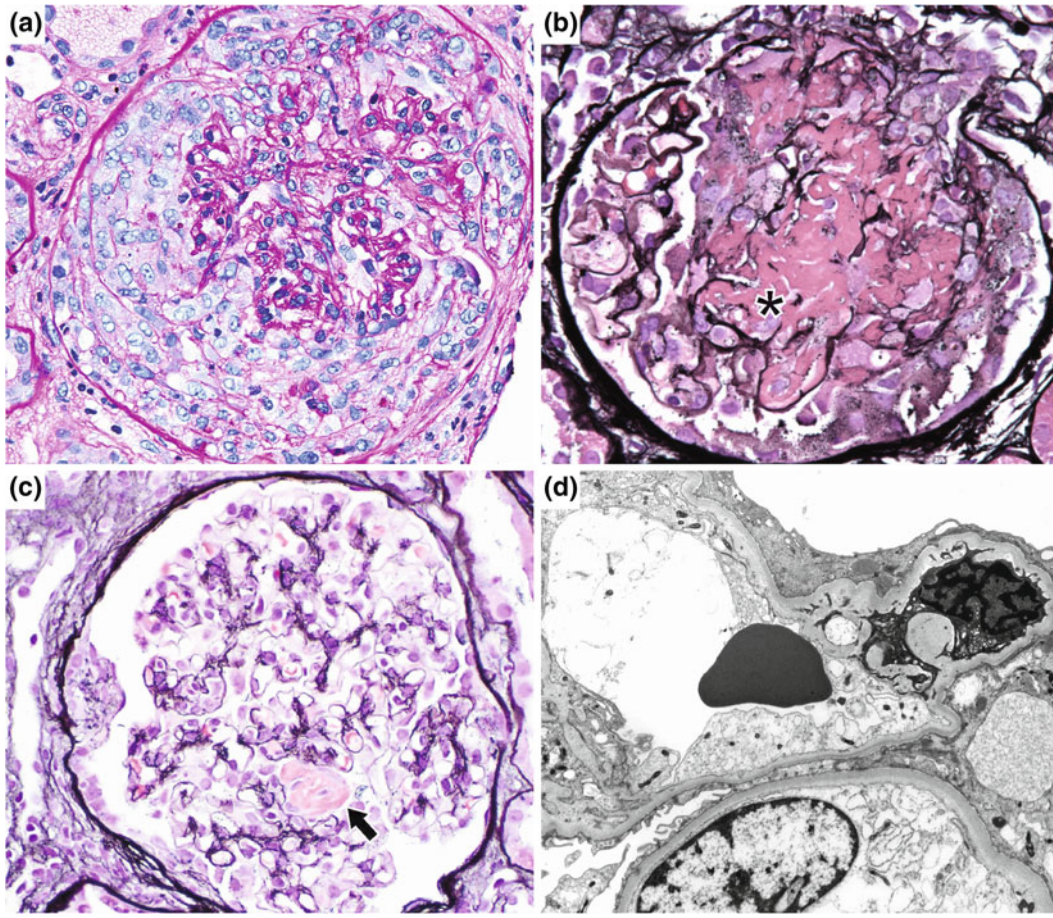

Fig. 3.2 Infection-related pauci-immune glomerulonephritis. **a** Glomerular crescents in a patient with subacute bacterial endocarditis and positive ANCA serology. Immunofluorescence staining for immunoglobulins and complements was negative (PAS, ×400). **b** Glomerular basement membrane rupture and extensive fibrin extravasation (*) (JMS, ×400). **c** Relatively preserved glomerulus with focal necrosis (*arrow*). Lack of prominent mesangial or endocapillary proliferation should suggest pauci-immune glomerulonephritis (JMS, ×400). **d** Ultrastructural examination confirms the lack of electron-dense deposits. Mild endothelial swelling and podocyte foot process effacement is seen (×6000).

evidence of circulating immune complexes showed acute proliferative glomerulonephritis. Membranoproliferative glomerulonephritis has also been reported with meningococcal infection. The immunofluorescence and electron microscopy shows features similar to poststreptococcal glomerulonephritis [45].

Syphilis

Syphilis is a sexually transmitted disease caused by a spirochete *Treponema pallidum* whose only natural hosts are humans [46]. Renal involvement is rare [47] and is due to direct tissue invasion by the spirochete or is precipitated by immune-mediated mechanisms. The overall seroprevalence is extremely low [48], but syphilis is undergoing resurgence over the last 2 decades in the developed world and the diagnosis can be missed if not suspected clinically [46]. The clinical presentation of syphilis varies widely and depends on the stage of disease. Primary syphilis presents as a painless ulcerated skin lesion (chancre) 2–6 weeks after infection. If untreated, 25% of patients progress to secondary syphilis in weeks to

months. It is represented by non-itchy generalized rash, lymphadenopathy, fever, and malaise due to disseminated spirochetal infection. Approximately, 20–40% of untreated secondary syphilis cases progress to tertiary syphilis over 1–30 years after the primary infection. Tertiary syphilis primarily affects the cardiovascular system and brain, and the formation of gumma, i.e., granulomatous locally destructive lesion, is common. Glomerulonephritis related to syphilis occurs during (a) secondary or tertiary syphilis stage, (b) congenital syphilis infection, or rarely (c) after initiation of anti-syphilis therapy [49–52] (Table 3.2). Congenital syphilis due to transmission of organisms from mother to baby during pregnancy or at birth is relatively rare in the Western countries, but membranous nephropathy in an infant should prompt a search for treponemal infection [53].

Proteinuria is the most common renal manifestation and occurs in up to 8% of secondary syphilis patients [49]. It can range from mild proteinuria to nephrotic syndrome in the setting of membranous nephropathy. Mild hematuria, acute nephritis syndrome, renal insufficiency, or rapidly progressive renal failure can all occur depending on the type of glomerulonephritis [54]. Hypocomplementemia is reported with proliferative glomerulonephritis. The most common glomerulonephritis associated with syphilis is membranous nephropathy with variable mesangial hypercellularity. Other patterns reported include proliferative glomerulonephritis (ranging from mild to diffuse ± neutrophils), crescentic glomerulonephritis, and minimal change disease [49, 54]. The immune-mediated glomerulonephritis has immunofluorescence evidence of immunoglobulin and complement

Table 3.2 Glomerulonephritis associated with treponemal infections

	Secondary/tertiary syphilis	Congenital syphilis	Therapy-related GN
Renal presentation	Nephrotic syndrome, less common nephritic syndrome	Nephrotic syndrome, nephritic syndrome or hematuria	Extremely rare: nephrotic syndrome, nephritic syndrome
Histology	Membranous nephropathy, Diffuse proliferative GN ± crescents, minimal change disease	Membranous nephropathy ± mesangial hypercellularity	Membranous nephropathy (rare)
	Membranous nephropathy ± mesangial hypercellularity most common		
	Tubulointerstitial nephritis with plasma cells, gumma formation; spirochetes on Warthin–Starry stain	Tubulointerstitial nephritis with plasma cells; spirochetes on Warthin–Starry stain	
Immunofluorescence microscopy	IgG and C3 granular deposits in mesangium and capillary wall	IgG and C3 granular deposits in mesangium and capillary wall	Treponemal antigen detected in immune complexes
	Treponemal antigen detected in immune complexes		
	Membranous nephropathy is PLA2R negative		
Electron microscopy	Subepithelial deposits ± spikes ± mesangial deposits in membranous nephropathy	Subepithelial deposits ± spikes ± mesangial deposits in membranous nephropathy	Subepithelial deposits ± spikes ± mesangial deposits in membranous nephropathy
	Subepithelial "humps" ± mesangial/subendothelial deposits in proliferative GN		

deposits. Tubulointerstitial inflammation is often present and tends to be plasma-cell rich. Demonstration of tissue spirochetes indicates direct tissue invasion. Although not specific, positive rapid plasma regain (RPR) or VRDL should raise concern for syphilis. Once suspected, a diagnosis of syphilis can be confirmed by treponemal antibody tests (*T. pallidum* hemagglutination assay and fluorescent treponemal absorption test). The organisms can also be detected in the tissue by Warthin–Starry silver stain, dark field microscopy, immunofluorescence microscopy, or polymerase chain reaction.

The glomerulonephritis is likely due to the glomerular deposition of treponemal antigen with subsequent binding of the circulating antitreponemal IgG antibody or deposition of circulating immune complexes. Antibodies have been eluted from the kidney biopsy and the treponemal antigen has been demonstrated in the immune deposits in both acquired and congenital syphilis-associated glomerulonephritis [22, 55, 56]. Treponemal antigen–antibody complexes deposited in the glomeruli activate the classical and alternate complement pathway.

Syphilis is treated with penicillin or ceftriaxone and requires 3–6 weeks of therapy. The resolution of glomerulonephritis can take 1–6 months after therapy. The consequent treponemal death triggers a massive release of bacterial antigens and endotoxins causing a systemic reaction referred to as Jarisch–Herxheimer reaction. It usually last only a few hours during which the patient develops fever, chills, tachycardia, flushing, and myalgias. Prominent skin rash can also occur and is thought to be due to immune complex formation and deposition. Rare case reports of renal involvement with transient nephrotic syndrome are also reported [52].

Lyme Disease

Lyme disease is the most common tick-borne infection in USA, seen especially in the Northeastern regions and Wisconsin [57]. It is a multisystem disorder caused by a spirochete *Borrelia burgdorferi* and transmitted by ticks of genus *Ixodes*. Renal involvement is rare and the diagnosis requires high index of clinical suspicion [57, 58]. The early symptoms of fever, fatigue, and the characteristic skin rash of erythema migrans might be forgotten by the patient at presentation. If left untreated, Lyme disease has frequent relapses and remissions manifested by arthritis, cardiac, and neurological symptoms. The diagnosis rests on serological confirmation including ELISA detection of IgM and IgG antibodies specific to *B. burgdorfer*i, western blot, and polymerase chain reaction detection of *B. burgdorferi* DNA in body fluids [59–61]. Unfortunately, all these tests are prone to false-positive and false-negative results, further complicating the diagnosis.

The renal symptoms are microscopic hematuria and proteinuria, but nephrotic syndrome is not uncommon and rare cases present with acute renal failure [58, 62, 63]. Although hypocomplementemia is helpful when present, C3 levels are often normal. Membranoproliferative glomerulonephritis is the most common histology on renal biopsy, but mesangioproliferative glomerulonephritis, membranous nephropathy, and IgA nephropathy have also been described [58, 61, 62] (Fig. 3.3). Mild interstitial inflammation accompanies the glomerular changes and the extent of chronic tubulointerstitial damage is variable. Interstitial foam cells have been described with chronic nephrotic range proteinuria. IgG and dominant C3 staining in the mesangium and capillary walls is typical and on rare occasion IgA staining has been described in mesangioproliferative glomerulonephritis [58, 62]. The electron-dense deposits are mostly in the mesangium and subendothelium with rare subepithelial deposits.

Lyme disease associated with glomerulonephritis is caused by chronic antigenemia, robust host response with antibody production, and immune complex formation. The circulating immune complexes deposit in the glomeruli and initiate tissue injury [57]. There may be a role for autoimmunity as *B. burgdorferi* antigens mimic self-antigens at the molecular level [64]. The treatment of Lyme disease includes oral doxycycline for 14–28 days or even longer in chronic infection [65]. The renal disease of membranous glomerulonephritis may respond to steroids,

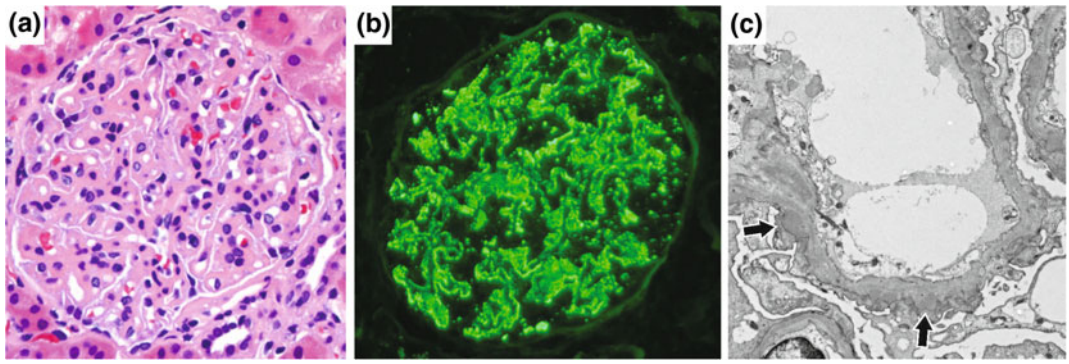

Fig. 3.3 Infection-associated membranous nephropathy. **a–c** Membranous nephropathy is less commonly seen in association with nonstreptococcal and nonstaphylococcal bacterial infections. This patient with Lyme disease presented with nephrotic syndrome. Diffuse thickening of the glomerular basement membranes is seen with mild segmental mesangial proliferation (**a** H&E, ×400). The glomerular capillary walls have diffuse granular capillary wall deposits that stain for IgG, C3, κ and λ (**b** IgG, ×400). Electron microscopy shows numerous small subepithelial deposits (*arrow*) in the capillary loops, confirming the diagnosis of membranous nephropathy (**c** ×9000).

intravenous immunoglobulin, and on occasion, plasmapheresis [61]. Although not universal, complete resolution of membranoproliferative glomerulonephritis has been described in the literature [61].

Bartonella "Cat-Scratch Disease"

Bartonella species are fastidious gram-negative organisms; *B. henselae* and *B. quintana* are associated with human disease. *B. Henselae* is the culprit in 'cat scratch' disease; organisms are carried by fleas, transmitted to cats, and then to humans through broken skin, most typically via scratch from a kitten [66]. In immunocompetent individuals, there is a self-limited regional lymphadenitis, but in immunosuppressed patients more widespread granulomatous inflammation can involve spleen, liver, central nervous system, and bone, and in severely immunocompromised patients angiomatosis (bacillary angiomatosis of the skin or peliosis of the liver–spleen) occurs [66, 67]. Patients with cardiac or valvular defects are at risk for *Bartonella* endocarditis, with *Bartonella* comprising up to 17% of endocarditis, and 28% of 'culture negative' endocarditis [66, 67]. Since *Bartonella* endocarditis is often blood 'culture negative,' it requires a high index of suspicion in conjunction with serologic or PCR studies for confirmation [68]. However, *Bartonella* serologic testing is not particularly specific, though very high titers have increased specificity (>1:800) [67, 68]. Cases of *Bartonella*-associated glomerulonephritis have been reported; one series cited "kidney failure" in 45% of patients with *Bartonella* endocarditis [68]. Importantly, in some cases the renal biopsy findings have prompted the rigorous search for an infectious process [68, 69].

As with other types of infection-associated glomerulonephritis, histopathologic findings in *Bartonella*-related glomerulonephritis have been variable. Light microscopy generally shows a proliferative and/or focal necrotizing-crescentic glomerulonephritis [66–72]. Immunofluorescence results are also variable, and have most commonly been reported as IgM-dominant or pauci-immune, but cases of 'full house' deposition, C3-dominant, or IgA-dominant staining have been documented [66–72]. Ultrastructural studies tend to show mesangial electron-dense deposits, most often without the classic subepithelial 'hump' deposits [66–72]. Thus, infection should be considered in glomerulonephritis with an IgM-dominant immunofluorescence pattern. Further, a *Bartonella* and other endocarditis-associated glomerulonephritides often are associated with positive ANCA serologies. Thus, an infectious

process should remain on the differential in cases of ANCA-positive necrotizing and crescentic glomerulonephritis [66, 71, 73] (Fig. 3.2).

Brucella

Brucellosis is a zoonotic infection caused by gram-negative coccobacilli *Brucella* sp., and is endemic in Middle East and Mediterranean countries. Close contact with infected animals, consumption of unpasteurized dairy products, and inhalation of aerosols leads to human infection [74]. All organ systems are affected and clinical picture can be varied. Although *Brucella* organisms can be isolated in 4–5% of infected patients, renal involvement is rare [75]. The renal histology in *Brucella* infection can be in the form of acute interstitial nephritis (due to direct invasion of bacterium), chronic granulomatous inflammation, renal abscess, and occasionally glomerulonephritis.

Derived from the limited literature related to *Brucella* glomerulonephritis, most patients present with hematuria, proteinuria (can be nephrotic range), and sometimes renal insufficiency. Low C3 levels can be seen, especially with membranoproliferative glomerulonephritis. The site of infection can vary, but glomerulonephritis has been reported with endocarditis, mycotic aneurysm, and others [74, 76]. Although the data is limited, the most common *Brucella* organism isolated is *B. melitensis*. The renal biopsy findings reported are membranoproliferative glomerulonephritis, mesangioproliferative glomerulonephritis, cryoglobulinemic glomerulonephritis, diffuse proliferative v, IgA nephropathy, and membranous nephropathy [76–81]. Definitive diagnosis rests on serological confirmation (serum agglutination test, ELISA) or isolating brucellae from blood or infected tissues. Polymearase chain reaction results in rapid confirmation of the infectious organism and is preferred over cultures [82]. Circulating immune complexes with glomerular deposition is the main mechanism involved, likely initiated by chronic antigenemia [83]. On occasion, proliferative and crescentic glomerulonephritis or renal vasculitis occurs in the absence of immune complexes [76]. It has been suggested that endotoxemia triggers a cellular inflammatory response within the glomerulus with subsequent injury in the absence of immune complexes as in ANCA-mediated injury [76]. Treatment of *Brucella* infection-related glomerulonephritis includes doxycycline in combination with rifampin, gentamicin, streptomycin, or trimethoprim/sulfamethoxazole. Additional steroid therapy may be helpful in the setting of crescentic glomerulonephritis and vasculitis [76].

Mycobacterium

Mycobacterium tuberculosis complex: The mycobacterial infections in humans include tuberculosis caused by members of *Mycobacterium tuberculosis* complex, mainly *M. tuberculosis* and rarely by a bovine tubercle bacillus, *M. bovis* [84]. Both are obligate pathogens while most other species within the genus mycobacterium are environmental saprophytes typically not associated with human disease in an immunocompetent state. On occasion, an environmental mycobacterium such as *M. avium* causes disseminated disease in an immunocompromised human host [85]. The kidney is mainly involved by *M. tuberculosis* in the form of genitourinary tuberculosis, while *M. avium* can infect the kidney as part of disseminated disease. Another mycobacterium, *M. leprae,* is known to affect the kidney in endemic areas [86].

Tuberculosis is caused by either reactivated latent *M. tuberculosis* infection in an immunosuppressed host or by dissemination of active pulmonary infection. Renal involvement in the form of genitourinary tuberculosis accounts for 14–41% of extrapulmonary tuberculosis in developed countries [84, 87]. The infected pelvic calyces and medulla undergo ulceration and destruction with accumulation of cheesy caseous material [84, 88]. Chronic tubulointerstitial nephritis with necrotizing caseating granulomas is not uncommon.

On rare occasion, *M. tuberculosis* infection can result in glomerulonephritis, especially in endemic areas [89]. The clinical manifestations of patients with tuberculosis-related glomerulonephritis include hematuria and proteinuria. The systemic symptoms related to tuberculosis

infection such as fatigue, mild fever, night sweats, weight loss, and hypertension are more common than local genitourinary symptoms such as urinary frequency, urgency, and flank pain. Accurate diagnosis depends on confirmation of active tuberculosis infection by demonstration of acid-fast bacilli (sputum), cultures (sputum, urine), polymerase chain reaction (renal biopsy tissue), or more recently Quantiferon test [84, 89, 90]. In one study, more than 70% of patients with tuberculosis-related glomerulonephritis had pulmonary or extrapulmonary tuberculosis [89]. Most patients with glomerulonephritis are over 40 years of age, likely reflective of prolonged tuberculosis infection predisposing to the development of glomerular disease. Over 72% of patients with tuberculosis-related glomerulonephritis had IgA nephropathy, but other glomerulonephritides have also been reported. These include mesangioproliferative glomerulonephritis, crescentic glomerulonephritis, collapsing glomerulopathy, membranous nephropathy, and membranoproliferative glomerulonephritis [91–96].

While the immune responses in *M. tuberculosis* are primarily cell-mediated, there is a humoral component as well [97–99]. High levels of immune complexes have been detected in patients with disseminated tuberculosis [100]. T cell suppressed environment with negative Mantoux skin test while not a requisite may predispose to development of circulating immune complexes [91, 99]. It appears that IgA antibodies directed against A-60 mycobacterial antigen play a role in the frequent association between tuberculosis infection and IgA nephropathy. These antibodies have been detected in the serum of patients with active tuberculosis as well as the immune complexes of IgA antibodies and mycobacterial antigens [97].

The diagnosis of tuberculosis-related glomerulonephritis is difficult due to nonspecific symptoms and insidious nature of the disease. High index of suspicion is needed. Treatment is mainly antituberculosis therapy and care should be taken to address multidrug-resistant tuberculosis [84]. Resolution of hematuria and proteinuria with treatment also supports the diagnosis of tuberculous glomerulonephritis [89, 99]. Interestingly, rifampin antituberculous therapy in turn can precipitate crescentic glomerulonephritis [101].

Mycobacterium leprae is a weak intracellular acid-fast bacillus that causes either tuberculoid leprosy or lepromatous leprosy base on robustness of the host response. The bacillus has a predilection for Schwann cells and skin. Leprosy is endemic in several developing countries. Although highly infectious with prolonged exposure, clinical disease is less common as *M. leprae* is slow growing with an incubation period of 2–12 years.

Tuberculoid leprosy is characterized by granulomatous inflammation and paucity of bacilli due to effective cell-mediated immunity. On the other hand, lepromatous leprosy is more common with multibacillary forms associated with weak host defenses. The renal lesions described include glomerulonephritis, granulomatous interstitial nephritis, AA amyloidosis, and pyelonephritis [102].

Glomerulonephritis represents the most frequent type of renal involvement in leprosy, found in approximately 30% of patients [103]. Lepromatous leprosy patients with abundant bacilli are particularly vulnerable. These bacilli trigger a robust humoral response, but these antibodies are not protective against the lepra bacilli. Immune complexes form in this high antibody milieu and glomerulonephritis may ensue. Antigens from other co-infections may also play a role. Skin erythema nodosum has similar pathogenesis and according to one study, there is a strong correlation between erythema nodosum and development of glomerulonephritis [104]. The potential mechanisms for glomerulonephritis and erythema nodosum include either deposition of circulating immune complexes or in situ deposition of lepra antigens. Circulating cryoglobulins have also been documented in leprosy [105]. Lepra bacilli antigens are released in massive amounts after the antibiotic therapy, and immune complexes can be formed in this setting as well [104].

Renal presentation of mild hematuria and proteinuria is common with leprosy-associated glomerulonephritis, but nephrotic syndrome also can occur, depending upon the type of tissue

injury [86, 103, 106]. A few patients also have functional tubular defects of acidification or urinary concentration. Histologically, the glomerular changes reported include membranous nephropathy, IgA nephropathy, mesangioproliferative, endocapillary proliferative, or membranoproliferative glomerulonephritis [102, 103, 107]. Crescents are rare and can result in acute renal failure [108]. The tubulointerstitium may show granulomatous inflammation with acid-fast bacilli demonstrated on Fite stain. Immunofluorescence reveals granular C3 and IgG deposits in the mesangium and along the capillary walls. The corresponding electron-dense deposits are in the mesangium and subendothelium. Antibiotic treatment of *M. leprae* with dapsone, rifampin, and clofazimine is main course of treatment. But steroids and nonsteroidal anti-inflammatory drugs might be of help in the setting of glomerulonephritis related to acute immunological episodes.

Others: There are many other bacterial infections reported in association with glomerulonephritis [44]. Patients with *Klebsiella* and *Mycoplasma* pneumonia develop proliferative glomerulonephritis [109, 110]. The renal presentation includes hematuria, proteinuria, or renal insufficiency, but glomerulonephritis may also be clinically occult. *Klebsiella* polysaccharide antigen has been demonstrated in the mesangial and glomerular capillary wall deposits and the eluate of the glomerulus-bound IgG antibody was specific to *Klebsiella* [109]. Similar evidence of mycoplasma antigen was found in a patient with *Mycoplasma* infection-associated diffuse proliferative glomerulonephritis [111]. The serum complement levels are reportedly low in *Mycoplasma*-associated proliferative glomerulonephritis and the immune deposits are predominantly in the mesangium [110, 111]. Recent reports of *Mycoplasma*-related crescentic glomerulonephritis and vasculitis have also been documented [112–114]. Following an infection with *Mycoplasma*, a patient developed MPO-ANCA with subsequent pulmonary-renal syndrome and glomerular crescents [114].

Renal involvement in *Salmonella* infections is reported to occur in 2–3% of patients, and it includes cystitis, pyelitis, pyelonephritis, and rarely glomerulonephritis [115]. However, it has been postulated that subclinical glomerulonephritis is not uncommon and kidney biopsies performed in three typhoid fever patients with no evidence of renal dysfunction did demonstrate immune complex glomerulonephritis [116]. Reported histological findings in typhoid glomerulonephritis include diffuse proliferation and IgA nephropathy, in addition to thrombotic microangiopathy [117–119]. Deposition of immunoglobulin and C3 is seen along with subepithelial humps on electron microscopy. *Salmonella* Vi antigen has been demonstrated in the glomerular capillary wall confirming the pathogenic role of *Salmonella typhi* [116].

Infection-Associated Amyloid

Amyloidosis as a complication of chronic inflammatory conditions including infection and autoimmune disease has been recognized for nearly a century [120]. Serum amyloid A (SAA), an acute phase reactant synthesized in the liver in response to IL-1, IL-6, and tumor necrosis factor [121], is the amyloid fibril constituent in this setting, as well as in Familial Mediterranean fever. In the developed world, the incidence of infection-associated SAA amyloid has decreased with reduction in chronic tuberculosis, leprosy, osteomyelitis, chronic decubitus ulcers in paraplegics, and infections in burn patients, hidradenitis suppurativa, dermatoses, and cystic fibrosis [120, 122–124]. However, some of these conditions remain prevalent in less-developed areas of the world [122]. Further, there was an 'epidemic' of SAA amyloid amongst illicit drug users with skin infections in the 1970s–1980s, and such cases have been seen continually since then, although infrequently reported [121–123, 125–133].

Menchel et al. and then Neugarten et al. characterized SAA amyloid amongst drug users in New York City. In a group of 150 drug addicts at autopsy, amyloid was identified in 6 of 44 (14%) subcutaneous drug users but in only 1 of 105 (1%) intravenous drug users. Of 23 drug addicts with skin infections, 6 had amyloid (26%) [131, 133]. In a subsequent study

incorporating these autopsy cases as well as larger group of biopsy cases, *Neugarten* et al. identified cutaneous suppurative lesions in 17/20 drug addicts with amyloid [131, 133]. The authors estimated that 25–50% of drug addicts biopsied for proteinuria had SAA amyloid in this era [126, 133]. Other glomerular findings in heroin addicts include focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, or infection-related proliferative glomerulonephritis (endocarditis, skin infection, other) [126, 128].

Patients with infection-associated SAA amyloid present with heavy proteinuria (range 1.5–29 gm/day) [126, 133]. They may have the full nephrotic syndrome, and generally also have elevated serum creatinine, with several reporting polyuria and polydipsia [126, 133]. Patients inevitably had a long history of intravenous drug use, and a more recent history (2–3 years) of cutaneous drug use, so-called 'skin-popping,' after veins are longer useable for injection [126, 133, 134]. In a series of renal biopsies from 35 heroin addicts, Dubrow et al. reported older age, longer duration of addiction, lower serum albumin, and lower blood pressure in those with renal amyloid as compared to those with focal segmental glomerulosclerosis [126]. In a contemporary study, skin infections in drug users were frequently polymicrobial, including both methicillin-sensitive and methicillin-resistant *Staph.* species, *Strep*. species, and a mixture of anaerobic organisms [135].

Histopathologically, features of SAA amyloid in the kidney are similar to other forms of

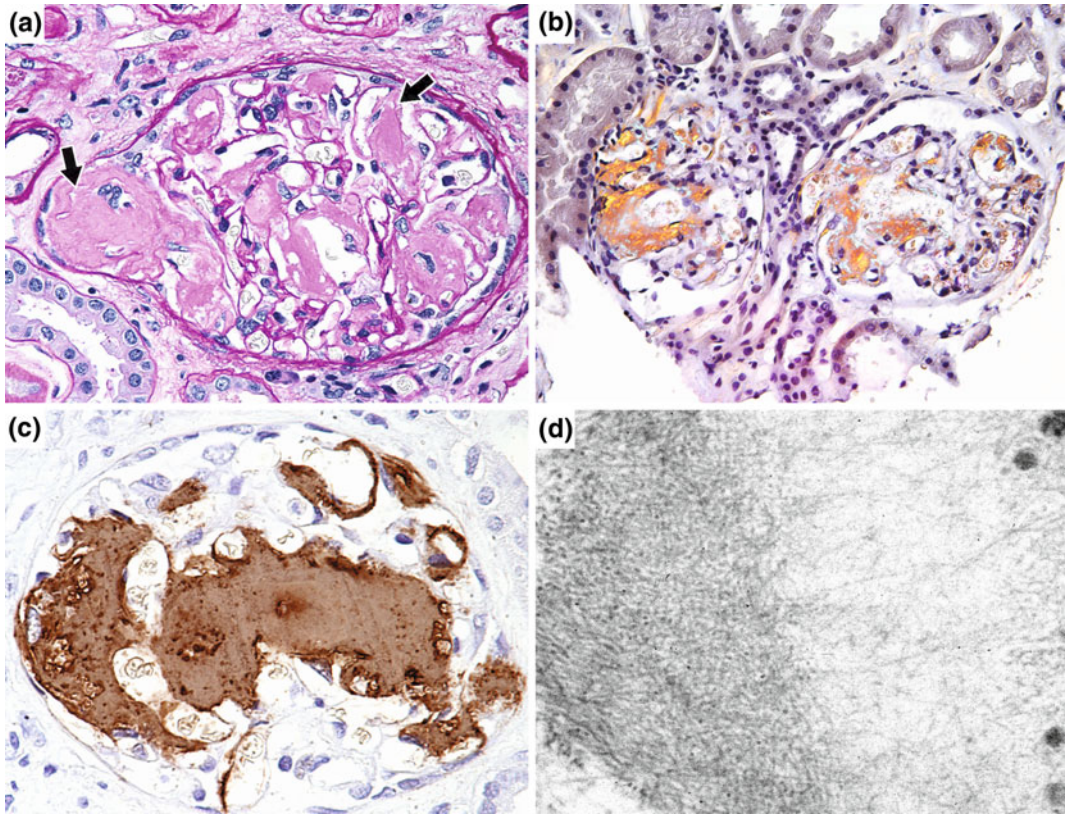

Fig. 3.4 Amyloid A deposition in chronic infections. **a** Pale amorphous deposits of amyloid (*arrow*) in the mesangium, capillary walls, and vascular pole in a patient with history of IV drug abuse who presented with nephrotic syndrome (PAS, ×400). **b** The Congo red stain under polarized light highlights the glomerular amyloid with patchy apple *green* birefringence (Congo Red, 200). **c** The amyloid subtype associated with chronic infections is AA type, as confirmed on immunohistochemical stain (Serum amyloid A stain, ×400).

amyloid. Amyloid deposits in glomeruli are seen in the mesangium and, with extensive deposition, involve and efface much of the glomerular tuft [136] (Fig. 3.4a). Unfortunately, skin infection-associated SAA is often biopsied at this late phase with extensive renal damage. Amyloid deposits are lightly eosinophilic and 'waxy' on H&E, pale on PAS, metachromatic (blue-purple) on trichrome, and silver negative [136]. Amyloid 'spicules' by light microscopy may be aligned perpendicular to the glomerular basement membrane. SAA amyloid frequently involves the interstitium as well as arteries and arterioles. Congo red staining is positive in amyloid with green birefringence on polarization (Fig. 3.4b). Fluorescent light may also be used to evaluate Congo red or thioflavin stains [136, 137]. By immunofluorescence microscopy, the amyloid deposits are essentially negative for immunoglobulin, light chain, and complement staining, but there is often nonspecific background in the amyloid. Serum amyloid A staining will be positive by immunofluorescence or immunohistochemical methods (Fig. 3.4c); alternatively, mass spectroscopy or other proteomic methods can be used to type the amyloid [138]. Electron microscopy shows deposits with the characteristic randomly oriented fibrils of 8–12 nm diameter [136] (Fig. 3.4d).

A few case reports demonstrate improvement of the proteinuria and partial histologic remission in the rare patient successfully cleared of infection and inflammation, with cessation of drug abuse [121, 123, 129]; however, renal disease is progressive in most [132–134]. Serum amyloid A protein levels may be monitored in the serum [122].

Special Circumstances

Deep-Seated Visceral Abscess

Initially described by Whitworth et al. and Beaufils et al. [139, 140], glomerulonephritis can occur in association with visceral abscesses in the absence of infective endocarditis. These deep-seated suppurative infections are caused by gram-positive or gram-negative organisms. *Staphylococcus* osteomyelitis in a diabetic patient is one of the more frequent associations, but others include lung abscesses, wound infections, subphrenic abscess, abdominal abscess, mediastinitis, and infected vascular Dacron prostheses caused by a variety of bacterial organisms [141, 142]. Case reports of associated nocardial cerebral abscesses are also known [143]. The duration of the abscess ranges from a few weeks to a few years. The blood cultures are usually negative and the serum complement levels are normal. Fever, hypertension, and oliguria are often present and glomerulonephritis is suspected in the presence of hematuria (gross or microscopic) and proteinuria. In the presence of circulating cryoglobulins, patients can have extrarenal manifestations of arthralgias and purpura.

The morphological spectrum of biopsy changes can range from mesangial hypercellularity in early disease when the infection is <2 months duration to diffuse proliferative/crescentic glomerulonephritis to membranoproliferative glomerulonephritis in long standing infections [140, 141]. One study demonstrated increased glomerular monocytic infiltration in visceral infection-associated glomerulonephritis even in the absence of cryoglobulinemia [144]. Immunofluorescence shows granular deposits in mesangium and glomerular capillary walls with C3 and less frequently IgG. Staphylococcal infections can show predominant or codominant IgA staining along with C3 (described in chap. 2). Electron-dense deposits are located in mesangium and subepithelium. Small subendothelial or intramembranous deposits can also occur. Immune complex deposition and activation of alternative complement pathway are the likely pathogenic mechanisms.

Eradication of infection with surgical approaches and antibiotics is the main course of treatment. Renal recovery occurs with successful antimicrobial treatment and the follow-up renal biopsies would show resolution of morphological changes with only mild residual mesangial hypercellularity, capillary wall thickening, and global glomerulosclerosis [140]. Failure to completely clear the infection results in persistence of glomerulonephritis with progression to an end-stage kidney disease.

Shunt Nephritis

Chronic glomerulonephritis associated with infection of ventriculoatrial shunts is referred to as shunt nephritis. These shunts are inserted for treatment of hydrocephalus and are prone to bacterial colonization. *Staphylococcus epidermidis* is the offending organism in over 75% of shunt infections. It is either inadvertently introduced from a skin source during the surgery or gets deposited during transient bacteremia. *Staphylococcus* also can form a biofilm around the catheter tips in vivo thus escaping the effects of antibiotics and colonizing the shunt. Other organisms associated with shunt infections include *Listeria monocytogenes, Peptococcus, Corynebacterium bovis, Bacillus subtilis, Mycobacterium gordonae, Micrococcus, diphtheroid species, and gram-positive anaerobic* rods such as *Propionibacterium acnes* [14, 15, 145, 146].

The incidence of ventriculoatrial shunt infection can be as high as 27%, but in most instances, this chronic infection is asymptomatic for several years [13, 147]. Blood and cerebrospinal fluid cultures are usually sterile possibly due to prior antibiotic therapy and the shunt infection can be demonstrated only on removal and culture of the shunt. Only a small proportion (4–5%) of patients with infected shunts actually develop glomerulonephritis and the time frame can be as early as 4 weeks or as late as 21 years after the shunt operation [13, 14, 145, 147]. Most shunt infections are in pediatric population, but are also seen in adults. The risk of developing shunt infections is much lower with ventriculoperitoneal shunts and they have largely replaced the ventriculoatrial shunts in hydrocephalus treatment [14].

The clinical features of shunt nephritis such as fever, malaise, and nausea are nonspecific and are likely due to bacteremia. On occasion, renal manifestations are the presenting symptoms. These include hematuria and mild proteinuria, although nephrotic syndrome can also occur. Oliguric acute renal failure has been reported. The systemic symptoms accompanied by renal dysfunction can lead to an erroneous diagnosis of urinary tract infection [14]. Patients may also develop hypertension, arthralgias, lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, and anemia. Serum C3 levels are low in up to 90% and C4 is low in 50% of patients with shunt nephritis. Hypocomplementemia in shunt infection typically indicates renal involvement. Some patients may have positive ANCA titers (anti-proteinase 3) and infection-related ANCA disease is a consideration [148]. Other laboratory investigations that are helpful in diagnosis of infection are elevated ESR, cryoglobulins, rheumatoid factor, and positive blood

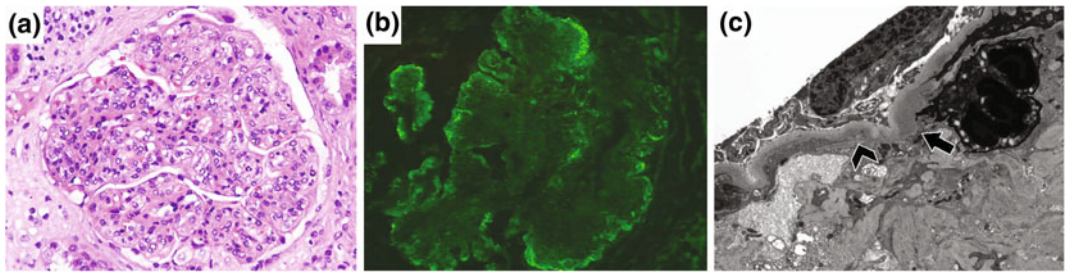

Fig. 3.5 Renal biopsy findings in shunt nephritis. **a** The glomeruli demonstrate lobular accentuation with mesangial and endocapillary proliferation and basement membrane double contours. The biopsy is from a 36-year-old male with ventriculoperitoneal shunt in place for more than 3 decades. The patient presented with increased serum creatinine, nephrotic proteinuria, hematuria, and hypertension. The serum complement levels were normal and the shunt was subsequently found to be infected with *Propionibacterium acne* (H&E, ×400). **b** Immunofluorescence microscopy revealed peripheral capillary wall and segmental mesangial deposits that were predominantly positive for C3 and to a lesser extent IgG (C3, ×400). **c** On ultrastructural examination, scant, weakly electron-dense deposits were seen in the paramesangium (*arrow*), subendothelium (*arrow head*) and occasional intramembranous locations (×6000). Figure courtesy of Tibor Nadasdy, with permission

cultures [13, 14]. Positive antinuclear antibody has also been noted in association with shunt nephritis.

The histological spectrum seen in shunt nephritis is similar to that seen with other infection-associated glomerulonephritis. Approximately, one-half of patients show membranoproliferative glomerulonephritis (Fig. 3.5a) and one-third show diffuse proliferative glomerulonephritis with mesangioproliferative glomerulonephritis in the remainder. On occasion, focal proliferative glomerulonephritis and crescentic glomerulonephritis have been reported [13]. A few neutrophils can be seen in glomeruli, but florid exudative glomerulonephritis is uncommon. Immunofluorescence microscopy typically has mesangial and capillary wall deposits that stain for C3 (Fig. 3.5b) and IgG; IgM can sometimes be the predominant immunoglobulin. C1q and C4 may be present, suggestive of classical complement pathway activation. The electron-dense deposits are in the mesangium and subendothelium (Fig. 3.5c) with occasional intramembranous and subepithelial deposits.

Immune complex deposition is the likely pathogenic mechanism, followed by classical and to a lesser extent alternative complement pathway activation [149]. Bacterial antigens have been demonstrated in the glomerular deposits [149]. Serum cryoglobulins can develop in shunt infections and can also activate classical pathway of complement.

Treatment of shunt nephritis is antibiotic therapy and removal of infected shunt. The renal function usually recovers completely within a few weeks of successful therapy. The hypocomplementemia and cryoglobulinemia, if present, resolves too [14, 145]. The glomerulonephritis improves and the residual changes may be mild mesangial hypercellularity [150]. The immune deposits and electron-dense deposits also disappear. Approximately, a third of the patients have persistent mild proteinuria, microhematuria, hypertension, and renal insufficiency. Depending on the extent of prior glomerular damage, global glomerulosclerosis and chronic tubulointerstitial damage may be significant, eventually leading to an end-stage kidney.

Shunt nephritis is increasingly a rare diagnosis. More recently, we encounter glomerulonephritis associated with infected central vein catheters, and other devices such as LVAD (left ventricular assist device) which has similar clinical and histological features as shunt nephritis [151, 152]. The most common pathogen in central venous catheter infections is also *S. epidermidis* (Tables 3.1 and 3.2).

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