Glomerulonephritis Secondary to Non-streptococcal Infections

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Contents

Abstract

Postinfectious glomerulonephritis (PIGN) is part of a larger group of infection-related glomerulonephritis (IRGN) that harbor the common PIGN and post-streptococcal glomerulonephritis (PSGN) and the less common infectious glomerulonephritis.

IRGN is considered to be a cluster of glomerular diseases resulted from immunologic insult secondary to systemic nonrenal infection. Two smaller groups of IRGN have been identified. The first is postinfectious glomerulonephritis (PIGN), which shares a clinical resemblance to PSGN and differs in the causing pathogen (see Table 1). The second is more scarce, with a somewhat different glomerular pathology and is secondary to active bacterial or (more common) viral infection (e.g., hepatitis C virus and HIV). This chapter reviews non-strep PIGN.

Keywords

End stage renal disease (ESRD) · Post-infectious Glomerulonephritis (PIGN) · Post-streptococcal Glomerulonephritis (PSGN) · Rapidly progressive Glomerulonephritis (RPGN)

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Introduction

The association between acute renal disease and infection is well known and was first described in the modern era by Sir Richard Bright in 1827, as part of the cluster of a glomerulonephritis (GN) that was called "Bright's disease" (Stratta et al. 2014). The disease, known today as post-infectious glomerulonephritis (PIGN), was first described secondary to streptococcal infection (pharyngitis or scarlet fever) and is an immune-complex-mediated disease. The condition is triggered by foreign pathogens, usually a bacterial infection, that cause secondary complement-mediated renal injury.

Until recently, most of the PIGN in the pediatric population was secondary to streptococcal throat or skin infections, and named

Table 1 Infective agents that might cause an acute post-infectious glomerulonephritis (PIGN) (Stratta et al. 2014; Jain et al. 2011; Garty et al. 2009; Asano et al. 2016; Kanodia et al. 2016; Kanjanabuch et al. 2009; Watanabe et al. 2003)

	Pathogen	Infectious syndrome
Bacteria	*Streptococcus*	
	Group A beta hemolytic type 12	Skin and throat infection
	Streptococcus pyogenes	Skin and throat infection
	Streptococcus equi	Skin and throat infection
	Streptococcus constellatus	Skin and throat infection
	Streptococcus viridance	Bacterial endocarditis
	Streptococcus pneumonia	Pneumonia
	Type M 1–4, 18, 25,31,49,52,55–57, 59–61	
	Group C	
	Group G	
	Staphylococcus epidermidis	*Shunt nephritis*
	Staphylococcus haemolyticus	
	Staphylococcus aureus	Bacterial endocarditis
	Escherichia coli	
	Pseudomonas	
	Acinetobacter	
	Serratia	
	Proteus	
	Klebsiella	
	Enterobacter	
	Salmonalla	
	Campylobacter	
	Legionella	
	Brucella	
	Neisseria meningococcus	
	Neisseria gonorrhea	
	Hemophilus	
	Serratia	
	Yersinia	
	Bartonella	
	Mycoplasma	*Pneumonia*
	Propionobacterium	*Shunt nephritis*
Parasyte	*Plasmodium vivax*	
	Plasmodium falciparum	
	Plasmodium malaria	

(*continued*)

Table 1 (continued)

	Pathogen	Infectious syndrome
	Schistosoma hematobium	
	Schistosoma mansoni	
	Toxoplasma gonadi	*Toxoplasmosis*
	Wuchereria bancrofti	*Filariasis*
	Trichinella spiralis	
	Echinococcus granolosus	*Hydatid disease*
	Entamobea histolytica	*Amoebiasis*
Spirochetes	*Borrelia*	
	Treponema	
Mycobacteria	*Tuberculosis*	
	Avium	
	Lapre	
Virus	*H1N1*	
	Parvovirus B-19	
	Adenovirus	
	Hepatits B virus	
	Varicella zoster virus	
	Epstein–Barr virus	
	Cytomegalovirus	
	HIV	
	Coxsackievirus	
	Echovirus	
	Hepatitis A virus	
	Hepatitis C virus	
	Dengue virus	
	Mumps virus	
	Measles virus	
	Hantavirus	
	Rotavirus	
Fungal infection	*Candida albicans*	
	Histoplasma capsulatum	
	Coccidioides immitis	

post-streptococcal glomerulonephritis (PSGN) (Chadban and Atkins 2005). However, during the last few years, more bacterial and viral pathogens cause IRGN, of which *Staphylococcus aureus* infection (Usui et al. 2016) is the most common PIGN in the elderly population.

Epidemiology

PIGN-like PSGN is more common during the winter season, and primarily affects children at the age of 3–12 years. Although uncommon, it can occur in infants younger than 2 years (Dagan et al. 2016).

The incidence of Streptococcal-related PIGN in the pediatric population in developing and developed countries is 24.3 and 6 per 100,000 person years, respectively, and in adults and children the incidence is 2 and 0.3, respectively (Nasr et al. 2013; Carapetis et al. 2005; Kanjanabuch et al. 2009). Acute PIGN, once a common pediatric disease, has almost completely disappeared from the developed (industrialized) countries, mainly because of antibiotic treatment and improvement in the socioeconomic status (Stratta et al. 2014). The accurate incidence of PIGN is

unknown while that of PSGN occurs with an estimated 472,000 cases per year, worldwide, of which 97% is in developing countries (Steer et al. 2007). In developed countries, PSGN is less common than *Staphylococcus aureus* PIGN, which is considered a disease of the elderly population, and associated with alcoholism and diabetes mellitus (Montseny et al. 1995).

Adult data on acute PIGN suggests male predominance, with male-to-female ratio 1.4–3:1, and the disease is more common in Caucasian and Asians populations (Nasr et al. 2013).

Pathogenesis

The glomerular damage in PIGN is the result of circulating immune complexes deposition and/or in situ formation of immune complexes containing bacterial antigens. In typical PIGN, the pathogenic endotoxin which circulates and binds to the glomeruli initiates activation of the complement alternative pathway through the mannose-binding lectin which induce an antibody response (Couser and Johnson 2014). The atypical PIGN is caused by deregulation of the complement alternative pathway (De Vriese et al. 2015).

The pathogenesis of most acute PIGN resembles that of acute PSGN, and both have an immune complex pathogenesis. While in acute PSGN nephritogenic toxins have been identified, in acute non-streptococcal PIGN, little is known on the specific immune-mediated pathogenesis of the renal injury (Rodríguez-Iturbe and Batsford 2007).

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV)-associated GN are not considered a PIGN but rather an IRGN because the genesis of HCV- and HIV-associated glomerular disease share a total dependence on the presence of active viral replication to sustain renal injury (Kupin 2017).

Clinical Characteristics

Acute nephritic syndrome, or glomerulonephritis (GN), is characterized by hematuria, proteinuria (nephrotic range or non-nephrotic range), edema, and often by hypertension and a mild degree of acute kidney injury (Kanjanabuch et al. 2009). The classic PIGN clinical presentation is a young child usually 3–7 years old, who abruptly develops eyelid edema followed by smoky and scant dark cloudy urine and increasing blood pressure a few days after a nonrenal infection. Anuria and nephrotic range proteinuria are occasionally observed, and a urine volume usually increases 4–7 days after hospital admission, indicating resolution of the glomerulonephritis.

PSGN usually presents 7–15 days after a throat infection and 3–5 weeks after a skin infection (Rodríguez-Iturbe and Batsford 2007). Most of the reports of PIGN show a latent period that resembles the latent period of the PSGN throat infection. PIGN develops 13 days after the presentation of *P. vivax* malaria (Kanodia et al. 2016), 12 days after Parvo B-19 (Marco et al. 2016) but only 2 days after the presentation of Influenza (H1N1) (Jain et al. 2011). The urinary volume increase is rapidly followed by resolution of the edema and normalization of blood pressure. Microscopic hematuria takes several months to resolve and can persist for 1 year after the acute attack (Kanjanabuch et al. 2009).

A quarter of all PIGN cases will have a subclinical GN (Yoshizawa et al. 1996). The patients usually present with acute, trivial, and self-limited infections develop subclinical glomerular disease, as indicated by low-grade proteinuria (<1 gram per day), pyuria, and microscopic hematuria (Kanjanabuch et al. 2009).

Laboratory

The classic serologic finding of PIGN is a reduction of C3 serum complement levels that occurs in 90% of the cases (Rodríguez-Iturbe and Batsford 2007). In regard to PIGN secondary to staphylococcal infection, the majority of cases will have IgA deposits in the renal biopsy and serum levels of IgA and IgG are elevated; other serological tests including complement, ANCA, cryoglobulins, and rheumatoid factor are usually in the normal range while small elevation in ANA can be seen (Zeledon et al. 2008).

Pathology

Most of the cases of PIGN are diagnosed by the clear clinical and laboratory signs obviating the need for a renal biopsy (Rodríguez-Iturbe and Mezzano 2016). In cases where renal biopsy is performed, the histology is characterized by extracapillary proliferation (Stratta et al. 2014), or in the case of a *Streptococcus aureus* infection, IgA-dominant deposition (Koyama et al. 2017). In most cases, enlarged hypercellular glomeruli with prominent endocapillary proliferation and infiltration with neutrophils and mononuclear cells, with variable degrees of immunoglobulin and complement deposits. The histologic picture consists of diffuse or focal, mesangial or mesangiocapillary proliferation with, in few instances, fibrocellular crescents.

Deposits of IgA, IgG, and C3 have been observed in both the mesangium and the peripheral capillary walls with subendothelial deposits have been reported, while sub-epithelial "humps" characteristic of PIGN are unusual (Zeledon et al. 2008; Fogo 2016). The granular deposition of complement C3 is often coupled with IgG and occasionally with IgM. IgA deposition is rare, except in patients with diabetes and secondary staphylococcal infection. "Full house" immunostaining (IgG, IgM, IgA, C3, C4, C1q) that resembles the pathologic finding of lupus nephritis is frequently reported (Kanjanabuch et al. 2009). The dominant IgA staining in staphylococcal PIGN can be distinguished from IgA nephropathy by electron microscopy (EM) appearance of the deposits (Usui et al. 2016; Fogo 2016; Nasr et al. 2007).

The histologic picture changes over the course of the disease with glomerular endocapillary proliferative GN in the active stage, mesangial proliferative GN in the healing stage, or both types during the subclinical stage, with C3-dominant deposits. In severe disease, crescents are present and rapidly progressive glomerulonephritis is expected. Under EM, small immune deposits are commonly present in the mesangial and subendothelial areas of the kidney with acute PIGN. However, the characteristic finding is large "humps" (dome-shaped deposits) under the effaced epithelium, particularly in the mesangial notch or waist region. The proliferative and exudative changes associated with non-streptococcal acute PIGN are not prominent as those observed in the classic PSGN (Kanjanabuch et al. 2009; Rodríguez-Iturbe and Mezzano 2016).

Treatment

A patient with PIGN suffers from two main problems: a postinfection (bacterial or viral) state and an acute nephritis syndrome (hypertension, acute kidney injury, edema). While managing the patient, these two problems need to be taken into consideration.

Pathogen Treatment

The first question to be considered related to the diagnosis of non-streptococcal PIGN is what is the causative pathogen and what is the best antibiotic (or anti-viral) treatment needed. While in PSGN the treatment of choice will be penicillin (or in cases of penicillin allergy – erythromycin), in the case of non-streptococcal PIGN, the cornerstone of the antibiotic treatment is to identify the correct pathogen. In cases of IgA-dominant GN secondary to staphylococcal infection, the antibiotic treatment depends on the bacterial sensitivity (MRSA vs. MSSA). In cases of other pathogens, the antibiotic or anti-viral treatment needs to be tailored to the specific pathogen (Rodríguez-Iturbe and Mezzano 2016).

Corticosteroid treatment is contraindicated while there is active infection, and can be use in selected cases of RPGN when active infection is no longer present (Rodríguez-Iturbe and Mezzano 2016).

Acute Nephritis Treatment

When treating a patient with glomerulonephritis secondary to a recent infection, the first thing to be considered is whether the patient needs to be

admitted to an inpatient facility or is able to receive sufficient treatment as an outpatient. A patient with subclinical nephritic syndrome with good urine output and without hypertension might benefit from outpatient treatment. In contrast, any patient with acute nephritic syndrome needs to be hospitalized (Rodríguez-Iturbe and Mezzano 2016), mainly for the follow up of any possible exacerbation of hypertension.

The cornerstone for managing of acute nephritis is bed rest, fluid restriction, and low salt diet (Rodríguez-Iturbe and Mezzano 2016). In cases of apparent fluid overload, that manifested as severe edema, elevated blood pressure, and circulatory congestion, the administration of loop diuretics orally or parenterally (Furosemide, 40 mg every 12 hours) is warranted. Antihypertensive medications are required in cases of severe hypertension that is not well controlled with diuretics in order to prevent hypertension-induced seizures. It is recommended to start with nifedipine (5 mg every 4–6 h) or parenteral hydralazine (Rodríguez-Iturbe and Mezzano 2016).

Prognosis and Complications

The overall prognosis of acute PIGN resembles that of acute PSGN, and in the short term, both share an excellent prognosis. Furthermore, the complications that was described during the acute phase are rare (Rodríguez-Iturbe and Mezzano 2016).There are, however, a few rare medical complications that affect the patients during the acute attack: acute kidney injury (Ayoob and Schwaderer 2016); severe hypertension with clinical sequela such as hypertensive encephalopathy, hyperkalemia, and pulmonary edema that might require acute dialysis; cerebral venous thrombosis (Morkhandikar et al. 2016); and posterior reversible leukoencephalopathy (Fux et al. 2006) that resembles hypertensive encephalopathy and manifests as mental disturbances, headaches, visual hallucinations, and convulsions. The last two are extremely rare, severe complications with grave prognoses.

Rapidly progressive glomerulonephritis (RPGN) that presents as dramatic loss of renal function over a few weeks to months is a rare but severe complication of PIGN. Approximately, half of the RPGN cases are associated with PIGN (Piyaphanee et al. 2016), and about one-third of the patients that develop RPGN will deteriorate to end-stage renal disease (ESRD) (Piyaphanee et al. 2016) over the course of time.

The long-term prognosis of acute PIGN in the pediatric population is much better than in the adult population, and deterioration to ESKD in children was reported in less than 1% of the cases (Rodríguez-Iturbe and Mezzano 2016). Non-nephrotic proteinuria was found in 7.2%, hypertension and microhematuria were found in 3% and 5.4%, respectively (Rodriguez-Iturbe and Musser 2008), and the history of PIGN has strong association with reduced glomerular filtration rate (<60 mL/min/1.73 m^2) in later life (Hoy et al. 2012).

References

Asano S, Mizuno S, Okachi S et al (2016) antineutrophil cytoplasmic antibody-associated vasculitis superimposed on infection-related glomerulonephritis secondary to pulmonary *Mycobacterium avium* complex infection. Intern Med 55(17):2439–2445. https://doi.org/10.2169/internalmedicine.55.6588.

Ayoob RM, Schwaderer AL (2016) Acute kidney injury and atypical features during pediatric poststreptococcal glomerulonephritis. Int J Nephrol 2016:2–6. https://doi.org/10.1155/2016/5163065

Carapetis JR, Steer AC, Mulholland EK, Weber M (2005) The global burden of group A streptococcal diseases. Lancet Infect Dis 5(11):685–694. https://doi.org/10.1016/S1473-3099(05)70267-X

Chadban SJ, Atkins RC (2005) Glomerulonephritis. Lancet 365:1797–1806

Couser WG, Johnson RJ (2014) The etiology of glomerulonephritis: roles of infection and autoimmunity. Kidney Int 86(5):905–914. https://doi.org/10.1038/ki.2014.49

Dagan R, Cleper R, Davidovits M, Sinai-trieman L, Krause I (2016) Post-Infectious Glomerulonephritis in Pediatric Patients over Two Decades: Severity-Associated Features. Isr Med Assoc J 18(6):336–340

De Vriese AS, Sethi S, Van Praet J, Nath KA, Fervenza FC (2015) Kidney Disease Caused by Dysregulation of the Complement Alternative Pathway: An Etiologic Approach. J Am Soc Nephrol 26(12):2917–2929. https://doi.org/10.1681/ASN.2015020184

Fogo AB (2016) Pediatric Renal Pathology. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F,

Goldstein S (eds) Pediatric Nephrology, 7th edn. Springer, Berlin, pp 705–742

Fux CA, Bianchetti MG, Jakob SM, Remonda L (2006) Reversible encephalopathy complicating post-streptococcal glomerulonephritis. Pediatr Infect Dis J 25(1):85–87. http://journals.lww.com/pidj/Fulltext/2006/01000/REVERSIBLE_ENCEPHALOPATHY_COMPLICATING.23.aspx

Garty BZ, Amir A, Scheuerman O, Hoffer V, Marcus N (2009) Post-infectious glomerulonephritis associated with adenovirus infection. Isr Med Assoc J 11(December):758–759

Hoy WE, White AV, Dowling A et al (2012) Post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease in later life. Kidney Int 81 (10):1026–1032. https://doi.org/10.1038/ki.2011.478

Jain T, Hemington L, Etuwewe B (2011) A case of post-infectious glomerulonephritis following infection with influenza A subtype H1N1. Pediatr Nephrol 26(1):151–152. https://doi.org/10.1007/s00467-010-1559-1

Kanjanabuch T, Kittikowit W, Eiam-Ong S. (2009) An update on acute postinfectious glomerulonephritis worldwide. Nat Rev Nephrol 5(5):259–269. https://doi.org/10.1038/nrneph.2009.44

Kanodia KV, Vanikar AV, Kute VB, Hargovind L (2016) *Plasmodium vivax* malaria associated with acute post infectious glomerulonephritis. Ren Fail 6049 (September):8–11. https://doi.org/10.3109/0886022X.2013.810119

Koyama A, Sharmin S, Sakurai H et al (2017) *Staphylococcus aureus* cell envelope antigen is a new candidate for the induction of IgA nephropathy. Kidney Int 66(1):121–132. https://doi.org/10.1111/j.1523-1755.2004.00714.x.

Kupin WL (2017) Viral-associated GN: hepatitis C and HIV. *Clin J Am Soc Nephrol* 12(8):1337–1342. https://doi.org/10.2215/CJN.04320416

Marco H, Guermah I, Matas L, Navarro M, Lopez D, Bonet J (2016) Postinfectious glomerulonephritis secondary to erythrovirus B19 (parvovirus B19): case report and review of the literature. Clin Nephrol 85(4):238–244. https://doi.org/10.5414/CN108694

Montseny JJ, Meyrier A, Kleinknecht D, Callard P (1995) The current spectrum of infectious glomerulonephritis experience with 76 patients and review of the literature. Medicine 74:63–73

Morkhandikar S, Priyamvada PS, Srinivas BH, Parameswaran S (2016) Cerebral venous thrombosis in a patient with acute postinfectious glomerulonephritis. Ind J Nephrol 26(3):209–211. https://doi.org/10.4103/0971-4065.161519

Nasr SH, Share DS, Vargas MT, D'Agati VDMG (2007) Acute poststaphylococcal glomerulonephritis superimposed on diabetic glomerulosclerosis. Kidney Int 71:1317–1321

Nasr SH, Radhakrishnan J, Agati VDD (2013) Bacterial infection – related glomerulonephritis in adults. Kidney Int 83(5):792–803. https://doi.org/10.1038/ki.2012.407

Piyaphanee N, Ananboontarick C, Supavekin S, Sumboonnanonda A (2017) Renal outcome and risk factors for end-stage renal disease in pediatric rapidly progressive glomerulonephritis. Pediatr Int 59(3):334–341. https://doi.org/10.1111/ped.13140

Rodríguez-Iturbe B, Batsford S (2007) Pathogenesis of poststreptococcal glomerulonephritis a century after Clemens von Pirquet. Kidney Int 71(11):1094–1104. https://doi.org/10.1038/sj.ki.5002169

Rodríguez-Iturbe B, Mezzano S (2016) Acute post-infectious glomerulonephritis. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein S (eds) Pediatric Nephrology, 7th edn. Springer, Berlin, pp 959–975

Rodriguez-Iturbe B, Musser JM (2008) The current state of poststreptococcal glomerulonephritis. J Am Soc Nephrol 19(10):1855–1864. https://doi.org/10.1681/ASN.2008010092

Steer AC, Danchin MH, Carapetis JR (2007) Group A streptococcal infections in children. J Paediatr Child Health 43(4):203–213. https://doi.org/10.1111/j.1440-1754.2007.01051.x

Stratta P, Musetti C, Barreca A, Mazzucco G (2014) New trends of an old disease: the acute post infectious glomerulonephritis at the beginning of the new millenium. J Nephrol 27(3):229–239. https://doi.org/10.1007/s40620-013-0018-z

Usui J, Tawara-iida T, Takada K, Ebihara I, Ueda A (2016) Temporal Changes in Post-Infectious Glomerulonephritis in Japan (1976-2009). PLoS One 11(6):e0157356. https://doi.org/10.1371/journal.pone.0157356

Watanabe T, Yoshikawa H, Abe Y, Yamazaki S, Uehara Y, Abe T (2003) Renal involvement in children with influenza A virus infection. Pediatr Nephrol 18(6):541–544. https://doi.org/10.1007/s00467-003-1143-z.

Yoshizawa N, Suzuki Y, Oshima S et al (1996) Asymptomatic acute poststreptococcal glomerulonephritis following upper respiratory tract infections caused by Group A streptococci. Clin Nephrol 46(5):296–301. http://europepmc.org/abstract/MED/8953117

Zeledon JI, McKelvey RL, Servilla KS et al (2008) Glomerulonephritis causing acute renal failure during the course of bacterial infections. Histological varieties, potential pathogenetic pathways and treatment. Int Urol Nephrol 40(2):461–470. https://doi.org/10.1007/s11255-007-9323-6