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REVIEW

New trends of an old disease: the acute post infectious glomerulonephritis at the beginning of the new millenium

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Abstract The association between acute renal disease and infection has been known since the mid '800s: acute post-infectious glomerulonephritis (PIGN) is a reactive immunological process against the kidney secondary to an infection, classically caused by a *Streptococcus*. The typical clinical presentation of PIGN is an acute nephritic syndrome with macro- or microscopic hematuria, proteinuria, hypertension, edema and renal function impairment of variable degree. The histology is characterized by an intracapillary glomerular proliferation, but may rarely be associated with an extracapillary proliferation. The classical childhood form is still present nowadays, even with severe cases, in developing countries, while in the last decades it almost disappeared in industrialized countries, where post-infectious GN are often found in elderly patients with multiple comorbidities. These clinical variants are usually related to other infective agents, like *Staphylococcus aureus*, both methicillin resistant (MRSA) and susceptible, and may be characterized by an IgA-dominant deposition. Kidney biopsy is rarely needed, especially in the child, while in the adult or old patient a biopsy is warranted if there is an atypical presentation or evolution, like rapidly progressive renal failure, absent or delayed function recovery, persisting low C3, nephrotic range proteinuria and persisting high proteinuria. Current therapy strategies rely on culture-guided systemic antibiotics, especially in the old patient, in which MRSA are relatively frequent, support therapy and only in very selected cases on steroids. These latter cases include the rare PIGN with crescents and those with a severe interstitial inflammation.

Keywords Acute glomerulonephritis · Post-infectious glomerulonephritis · Post-staphylococcal glomerulonephritis · Post-strepotococcal glomerulonephritis

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Introduction

The association between renal disease and infection has been known since the time of Bright, in the mid-1800s. Last century, group A beta-hemolytic *Streptococcus* was identified as the main pathogenetic trigger of acute post-infectious glomerulonephritis (PIGN), which has been classified as an immune-complex mediated disease triggered by bacterial antigens and secondary complement-mediated injury. The typical clinical presentation is an acute nephritic syndrome with hematuria, proteinuria, hypertension and edema with a variable degree of renal function impairment. The histology is characterized by a classical intracapillary glomerular proliferation with polymorphonuclear cell infiltration, and is rarely associated with an extracapillary proliferation.

Even though PIGN is a typical childhood disease, it has been found also in the adult, often related to other infective agents. The classical pediatric form is still present but severe cases are now found almost exclusively in developing countries while, in the last decades, it has almost disappeared in industrialized countries. In developed countries PIGN is now often found in elderly patients with complex comorbidities, and is related to methicillin-

resistant *Staphylococcus aureus* (MRSA) and characterized by an immunoglobulin A (IgA)-dominant deposition [1, 2]. Even if acute glomerulonephritis (GN) episodes have been related to sub-acute endocarditis and infected ventricular-atrial shunts, these entities are nowadays relatively rare and may have a different underlying pathogenesis—so they will not be discussed in this review.

Epidemiology outline

Acute PIGN was once a typical childhood disease developing after a pharyngitis or impetigo by beta-hemolytic *Streptococcus*, so that it is often referred to as acute post-streptococcal GN. This disease has almost completely disappeared from developed countries because of the improvement of the socio-economic status and the spread of antibiotic therapies for upper airways infections. However it is still common in developing countries, with an estimated incidence of more than 200 cases per million population (pmp)/year [1, 3] (Table 1). Moreover, in these countries there are frequent epidemics with clusters of PIGN and probably some "epidemic foci" are not registered by public health authorities, so the incidence of PIGN could be even higher [1, 4].

On the other hand an epidemiologically relevant phenomenon that is a completely new event in western countries is the emergence of PIGN in elderly patients. It may be due to a longer life expectancy and the potential increased severity of infections in elderly patients with predisposing factors (e.g. diabetes, severe vasculopathy and malignancy) or in debilitated adults such as alcohol- or intravenous (iv) drug-abusers [4]. The first evidence of such a change came to light at the end of last century: an epidemiological evaluation performed in Piedmont (Italy) showed an incidence of PIGN in elderly patients that was more than double that of the pediatric population (Table 1) [5]. However, a new "variant" of PIGN has also been described, particularly in the elderly, which includes abundant immunoglobulin IgA deposits and a more aggressive evolution towards end-stage renal disease (up to 60 %). This newly defined entity is called IgA-dominant post-staphylococcal GN and may account for up to 20 % of PIGN in patients aged 65 years or older [1, 6].

Acute PIGN is increasing in the elderly population, both in western countries and in the developing world: while in the past a PIGN was reported only in 3–6 % of all renal biopsies of patients 65 years or older, more recent data suggest a prevalence of up to 34 % in the same age-group [1, 5] (Table 1). In developed countries, PIGN is moving toward elderly patients with an augmented infective risk (e.g. patients with diabetes, malignancy) and infection sites and agents differ from those of the classical childhood disease.

Table 1 Epidemiology of acute post-infectious glomerulonephritis (PIGN) in industrialized and developing countries, according to patient age

	Overall incidence (cases/pmp/year)		Prevalence in kidney biopsy registries (%)
	Industrialized countries	Developing countries	
Children and young adults	3 (Italy)	240–280	<3 % (Italy, end of '90s)
Elderly (>65 years)	9 (Italy)	20–90	70 % (India, end of '90s)

pmp per million population

Table 2 Prevalence of infective agents that may cause an acute post-infectious glomerulonephritis (PIGN)

	Species	Children and young adults	Elderly (>65 years)
Bacteria	*Streptococcus*	>95 %	16–30 %
	Group A Beta-hemolytic type 12		
	Type M 1–4, 18, 25, 31, 49, 52, 55–57, 59-61		
	Group C		
	Group G		
	Staphylococcus epidermidis, *S. haemolyticus*, *S. aureus*	Uncommon	24–60 %
	Escherichia coli	Very rare	5–10 %
	Pseudomonas		3 %
	Acinetobacter		
	Serratia, *Proteus*		2 %
	Klebsiella, *Enterobacter*		2 %
	Haemophilus influenzae	Very rare	1–2 %
	Enterococcus		0–2 %
	Salmonella, *Campylobacter*	Very rare	Rare (<1 %)
	Legionella, *Brucella*		Rare (<1 %)
	Borrelia, *Treponema*		Rare (<1 %)
	Mycobacteria (tuberculosis, avium, laprae)—might be associated with chronic GNs		Rare (<1 %)
	Neisseria (mainly associated with membranoproliferative GN and subacute endocarditis)		Rare (<1 %)

GN glomerulonephritis

Update on PIGN etiology

Even if the association between infection and PIGN ("edematous swelling with scanty, dark and at times totally

Table 3 Main mechanisms involved in the pathogenesis of acute post-infectious glomerulonephritis (PIGN)

Hypothesis	Mechanism of kidney damage/injury	
	Post-streptococcal acute glomerulonephritis	Post staphylococcal acute GN with IgA-dominant deposits
Circulating immune-complexes	Glomerular deposition of immune-complexes (Ig and bacterial antigens) and activation of the alternative pathway of the complement	Exotoxin superantigens stimulate an abnormal IgA production, forming IgA immune-complexes
"In situ" formation of immune-complexes	"In situ" formation of immune-complexes, due to the deposition of streptococcal antigens	Might be a result of the exaggerated IgA production
Infiltrating cells	Granulocytes, monocytes and lymphocytes, attracted by the complement activation (through either the classical or alternative pathway)	Exotoxin superantigen TSST-1 stimulates an abnormal cytokine production, recruiting inflammatory cells
Autoimmune reactions	Molecular mimicry with glomerular proteins (laminin, vimentin, collagen)	Cryoglobulinemia and rheumatoid factor formation due to the overall altered immune response to bacterial antigens and superantigens
	Anti IgG autoantibody production due to the structural modification of IgG after the binding to bacterial surface and proteases/aminidases	
Bacterial nephritogenic antigens	NAPlr and SPEB, with capacity of binding activated plasmin inside the glomerular tuft and penetrating through the basal membrane	Possible role of staphylokinase, which is able to activate plasmin and might play a role in local glomerular inflammation
Host predisposition	Class II HLA gene alleles (DRB1 and DPA1-DPB1)	Local morphological features with reduced IgA clearance and favouring IgA deposition, like aberrant glycosylation and an underlying diabetic nephropathy
	Probably other—yet undefined—host immune system characteristics which may account for a familial clustering of PIGN, including abnormalities in the complement system	

GN glomerulonephritis, *Ig* immunoglobulin, *NAPIr* nephritis-associated plasmin receptor, *SPEB* streptococcal pyrogen exotoxin B, *HLA* human leukocyte antigen, *TSST* toxic shock syndrome toxin

suppressed urine") has been known since the mid-1800s (Burserius), its etiological steps were not clarified until the 1900s, when a greater knowledge of the immune system led to different pathogenetic hypotheses for PIGN.

In the past, the etiology of PIGN was almost exclusively related to a streptococcal infection, whereas nowadays there is a much wider spectrum of possible causing agents, including staphylococci, Gram-negative bacteria, intracellular bacteria (*Chlamydia*, *Mycoplasma*), viruses (HSV, CMV, EBV, HBV, influenza, RSV), fungi (*Candida*, *Histoplasma*) and parasites (*Toxoplasma*, *Plasmodium malariae*) [7, 8] (Table 2). Among the Streptococci, group A beta-hemolytic *Streptococcus* type XII has been typically considered a causing agent of PIGN, but more strains have recently been identified, e.g. M type 1, 2, 4, 12, 25, 49, 57, 59, 60, and 61 [9] and *Streptococcus zooepidemicus* (which is mainly related to the intake of unpasteurized milk/cheese), giving evidence of a potential nephritogenic effect shared by different streptococci groups [10, 11]. Among the Staphylococci, an association with PIGN has been reported for *Staphylococcus epidermidis*, hemolytic and *aureus*, both methicillin-sensitive and -resistant (methicillin-resistant *Staphylococcus aureus*, MRSA) [8]. However it is now clear that post-streptococcal and post-staphylococcal PIGN may follow different pathways and warrant a separate discussion (Table 3).

Pathogenetic hypotheses of post-streptococcal PIGN

1. *Circulating immune-complexes* The immune-complex is formed in the bloodstream by a nephritogenic Streptococcal antigen and its antibody; during the 1970s and '80s it was considered the main etiologic agent of PIGN because it was trapped in glomerular capillaries, as observed by Dixon and Germuth in serum sickness.
2. *In situ formation of immune-complexes* In situ formation of immune-complexes with a secondary activation of complement was thought in the late '70s to be an alternative trigger of glomerular damage. Whether deposited or formed in situ, the presence of immune-complexes activates the classical pathway of the complement system, recruiting inflammatory cells and triggering a leukocyte-mediated injury.
3. *Infiltrating cells* The role of infiltrating cells (granulocytes, monocytes and macrophages) has been considered a possible element of direct glomerular damage due to chemotactic and pro-inflammatory cytokines (possibly triggered by complement activation) and has been related to the degree of proteinuria [12, 13].
   (a) *Autoimmunity* Molecular mimicry: soluble streptococcal antigens (e.g. SpeB and FimH) may

cross-react with glomerular proteins (laminin, collagen and vimentin) causing a secondary antibody-mediated damage and loss of the anion charge of the glomerular basal membrane, leading to proteinuria [14].

(b) Production of anti-IgG autoantibodies may be due to structural changes of the host IgG when they contact the bacterial surface and antigens: these changes are caused by the interaction of heavy chains with the bacterial wall enzymes, which are able to change the Ig glycosylation (e.g. neuroaminidases) and might "reveal" or "create" hidden antigens and epitopes. Moreover some bacterial surface proteases have an IgA protease activity (IgAase) that may uncover some antigenic Ig fragments. Their consequences may be the start of an autoimmune reaction mediated by anti-IgG, IgGs and IgMs. This "overwhelming" immune response could thus lead to the appearance of autoantibodies and immune-complexes with rheumatoid factor activity and even to cryoglobulinemia [8]. The presence has also been described of more specific autoantibodies such as anti-neutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA) and anti-complement antibodies, closely related to the presence of the infection, but their pathogenetic role in acute GN is not clear.

4. *Nephritogenic streptococcus antigens* Two major proteins have been found to have "nephritogenic" activity: the bacterial glyceraldehyde-3-phosphate dehydrogenase nephritis-associated plasmin receptor (NAPlr) and the cationic cystein proteinase streptococcal pyrogen exotoxin B (SPEB). Both NAPlr and SPEB have been shown in biopsy from post-streptococcal PIGN and high antibody titres are found in more than 90 % of recovering patients [15]. Both these proteins are able to activate the alternative pathway of the complement cascade, starting chemotaxis and interleukin (IL)-6 production by mesangial cells, leading to inflammation and expression of adhesion molecules on the endothelium [16]. Moreover, different "nephritogenic" antigens (NAPlr, SPEB or others) have been found in different populations (Japan, Europe, North America), confirming that different antigens may act in different populations with different genetic backgrounds.
5. *Host predisposition* The immune system characteristics favouring the development of a PIGN are still not well defined, but they may possibly explain a greater susceptibility to PIGN in some families, by which 20–40 % of relatives of patients will later develop a PIGN. This hypothesis has been evaluated with correlation studies of human leukocyte antigen (HLA) genes, leading to stimulating, but not clinically interesting, results [1, 2, 4]. Class II HLA genes—which are crucial in the antigen presentation process—have been associated with a higher incidence of PIGN, e.g. Egyptian children with the allele HLA-DRB1*03011 or HLA-DRB1*1105 had a relative risk of developing a PIGN of 3.71 and 3.57 respectively [17]. Also in a Japanese study, although no correlation was found with any HLA-DRB1 allele, a significant increase of PIGN incidence was found in children with an HLA-DP5 (HLA-DPA1*02022 and HLA-DPB1*0501) [18].

Pathogenetic hypotheses of IgA-dominant post-staphylococcal GN

The pathogenesis of post-staphylococcal PIGN with IgA-dominant deposits is not completely clear and may differ from "classical" PIGN (Table 3). Some factors related to the bacterial characteristics seem to be crucial, especially in MRSA: nephritis may be induced by a superantigen (exotoxin toxic shock syndrome toxin,TSST-1) which stimulates high cytokine activity, IgA production and IgA immune-complex formation and deposition [19]. However, also host-related factors have been investigated to explain the predominant IgA deposition: diabetic patients are frequently affected by sub-clinical mucosal infections and have also a reduced IgA clearance due to the hyper-sialylation of IgA, which may be responsible for their deposition in the glomerulus [20, 21].

Critical pathological elements for the diagnosis

Classical acute post-infectious glomerulonephritis

Light microscopy

The most common histological picture in post-streptococcal PIGN is a proliferative glomerulonephritis with diffuse hypercellularity. In the early phases the cellular infiltration is "exudative" and characterized by the endocapillary presence in every glomerulus of neutrophils, endothelial cells, monocytes and rare lymphocytes (CD68, CD3, CD20), with an expansion of the tuft and a reduction of capillary lumens and urinary space (Fig. 1a). In severe cases an extracapillary proliferation may be present, but usually it has a focal distribution and does not affect more than 50 % of glomeruli. Using Masson's trichrome staining the typical subepithelial fucsinophil (red) humps are

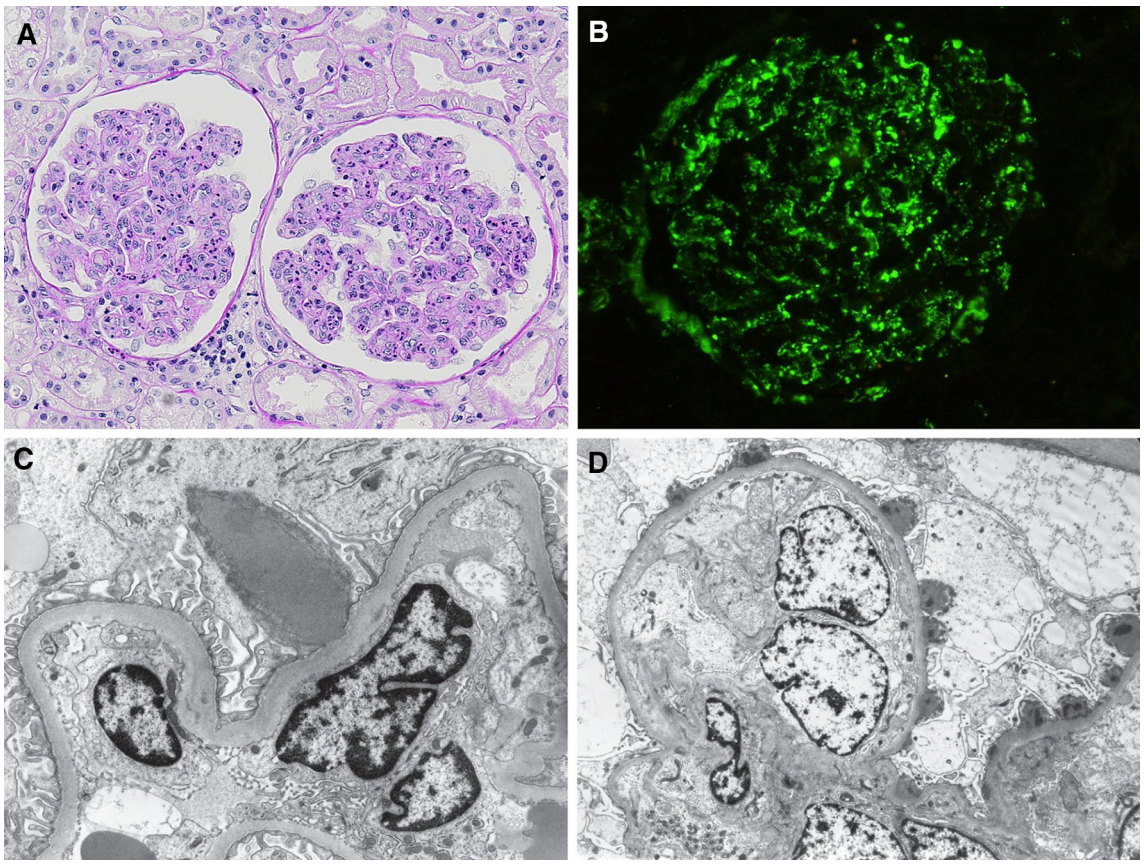

Fig. 1 Early phase of acute post-infectious glomerulonephritis (PIGN). **a** Diffuse proliferative endocapillary lesions (Periodic acid-Schiff solution, PAS ×200). **b** A "starry sky" immunohistochemical pattern with anti-C3 antiserum (×400). **c** A typical ultrastructural pattern with a huge hump (original magnification ×5000). **d** A capillary lumen with endothelial proliferation and several humps, corresponding to the garland immunohistochemical pattern (original magnification ×2000)

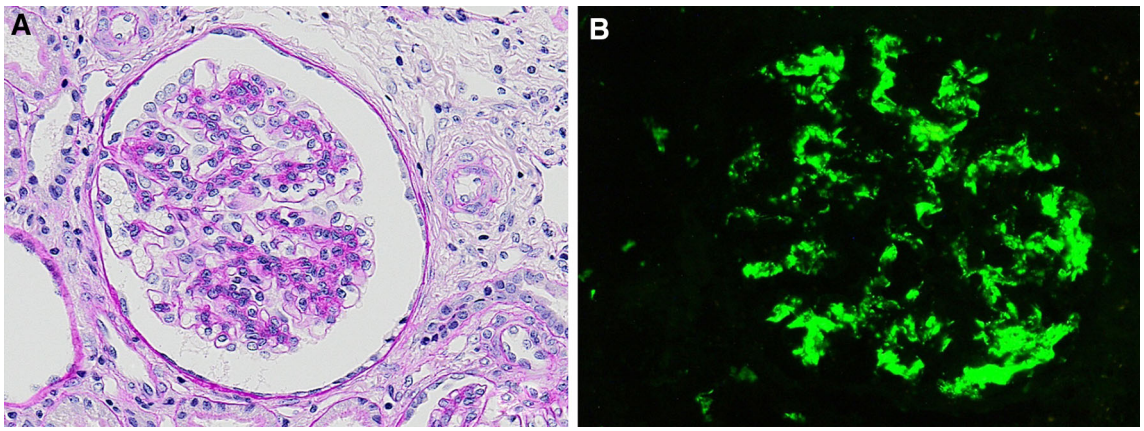

Fig. 2 Late phase of acute post-infectious glomerulonephritis (PIGN). **a** Segmental mesangial proliferative lesions (PAS ×300). **b** A "mesangial" immunohistochemical pattern with C3 deposits prevailing located in the mesangium (×400)

observed, which are sometimes better shown by PTAH or AFOG stains in which they assume respectively a violet-blue and an intense red staining.

In a later phase of the disease (starting about 2 weeks after onset), the glomerular hypercellularity is progressively reduced and the histology is characterized by a mesangial hypercellularity with a mesangial expansion of variable degree (Fig. 2a) and a complete recovery of glomerular damage in the following weeks. If the active glomerular infiltration persist for more than 6 months after the

onset of the disease another infection-related GN should be considered.

Immunofluorescence

Immunohistochemical findings follow the same time pattern observed in light microscopy, varying as changes of the proliferative patterns. C3 deposition is always present and IgG deposits are the most commonly observed antibodies in early biopsies, while IgM, IgA and other complement fractions (i.e. C1q) are rarely seen. Three different immunohistochemical patterns have been identified [22]. The "starry sky" pattern is characterized by subepithelial granular deposits with a scattered distribution in the tuft: it is typical of the early phases of the disease and is usually associated with a diffuse endocapillary proliferation (Fig. 1b). The "garland" pattern is also found in about 25 % of biopsies made in the early phases of the disease: it is characterized by large granular deposits in the basal membrane, which are often merging and may be more frequently associated to subendothelial and mesangial deposits. This immunofluorescence pattern is usually related to more severe clinical manifestations and prognosis. In the later phases of the disease, corresponding to mesangial proliferation, the deposits are almost exclusively composed of C3 and are located in the mesangium, defining a "mesangial pattern" (Fig. 2b).

Electron microscopy

In the early phases of the disease, capillary lumens are closed by the cellular infiltrate and humps may be commonly seen in the capillary walls. These are large, electron-dense deposits with a diameter of 1–3 μ with either homogenous or variegated aspect and are located on the epithelial side of the basal membrane over the lamina densa. There may be just a few deposits scattered in the tuft or numerous deposits close to each other, corresponding respectively to the starry sky and garland immunofluorescence patterns (Fig. 1c, d). In later phases of the disease, when subepithelial deposits are reduced, new deposits appear in the mesangium, corresponding to the mesangial immunohistochemical pattern.

Differential diagnoses

The pathological findings of post-streptococcus PIGN should be differentiated from those of other immune-complex mediated GN: membrano-proliferative GN type I and II (dense deposit disease), cryoglobulin-associated nephritis, lupus nephritis and IgA nephropathy. Immunohistochemical and ultrastructural studies are very helpful in distinguishing PIGN from other nephrites, as well as the presence of clinical and laboratory signs of a systemic disease. In particular, dense deposit disease may present "hump-like" subepithelial deposits, but there is no electron-dense deposit in the basal membrane. Similarly C3 glomerulonephritis [23] shares with PIGN the mesangial proliferation and the presence of C3-only epimembranous and mesangial deposits. In this case the differential diagnosis is based on the absence of clinical and laboratory signs of recent infection, and genetic analyses of the alternative pathway of the complement (factor H, factor I and membrane cofactor protein, MCP).

Acute post-infectious glomerulonephritis with IgA-dominant deposits

This form of PIGN is mainly secondary to a *Staphylococcus* infection [20] and shares most histological features

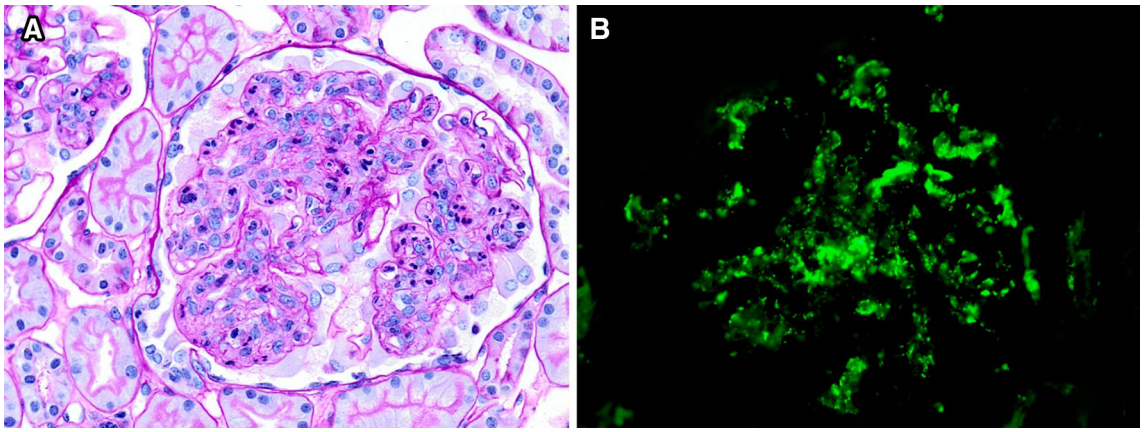

Fig. 3 Acute post-infectious glomerulonephritis (PIGN) with IgA dominant deposits. **a** Marked endocapillary hypercellularity with numerous neutrophils (PAS ×200). **b** A granular glomerular staining in the subepithelial site of the glomerular capillary wall and in the mesangium (×400)

Table 4 Clinical and prognostic variability of acute post-infectious glomerulonephritis (PIGN) in different sub-populations

	Children		Adults	Elderly
	Industrialized countries	Developing countries		
Most affected sex	Male	Male	Male	Male
Reduced immune response	Rare	Rare	32 %	61 % (diabetes, malignancy, alcohol)
Infection sites	Pharynx	Skin[a]	Pharynx: 32 %	Skin: 28 %
			Lung: 16 %	Lung: 16 %
			Skin: 11 %	UTIs: 13 %
			UTIs: 4 %	Pharynx: 10 %
Latency duration	1–6 weeks		Variable	Variable
				Absent in 50 %
Dialysis need at presentation	Rare	4.6–51.6 %	25 %	33 %
Complete renal function recovery	>95 %	<30 %	44 %	22 %
IgA deposits	Rare	Rare	5 %	17 % (mostly diabetic)
Death within 2 months from the diagnosis	Exceptional	Very variable, but possible	5–15 %	20–25 %
Long term progression to chronic kidney disease	Rare	Unknown	10 % (mostly if there are persistent urinary abnormalities)	60 % (mostly if associated with other comorbidities)

[a] Skin infection may include impetigo (most common), but also erysipelas and secondary bacterial infections of viral or parasitic lesions (e.g. scabies in Africa)

UTI urinary tract infection

with post-streptococcus PIGN (Fig. 3a). However the immunofluorescence study shows IgA deposits associated with the deposition of C3. In most cases C3 deposits are more pronounced than IgA deposits: this aspect is of crucial importance in the differential diagnosis with IgA glomerulonephritis (Fig. 3b). Moreover the presence in IgA-PIGN of both kappa and lambda light chains may be helpful since in primary and secondary forms of IgA glomerulonephritis there is a predominant IgA deposition with clonal restriction to lambda chains [6]. Since this PIGN is often observed—but not exclusively—in diabetic patients, signs of diabetic nephropathy (diabetic glomerulosclerosis) may often be present [24].

Clinical features and laboratory parameters

The classical clinical presentation of PIGN is an acute nephritic syndrome, defined as the presence of macro- or microscopic hematuria, proteinuria, edema, arterial hypertension and acute kidney injury of variable degree (up to acute renal failure). A low circulating C3 level is almost always found due to the activation of the alternative complement pathway, and is restored within 6–8 weeks: if the C3 level is still low after this period other diseases should be considered (C3 nephritis, membrano-proliferative GN, subacute endocarditis). Moreover most patients with PIGN have a transient hypergammaglobulinemia, a type III polyclonal cryoglobulinemia and often high levels of circulating immune-complexes, but may present also with circulating ANCA and ANA.

Classical acute post infectious glomerulonephritis of the child

The classical PIGN begins one to 6 weeks after an infection of the upper airways or of the skin (Table 4). During the latency phase, isolated urinary abnormalities may be found: after this period the nephritis may present as a subclinical disease or with a clear nephritic syndrome, the first having a fivefold higher frequency during epidemics [1].

In the nephritic forms the urinary findings are usually very active, with dysmorphic erythrocytes, leukocyturia, and granulous and epithelial cylindruria. Macroscopic hematuria may be reported as "coffee-colored", "dark urine like Coca-Cola or syrup" and may be associated to flank pain from renal capsule distension. The activity of the urinary findings is strictly related to the flourishing phase and becomes less intense with its progressive recovery. Proteinuria is almost always present, but a nephrotic syndrome is quite uncommon (5–10 %), but may reach 25 % of patients during epidemics [25].

Arterial hypertension and edema are very common and due to water and salt retention as a consequence of an

impaired glomerulo-tubular feedback. Edema is the most common symptom prompting the patient to seek medical advice. It may be localized, but also diffuse, particularly on the face and lower extremities, with a hard consistency and erythematous aspect due to the diffuse—not only renal—capillaritis. Even if volume-dependent hypertension is very common, nowadays hypertensive encephalopathy, seizures, acutely decompensated heart failure and pulmonary edema are rare.

Usually the recovery starts a few days after the onset of the nephritis, starting with the ending of the salt-water and is complete within few weeks. Isolated microhematuria might however continue for some months: in the 2000s children with a follow up of 15–18 years showed persisting urine abnormalities in about 20 % of cases; however renal failure is a very rare event (less than 1 %). On the other hand, children in developing countries have usually more severe disease and therefore a more severe prognosis: at the presentation about 30 % of them have renal failure requiring dialysis and less than 30 % have a full recovery [10, 25, 26].

In post-streptococcal PIGN most patients have circulating antibodies against streptococcal antigens, like anti-streptolysin O (ASO), anti-streptokinase, anti-hyaluronidase and anti-desoxyribonuclease B (anti-DNAse B). Particularly used is the ASO: a rapidly rising titre is specific for recent infection and may confirm the diagnosis of PIGN [1, 2, 5, 27].

Acute post infectious glomerulonephritis in adults

The clinical presentation of PIGN in the adult is the same as in the child, but the infection site can be upper airways, skin, but also lower airways, lung or urinary tract and the infection may have very few symptoms (subclinical infection). Often (in 30 % of cases) a PIGN is diagnosed in immunocompromised patients, including AIDS patients and iv drug abusers. However often the disease is more aggressive than in the pediatric population: 25 % of adult patients may need dialysis and a complete recovery is seen in only 40–50 % of patients. In the remaining patients there is a persistent active urinary sediment, arterial hypertension and chronic kidney disease in up to 10 % of patients [1, 2, 5, 26, 27].

Acute post infectious glomerulonephritis in the elderly (>65 years)

In elderly patients PIGN may have different characteristics (Table 4). This disease is more common in immunocompromised patients and those with multiple comorbidities, in particular diabetes, malignancy (especially carcinomas), diffuse vascular disease and alcohol abuse [28]. Age itself nowadays may be considered a risk factor for PIGN: 40 years ago only 4–6 % of adults with PIGN were 65 years or older [29], whereas in recent reports they represent about 34 % [4]. The primary infections are often localized in the skin, including surgical wound infections and iv line infections, but also in the lung, upper airways, oral cavity and urinary tract [2]. The latency between infection and nephritis is in most cases absent, so that an infection is diagnosed at the same time as the nephritis in almost 50 % of cases [27]. An infective disease in these patients may be misrecognized for a long time, since the classic signs and symptoms of an infection may be aspecific or missing: fever may be absent in 20–30 % of these patients [2].

An MRSA-related PIGN in an elderly patient was first reported in 1995 by Koyama [19]. This type of PIGN is followed by a rapidly progressive renal failure starting about 10 days thereafter and has frequently (20 %) a nephrotic range proteinuria [5, 30]. Since the 2000s it has progressively diminished, probably because of a better management of MRSA with new antibiotics and because of the change of staphylococci themselves, like a change in the production of TSST-1 observed in Japan [21].

However, independently of the type of PIGN, this disease in elderly patients is far more complex and severe than in children or adults (Table 4): most patients have renal failure "ab initio", with need of renal replacement therapy in more than 30 % of cases [8]. The overall clinical picture is often complicated by the underlying comorbidities, like hypertension, coronary artery disease and diabetes, and an acutely decompensated heart failure due to water and salt retention may be relatively common. A complete recovery is uncommon and a residual chronic kidney disease is observed in about 60 % of patients [2]; death may be a relatively common complication of PIGN in these patients (20–25 %) [2, 30]. Among the main prognostic factors are the presence of diabetic glomerulosclerosis, tubular atrophy, interstitial fibrosis and number of crescents, as well as patient age, creatininemia at presentation, need of renal replacement therapy and the degree of the residual proteinuria after the resolution of the acute disease: all of these elements are predictive of end-stage renal disease in the long term [6, 19–21, 24].

In the *Staphylococcus*-related, IgA-dominant PIGN, laboratory testing is aimed at the isolation of bacterial antigens from the infection site and characterization of the involved bacterium [6, 19].

Differential diagnosis

A differential diagnosis of PIGN is not usually needed in children with classical disease, but it may become necessary in adults presenting with an acute nephritic syndrome

with a persistent (more than 6 weeks) low circulating C3. It is a wide differential diagnosis and may include lupus nephritis, cryoglobulinemic glomerulonephritis, C3 glomerulopathy, IgA nephropathy and ANCA-associated glomerulonephritis [31].

These diagnoses should be considered especially in adult patients in whom an infective agent is not recognized or when presenting without any history of fever or any sign of recent infection. However, since an acute symptomatic infection might not be found in up to one-third of adult patients with PIGN, patients with an acute nephritic syndrome may require a renal biopsy to identify its cause and to rule out other acute immune-mediated nephrites [28, 31]. The presence of exudative glomerulonephritis on light microscopy, a positive glomerular immunofluorescence for C3 with weaker or no staining for IgG or C1q, and the ultrastructural demonstration of subepithelial humps strongly suggest a PIGN over other immune-mediated nephrites.

The differential diagnosis with C3 glomerulonephritis could be a real challenge since it may have the same histology as PIGN, with a sole positivity for C3 and the absence of a membranoproliferative pattern. The lack of an identifiable infection, the persistence of low circulating C3 and of active urinary sediment for more than 2 months are consistent with a diagnosis of C3 nephropathy over PIGN: in these patients a work up for abnormalities in the complement system (particularly the alternative pathway) would be recommended, since most—if not all—"atypical" PIGN with persisting low C3 may be related to mutations in complement-regulating proteins and antibodies to the C3 convertase (C3 nephritic factor) [31].

Since usually the diagnosis of an IgA-dominant PIGN is achieved by histological examination of a kidney biopsy, its main differential diagnoses include IgA-mediated nephrites such as IgA nephropathy and Henoch-Schönlein purpura (as described above) [28].

Therapy rationale

There is no specific therapy for PIGN. Therapy is based on the eradication of the involved infective agent by systemic antibiosis and on supportive therapy waiting for the natural recovery of renal function and kidney damage. In typical forms a steroid or immunosuppressive therapy is not indicated.

Infection therapy

Streptococcus is usually treated with penicillin, penicillin-derived antibiotics or macrolides in penicillin-intolerant patients: a few studies compared a 5-day course of cephalosporins with a 10-day course of penicillin without finding any difference [32]. However a bacterial isolation is recommended because of the possible different etiologies and to evaluate antibiotic susceptibility. Only if there is no bacterial isolation is an empiric therapy allowed. Bacterial identification and characterization is critically important for *Staphylococcus aureus* in which a targeted therapy is needed in case of MRSA, since new agents like vancomycin, teicoplanin, linezolid, fluoroquinolones, and daptomycin are highly effective against MRSA,

Therapy of the acute nephritic syndrome

If the acute nephritic syndrome presents with oligo-anuria, severe hypertension or renal failure hospital admission is needed [27]. Water and salt restriction is warranted in all cases, together with diuretics (e.g. furosemide, at a dose determined according to the degree of renal failure and diuresis). Hypertension usually has a good response to diuretic therapy; however if there is a persistent high diastolic pressure (>100 mmHg) more hypotensive drugs are needed, like calcium channel blockers, vasodilators, angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor antagonists, keeping in mind the risk of potentially fatal hyperkaliemia when using the latter two drugs [2]. If there is a persisting severe hypertension and the patient is at high risk of hypertensive encephalopathy an iv hypotensive drug (alpha–beta blockers, nitroprusside or other iv vasodilators) is usually adopted. If the patient develops severe renal failure, renal replacement therapy is warranted. The acute phase of the disease in which close medical care is needed usually lasts one or 2 weeks.

Immunosuppressive therapy

These drugs have no indication in most PIGN cases, but may have a role in PIGN with a rapidly progressive renal failure and crescents in 30–50 % of glomeruli, which is a strongly negative prognostic factor [33]. In this case the preferred therapy is usually based on iv steroid pulses (500–1000 mg or 10–15 mg/kg each) for three consecutive days, followed by oral steroids according to clinical evolution and renal function recovery. If the biopsy shows a severe interstitial infiltrate, which may be a negative prognostic factor, a short course of oral steroids seems to be useful [26].

There are no controlled studies investigating these therapies in adults or elderly patients with crescentic PIGN, but uncontrolled studies and case reports suggest a success rate of pulse steroids of about 60 % of treated patients [27].

Conclusions

Acute post-infectious glomerulonephritis is a newly changed nosographic entity: deep changes in its epidemiology, etiology, pathology and clinical management have emerged. The epidemiology of PIGN is changing in western countries along with the progressive aging of the population. PIGN should always be considered in the differential diagnosis of elderly patients with acute renal failure and active urinary sediment. A good knowledge of its atypical presentations and evolutions in the aged patient is crucial for a correct diagnosis and prompt treatment.

Kidney biopsy is rarely needed, especially in the classical forms of the child: PIGN may be simply diagnosed by the finding of an acute nephritic syndrome with low C3 if it has a typical clinical presentation. In the adult or elderly a biopsy is more frequently done to confirm diagnosis and it is warranted if there is an atypical presentation or evolution (persisting renal failure, rapidly progressive renal failure, absent or delayed functional recovery, persisting low C3, nephrotic range proteinuria or persisting significant proteinuria).

Differential diagnosis should be made with IgA nephritis, in which the infection is concomitant with the onset of the nephritis, has a usually relapsing macroscopic hematuria and in which renal failure at presentation is rare, and with membrano-proliferative GN which has a persisting low C3 and does not recover without specific therapy. A major indication to perform a kidney biopsy is when an IgA-dominant PIGN is suspected, because a precise histological definition is needed in order to perform a differential diagnosis with IgA nephropathy (both primary and secondary forms), in which a deeply different therapeutic approach is adopted: antibiotics in PIGN and steroids/immunosuppressive therapies in IgA nephropathy.

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