

Post-Infectious Glomerulonephritis and variants

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1. Acute Post-infectious glomerulonephritis (APIGN)

Post-infectious glomerulonephritis occurs following various infections, including bacterial, viral, parasitic, rickettsial and fungal infections (**Figure 1**). *Group A beta-hemolytic Streptococcus* is a typical and classical type, however *Staphylococcus*-related PIGN shares the main cause to date. The majority of PIGN cases reveal acute glomerulonephritis by clinically and pathologically. In the predominant course of APIGN, the symptoms of acute glomerulonephritis appears in few weeks after infection, however the latency period to glomerulonephritis varies and may depend on the site, and cause of infection (**Table 1**). The nephritis is thought to be induced by immune-complex type glomerulonephritis with type 3 hypersensitive reaction, yet nephritogenic antigens are not fully identified.

Figure 1

Box 1 Infections associated with postinfectious glomerulonephritis ¹⁻²	
Infectious syndromes¹⁹ <ul style="list-style-type: none"> ▪ Skin and throat infections (<i>Streptococcus pyogenes</i>, <i>Streptococcus equi</i>,⁷⁸ <i>Streptococcus constellatus</i>⁹²) ▪ Bacterial endocarditis (<i>Staphylococcus aureus</i>, <i>Streptococcus viridans</i>) ▪ Pneumonia (<i>Streptococcus pneumoniae</i>, <i>Mycoplasma pneumoniae</i>) ▪ Visceral abscesses (dental abscesses, deep-seated abscesses, osteomyelitis) ▪ Shunt nephritis (<i>Staphylococcus epidermidis</i>, <i>Propionibacterium</i>) 	Viruses^{17,33} <p>DNA viruses</p> <ul style="list-style-type: none"> ▪ Hepadnaviridae (hepatitis B virus) ▪ Herpesviridae (varicella zoster virus, Epstein-Barr virus, cytomegalovirus) ▪ Parvoviridae (parvovirus B19)⁹⁵ ▪ Adenoviridae (adenovirus) <p>RNA viruses</p> <ul style="list-style-type: none"> ▪ Retroviridae (HIV) ▪ Picomaviridae (coxsackievirus, echovirus, hepatitis A virus) ▪ Flaviviridae (dengue virus, hepatitis C virus) ▪ Paramyxoviridae (mumps virus, measles virus) ▪ Bunyaviridae (hantavirus) ▪ Reoviridae (rotavirus) <p>Parasitic infestations^{2,47}</p> <ul style="list-style-type: none"> ▪ Malaria (<i>Plasmodium falciparum</i>, <i>Plasmodium malariae</i>)^{32,93,96} ▪ Schistosomiasis (<i>Schistosoma hematobium</i>, <i>Schistosoma mansoni</i>)^{53,93} ▪ Toxoplasmosis (<i>Toxoplasma gondii</i>)^{93,97} ▪ Filariasis (<i>Wuchereria bancrofti</i>)⁹³ ▪ Trichinosis (<i>Trichinella spiralis</i>)⁹³ ▪ Hydatid disease (<i>Echinococcus granulosus</i>)⁹⁸ ▪ Amoebiasis (<i>Entamoeba histolytica</i>)⁹⁹
Specific bacterial diseases^{19,47} <ul style="list-style-type: none"> ▪ Infection with Gram-positive bacteria (streptococci, staphylococci, pneumococci, enterococci, <i>Listeria monocytogenes</i>) ▪ Infection with Gram-negative cocci (<i>Meningococcus</i>, <i>Neisseria gonorrhoeae</i>) ▪ Infection with Gram-negative coccobacilli (<i>Hemophilus</i>) ▪ Infection with Gram-negative bacilli (<i>Salmonella</i>, <i>Klebsiella</i>, <i>Serratia</i>, <i>Yersinia</i>, <i>Proteus</i>, <i>Pseudomonas</i>)⁴¹ ▪ Other infections (legionellosis, brucellosis,³⁰ bartonellosis) 	
Mycobacterial, rickettsial, mycoplasmal, chlamydial, and spirochetal diseases^{2,42,93} <ul style="list-style-type: none"> ▪ Tuberculosis and nontuberculous mycobacterial infection ▪ Syphilis (<i>Treponema pallidum</i>) ▪ Leptospirosis (<i>Leptospira interrogans</i>)⁹⁴ ▪ Rickettsial diseases (<i>Coxiella burnetii</i>) ▪ Infection with <i>Mycoplasma pneumoniae</i> ▪ Infection with <i>Chlamydia pneumoniae</i> 	

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Table 1

Site of Infection	No. of Patients (%)	Infectious Agent	No. of Patients (%)
Upper respiratory tract	20 (23.3)	Streptococcus	24 (27.9)
Skin	15 (17.4)	Staphylococcus	21 (24.4)
Pneumonia	15 (17.4)	Pneumococcus	1 (1.2)
Endocarditis	10 (11.6)	Pseudomonas	1 (1.2)
Osteomyelitis	4 (4.7)	Enterococcus	1 (1.2)
Urinary tract infection	4 (4.7)	Propionibacterium acnes	1 (1.2)
Deep-seated abscess	2 (2.3)	Candida	1 (1.2)
Ventriculoperitoneal shunt	1 (1.2)	Unknown	36 (41.9)
Phlebitis	1 (1.2)		
No clinical evidence of infection	14 (16.3)		

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Prognosis of APIGN is generally good; especially post Streptococcal GN in children. However in adults or other infection-caused GN occasionally undergoes unfavorable outcome. Prevalence of PSGN in the developing countries is still high, but it declines in the industrial ones. Previously, Group A beta-hemolytic streptococci was typical culprit, however other infection-caused PIGN increase to date. Elderly with complications (ex. DM) may have risk for APIGN.

2. Post Streptococcal acute glomerulonephritis (PSAGN)

PSAGN is the major disease among PIGN.

Clinicals

Onset of nephritis: Full acute nephritis syndrome (heavy proteinuria, gross hematuria, hypertension, renal failure) in typical cases, but cases with asymptomatic microhematuria/proteinuria is occasional.

Latency period: 10-21days. (Not all cases reveals distinct infection episode)

Data: Low C3 (but not C4), high ASLO and Anti-hyaluronidase antibody (not all are elevated).

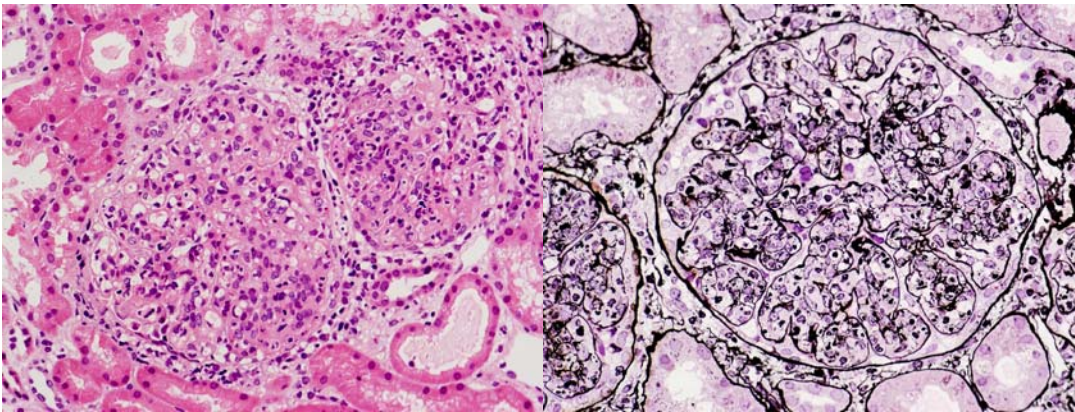
Therapy: Antibiotics may prevent further antigen production. Steroid seems to be no definite effect or it even worsens the out come. But occasionally it is sometimes administered in case with RPGN.

Prognosis: ca. 60% cases are good (CR). Young, lower S-Cr at biopsy, less crescents and absence of complications (ex. DM) are the good prognostic indicators.

Recurrence: Uncommon.

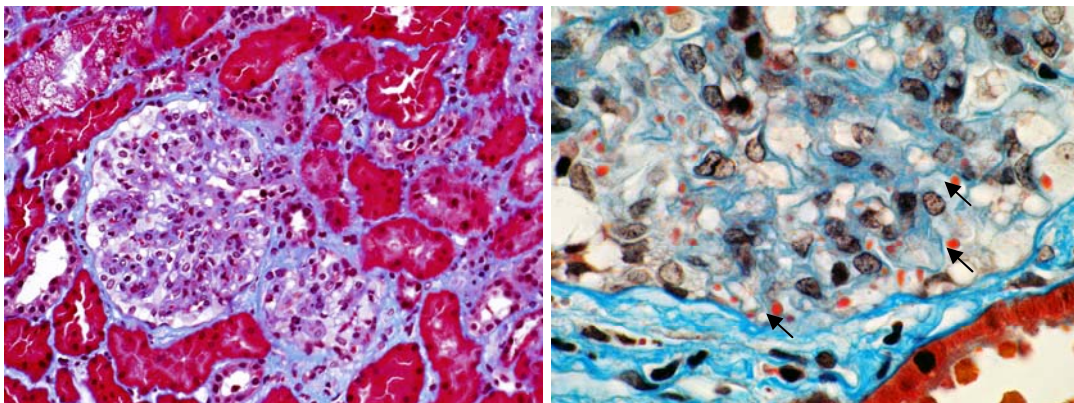
Histology

a) Light microscopy



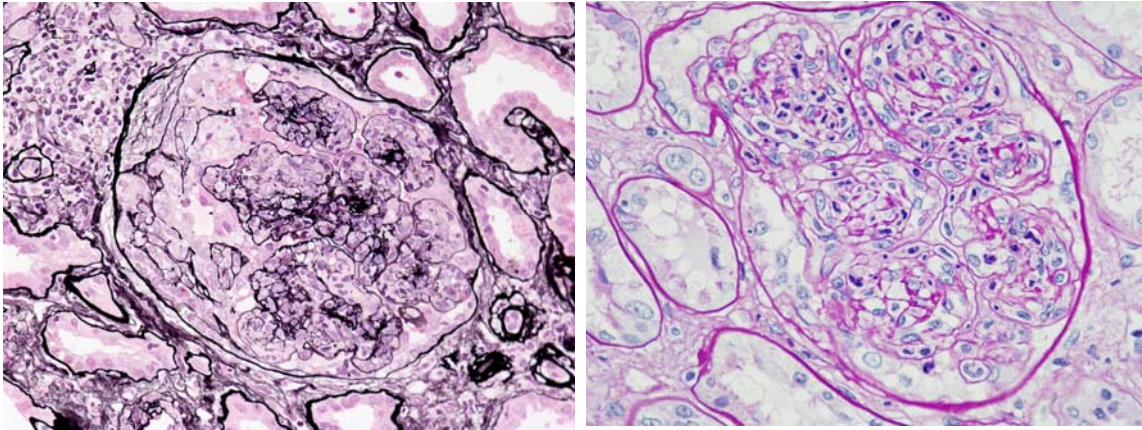
Left: Diffuse global endocapillary hypercellularity with neutrophils predominant infiltration (HE).

Right: Global endocapillary hypercellularity with mesangiolysis/microaneurysm (PAM)



Left: Mesangial and endocapillary hypercellularity (MT).

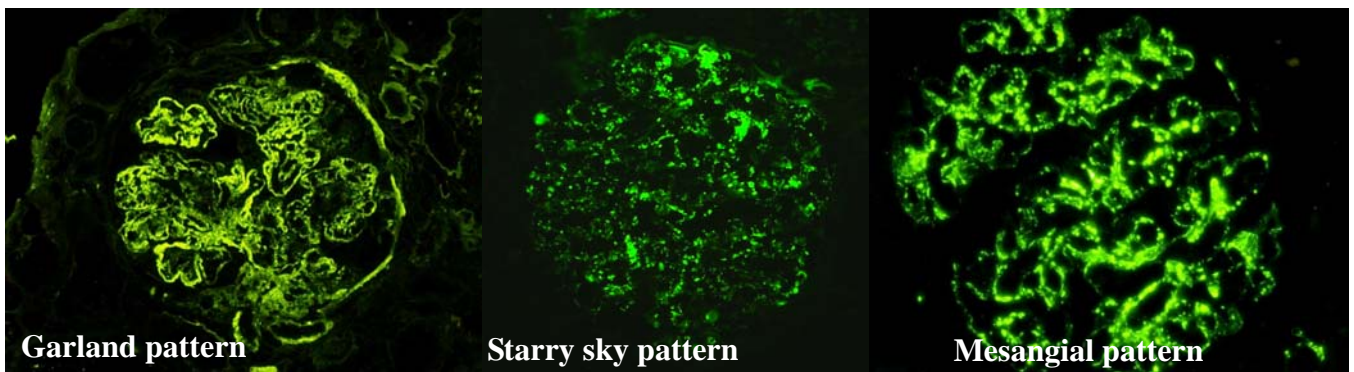
Right: Numerous humps (arrows) are visible by LM (MT)



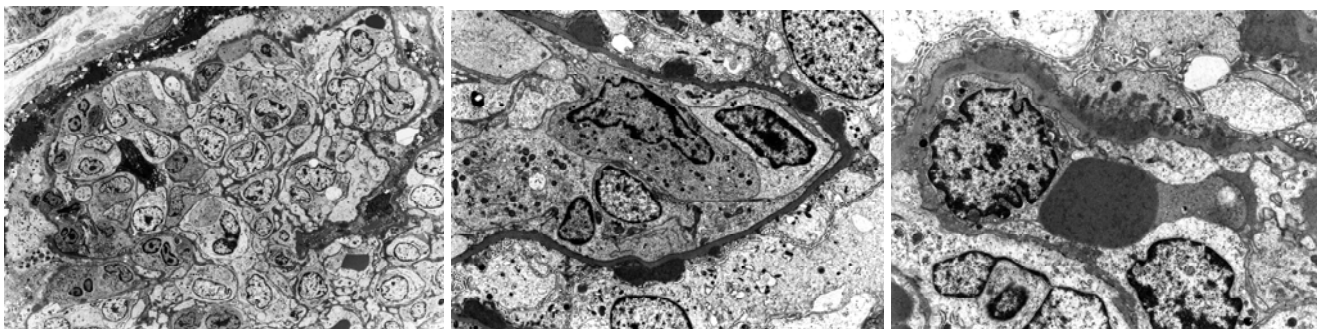
Left: Endocapillary hypercellularity with crescentic formation (PAM).

Right: Endocapillary hypercellularity on the nodular background of diabetic nephrosclerosis (MT)

b) Immunofluorescence



c) Electron microscopy



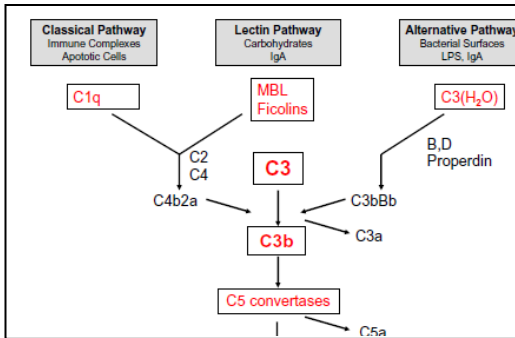
Left: Endocapillary hypercellularity with numerous inflammatory infiltrates.

Middle: Large hemispherical subepithelial deposits (Humps). Hump partly consists of IgG, C3, and antigens (SPEB).

Right: Band-like subepithelial/intramembranous deposits in case with Garland type by IF.

Differential diagnosis: Membranoproliferative glomerulonephritis type 1 sometimes features acute nephritis syndrome with high ASLO and low C3 levels. Histology reveals diffuse proliferative glomerulonephritis with neutrophils influx and often shows humps. This is indistinguishable for PSAGN in the initial several months. Spontaneous C3 elevation without steroid in three months observation may help the diagnosis as PSAGN.

3. Mechanism of Immune complex type glomerulonephritis and complement activation



Usually decrease of C3 is greater than that of C4.

PIGN is an immune complex mediated glomerulonephritis and all three complement pathways have been shown to be involved in. Immune complex deposition in the glomerulus activates serum derived complements *in situ*. Complement activation attracts inflammatory cells which actively synthesize pro-inflammatory cytokines *in situ* resulting glomerular inflammation.

4. Nephritogenic antigens

1) Nephritogenic antigens in PSAGN.

a) Nephritogenic *group A Streptococci*-produced streptococcal pyogenic exotoxin B (SEPB) and its precursor zymogen are suggestive antigens. Anti-SPEB antibody is present in majority of patients and correlate well with disease activity (KI 509, 1998).

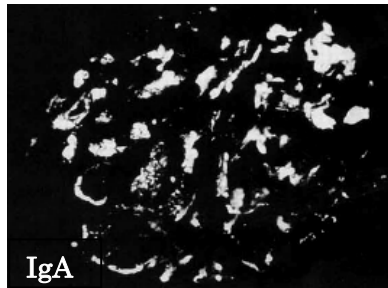
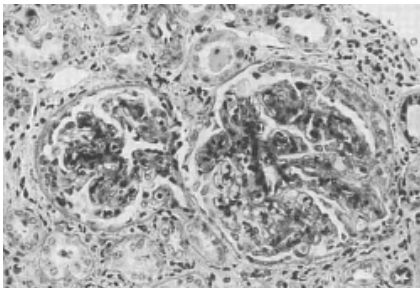
b) Nephritis-associated plasmin receptor (NAP1r) was isolated from group A streptococcus and it binds plasmin(ogen). NAP1r exhibited GAPDH activity and activates the complements cascade *in vitro*. NAP1r colocalized with C3 on the glomerular profile and its antibody was present in sera of PSAGN patients.

2) *Staphylococcus-aureus* cell envelope antigen was detected in glomeruli of 75% of MRSA-related glomerulonephritis.

5. Variants of PIGN

1) *Staphylococcus* infections including MRSA/MSSA (ex. MRSA-related glomerulonephritis)

Histology: Mesangial proliferative glomerulonephritis with predominant mesangial/periphery IgA deposition. Nephritogenic antigens are yet to be determined. Superantigens have been suggested in MRSA-related GN.



In MRSA-related GN, LM reveals diffuse mesangial proliferative GN with mesangial predominant IgA, IgG and C3 deposits. This is very similar to IgA GN.

(Koyama et al, reference 6)

2) Low-grade infection or deep abscess formation such as shunt nephritis (*Staph. epidermidis*) infective endocarditis (*Staph. aureus*, *Strept. viridans*) and visceral abscess formation

Histology: Membranoproliferative glomerulonephritis.

3) Malarial nephropathy, congenital syphilis and Loa loa infection

Histology: Membranous glomerulonephritis.

4) Parvovirus B19-associated glomerulopathy

Histology: Proliferative glomerulonephritis, collapsing glomerulopathy, FSGS, thrombotic microangiopathy.

5) Hepatitis virus

Histology: Membranoproliferative glomerulonephritis often with cryoglobulinemic nephropathy (HCV)

Membranous glomerulonephritis (HBV)

6. Conclusions

Varieties of infections induce post infectious glomerulonephritis (PIGN). Nephritogenic *Streptococcus* was the main organism but *Staphylococcus* came up to another major cause of PIGN. Clinical findings and laboratory-data help the diagnosis and glomerular pathology *per se* is sometimes indistinguishable.

Several factors may influence morphological variation in PIGN. Diffuse global endocapillary hypercellularity with predominant neutrophils influx is the typical pathology in PSAGN, however various glomerular features are also seen in PIGN in general. It might be modified by age, cause and magnitude of infection, presence of complications, administration of antibiotics or steroid, and timing of renal biopsy. As disease became inactive, endocapillary hypercellularity shift to mesangial proliferation with less leukocyte influx and finally it reverse to minor abnormalities. Crescents and severe C3 deposition (Garland pattern) are the histologic predictors of unfavorable outcome.

Staphylococcus aureus (both MSSA and MRSA) is another major cause of PIGN showing mesangial proliferative GN with mesangial IgA deposition. MRSA-related GN reveals various levels of hematuria and frequently progresses to renal dysfunction. In addition, it has been reported that IgA-dominant PIGN was associated with *Staphylococcus* infection and the disease also occasionally progress to renal failure.

Other infection-associated GN also tends to show each histologic pattern and thus the knowledge and clinical information helps nephrologists for pathologic diagnosis of PIGN.

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