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Gross hematuria and congestive heart failure – two sides of the same coin

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ABSTRACT

Poststreptococcal glomerulonephritis (PSGN) is an immune-mediated disease following infection with nephritogenic strains of group A β-hemolytic Streptococcus (GAS), affecting children aged of 2 to 10.
We report 2 different presentations of PSGN from "Grigore Alexandrescu" Hospital.
Case 1: A 5 years old girl was admitted for gross hematuria. Investigations revealed: anemia, inflammatory syndrome, mild nitrogen retention syndrome, elevated ASO and low levels of serum C3, nephritic-range proteinuria and severe hematuria. she received antibiotic treatment with initial improvement. A relapse occurred in one week, a second course of antibiotic and corticosteroids was necessary.
Case 2: A 15-year-old girl was admitted for acute cardiac failure, hypertension and oliguria. Investigations revealed anemia, nitrogen retention, dyslipidemia, inflammatory syndrome, high ASO titers, low serum C3, microscopic hematuria, nephrotic-range proteinuria. She had fluid build-up in both lungs and pericardium. The diagnosis was PSGN and congestive heart failure (volume overload). She received antibiotics, diuretics and ACE inhibitors.
PSGN is re-emerging in pediatric practice due to the resurgence of streptococcal infections within children's communities. The clinical presentation might be highly variable, ranging from hematuria to heart failure. Clinicians should be aware and actively consider this diagnosis.

Keywords: poststreptococcal glomerulonephritis, hematuria, proteinuria, group A Streptococcus, nephritic syndrome

Abbreviations

ACEI – Angiotensin-converting enzyme inhibitors
ANA – Antinuclear antibody
ARB – angiotensin receptor blockers
ASO – Antistreptolysine O
BMI – Body mass index
BP – blood pressure
CKD – Chronic Kidney Disease
CRP – C-reactive protein
DsDNA – Double-Stranded DNA
eGFR – Estimated glomerular filtration rate
GAS – Group A β-hemolytic Streptococcus
HAV – Hepatitis A Virus
HBV – Hepatitis B Virus
HCV – Hepatitis C Virus
HIV – Human Immunodeficiency virus
HR – heart rate
IgA – Immunoglobulin A
IgG – Immunoglobulin G
NAPlr – Nephritis-associated plasmin receptor
PSGN – Poststreptococcal glomerulonephritis
SpeB – streptococcal pyrogenic exotoxin B

INTRODUCTION

PSGN is an acute renal disorder that arises after GAS infections, predominantly affecting children following pharyngitis or skin infections such as impetigo [1].

The global prevalence of PSGN has been declining, yet it is still the predominant cause of glomerulonephritis in pediatric populations. The overall decline in PSGN prevalence is largely due to a significant reduction in skin infections over the past

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fifty years, resulting in postpharyngitic PSGN being most commonly observed in developed countries [2].

It can manifest either sporadically or during an epidemic of GAS infections. During a GAS epidemic, the incidence of clinically detectable PSGN in infected children is 5-10% following pharyngitis and 25% following skin infections. Less than 2% of sporadic cases of infection with nephritogenic strains of streptococci will exhibit clinical signs of glomerulonephritis [1-3].

Although the precise mechanisms underlying glomerular impairment in PSGN remain unclear, the injury appears to be primarily mediated by an autoimmune response to nephritogenic streptococcal antigens. This response leads to formation of immune complexes and activation of the alternative complement pathway, resulting in glomerular damage. Key components of the pathology include molecular mimicry, immune complex formation and complement activation. Nephritis-associated plasmin receptor (NAPlr) and streptococcal pyrogenic exotoxin B (SpeB) are streptococcal antigens that play critical roles by mimicking host antigens, leading to the production of autoantibodies and subsequent glomerular immune complex deposits [1,4], which activate the complement system, particularly the alternative pathway, resulting in glomerular inflammation and injury [5]. Additionally, in situ immune complex formation within the glomeruli exacerbates the inflammatory response [6]. The involvement of immune complexes and complement activation highlights the importance of these processes in the pathogenesis of PSGN, contributing to the characteristic histopathological findings of hypercellularity and immune deposits in the glomeruli [7,8]. Immune complexes deposits and the subsequent complement activation lead to the clinical manifestations of PSGN, including hematuria, proteinuria, and reduced renal function [9]. Rapidly progressive ("crescentic") glomerulonephritis occurs in fewer than 0.5% of cases (3,10-12).

The diagnosis of PSGN is typically confirmed through medical history: evidence of a recent streptococcal infection, and supported by specific laboratory findings.

The risk of developing PSGN is elevated in 5 to 12 year olds, while it is uncommon in children under 3. PSGN occurs twice as frequently in males compared to females [13-16].

PSGN can present clinically in multiple ways, from asymptomatic microscopic hematuria to acute nephritic syndrome, which includes hyperpigmented urine, proteinuria (potentially reaching nephrotic levels), edema, hypertension and high levels of serum creatinine. Most children, however, are asymptomatic. For instance, in an American study of 248 children with GAS infection, 8% developed renal impairment and a transient reduction in serum complement activity, but only one child (0.4%) exhibited clinical symptoms.

Laboratory findings in post-streptococcal glomerulonephritis typically include evidence of both renal impairment and immune response to a preceding streptococcal infection. Common findings are hematuria and proteinuria, with urinalysis often revealing red blood cell casts indicative of glomerular injury. Blood tests generally show elevated serum creatinine and blood urea nitrogen (BUN) levels, reflecting reduced renal function. Complement studies usually demonstrate decreased serum C3 levels, which return to normal within 6 to 8 weeks, while C4 levels typically remain normal. Serological tests may confirm a recent streptococcal infection: elevated/increasing levels of antistreptolysin O (ASO) or anti-DNase B antibodies. These findings collectively help distinguish PSGN from other glomerulonephritis [17,18].

Rapidly progressive („crescentic") glomerulonephritis can be found in fewer than 0.5% (3,10-12). The characteristic histopathological findings associated with poststreptococcal glomerulonephritis (PSGN) include diffuse endocapillary proliferation, which is typically seen on light microscopy. This is characterized by an increase in cellularity within the glomeruli due to the proliferation of endothelial and mesangial cells, along with the influx of inflammatory cells, primarily neutrophils and monocytes. Additionally, immunofluorescence studies usually reveal granular deposits of immunoglobulin G (IgG), immunoglobulin M (IgM), and complement component C3 along the glomerular basement membrane and mesangium, reflecting the immune complex-mediated nature of the disease. Electron microscopy often shows subepithelial "humps," which are electron-dense deposits representing immune complexes.

Figure 1 represents different histopathological findings in PSGN.

Management primarily involves supportive care, focusing on controlling hypertension and managing fluid overload, while antibiotic therapy is reserved for eradicating the underlying streptococcal infection to prevent recurrence [1,20].

Research has demonstrated that corticosteroids, such as methylprednisolone and prednisolone, are effective in decreacing proteinuria and improving renal outcomes in severe cases of acute poststreptococcal glomerulonephritis. Specifically, methylprednisolone pulse therapy followed by oral prednisolone has been proven to significantly decrease serum creatinine levels and proteinuria in cases

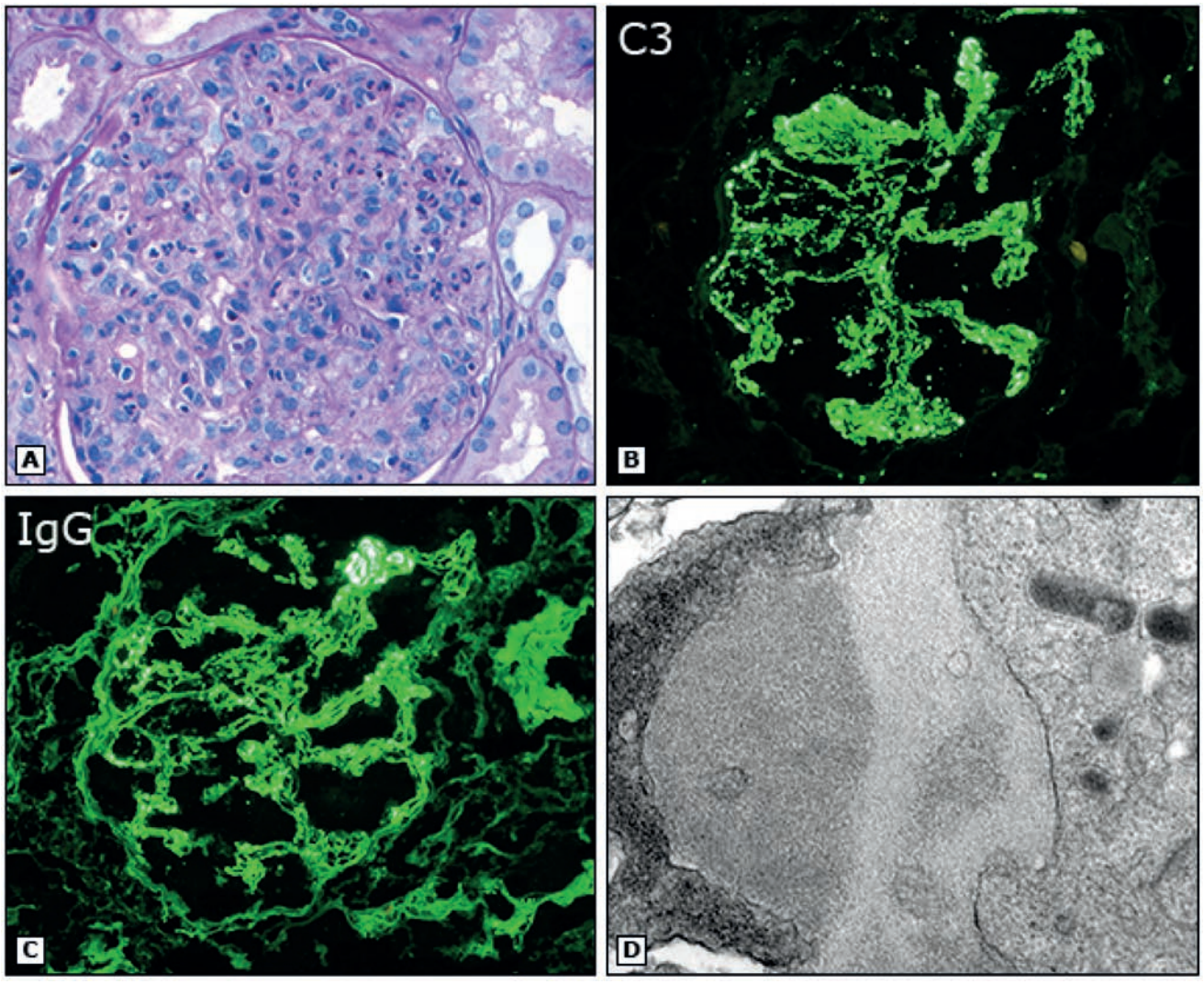

FIGURE 1. Proliferative glomerulonephritis: (A) exudative glomerulonephritis: large numbers of neutrophils within glomerular capillaries (optic microscopy, Periodic Acid Schiff, 40x). (B) Bright granular capillary wall staining for C3 (immunofluorescence microscopy, 40x). (C) bright granular capillary wall staining for IgG (immunofluorescence microscopy, 40x). (D) Subepithelial humps (electron microscopy 79900x) [19]

with acute interstitial nephritis associated with PSGN [21]. Current expert consensus recommends the administration of steroids for patients exhibiting more than 30% crescent formation on renal biopsy, reflecting a tailored approach based on specific histopathological findings [22].

Thiazide diuretics are efficient as first choice therapy for supportive care in PSGN. However, in patients with edema and renal dysfunction, especially when estimated glomerular filtration rate (eGFR) decreases <30 mL/min/1.73 m², loop diuretics may be more appropriate. Hypertension associated with PSGN may be managed using diuretics alone or in combination with a calcium-channel blocker. Additionally, angiotensin-converting enzyme inhibitors (ACEI) may provide better control of blood pressure and edema in PSGN compared to diuretics. Still, the use of ACEIs or angiotensin receptor blockers (ARB) is largely avoided in acute phase due to their potential to exacerbate reductions in glomerular ultrafiltration and induce hyperkalemia [21] .

During the acute phase of PSGN, various complications may occur, including pulmonary edema/ congestive heart failure, severe hypertension-induced encephalopathy. Life-threatening events such as hypertensive emergencies (21.5%), congestive heart failure (12.3%), encephalopathy (4.6%) and retinopathy (1.5%) have been reported [21] .

Although the prognosis for most pediatric cases is good, with spontaneous restitutio ad integrum occurring in weeks-months, adults with PSGN may experience a more protracted course and the risk for chronic kidney disease (CKD) is higher, 1-2% [19].

AIM

The authors report 2 different presentations of PSGN, cases diagnosed in the Pediatric Department of „Grigore Alexandrescu" Emergency Children's Hospital in 2019 and 2024.

SERIES OF CASES

Case 1

A 5-year-old girl was admitted to our department for gross hematuria, mild dysuria and discrete suprapubic pain. Symptoms began 7 days prior, during Augmentin p.o treatment for acute otitis media. The patient was afebrile and presented at the emergency unit. Investigations revealed nitrites on dipstick testing, erythrocytes, and proteins on urinalysis. She was diagnosed with urinary tract infection and was given Cefixime treatment for 7 days, without improvement. Patient history revealed recent contact with 2 cases of tonsillitis with group A beta-hemolytic Streptococcus and 1 case of scarlet fever.

On admission the patient presented with weight = 24 kg, height = 119 cm, BMI= 16.7 kg/m^2. She was afebrile, with a heart rate (HR) of 90 bpm and blood pressure (BP) at rest of 110/60 mmHg, with no edema. Pulmonary, cardiovascular, and abdominal examination were normal, except for a mild discomfort in the infra-umbilical area on palpation and mild dysuria. She had gross macroscopic hematuria, turbid and foamy urine.

Laboratory evaluation indicates inflammatory anemia, normal ionogram, acid-base status and coagulation status, inflammatory syndrome with elevated ESR and fibrinogen, and normal levels of CRP. Renal function tests show increased BUN and normal creatinine and uric acid levels. Immunology tests revealed elevated titers of ASO, low C3 and high C4, negative ANA, dsDNA antibodies, and elevated levels of IgG. Hepatitis B, C and HIV serology were negative, also Quantiferon. Throat and nose cultures and rapid streptococcal antigen testing were negative. Urinalysis indicated large amounts of blood and protein, but no nitrites, no urinary casts. Stansfeld Webb revealed 450 erythrocytes and 330 leucocytes /mm3. 24h urine revealed nephritic proteinuria 0.02 g/kg/day, multiple negative urine cultures. Abdominal and cardiac ultrasound, chest X-ray returned normal findings.

Other causes of dark-colored urine were excluded: false hematuria – foods and medications that alter the macroscopic appearance of urine, lead/mercury poisoning. Extrarenal gross hematuria causes were also ruled out - hemorrhagic diathesis was highly unlikely due to normal coagulation status. At this point, renal causes of gross hematuria were taken into consideration. We excluded renal abscess, acute pyelonephritis, renal trauma, and renal masses due to the patient history and normal ultrasound.

Bearing in mind both clinical and paraclinical investigations, the patient was diagnosed with glomerulonephritis, meeting the following criteria: hematuria, nephritic range proteinuria, inflammatory syndrome, nitrogen retention syndrome.

Multiple etiologies were ruled out (IgA Nephropathy, Systemic lupus erythematosus nephritis, HIV, HVB, HVC, Tuberculosis). Considering the subsequent diagnostic criteria, the streptococcal etiology of glomerulonephritis was confirmed: contact with 3 cases of group A beta-hemolytic Streptococcus infection, onset of the disease during treatment for acute otitis media, inflammatory syndrome with normal levels of CRP, low levels of serum C3, elevated titers of ASO with an upward trend from 700 IU to 1200 IU, nephritic range proteinuria, nephritic syndrome, persistent hematuria despite the correct and complete administration of antibiotic treatment.

The patient received treatment with penicillin and Ibuprofen for 10 days with normal macroscopic urine and the improvement of the laboratory parameters.

Figure 2 illustrates the progressive normalization of the macroscopic appearance of urine during the course of antibiotic treatment.

One week later, the patient was admitted again with gross hematuria, turbid urine and tibial edema. Laboratory evaluation showed ascending titers of ASO, low levels of serum C3 and normal levels of serum C4, nitrogen retention syndrome, and inflammatory syndrome. The urinalysis revealed nephritic proteinuria and gross hematuria with abnormal erythrocyte morphology. She received Ceftriaxone for 7 days and a short course of Methylprednisolone (2 weeks) with significant improvement of clinical and paraclinical parameters.

FIGURE 2. Macroscopic appearance of urine upon admission (left), after 5 days of antibiotic (center) and before discharge (right)

Case 2

A 15-year-old girl was admitted to our department for dyspnea with orthopnea, tibial edema and oliguria. Symptoms began 5 days prior with nocturnal dyspnea, cough, headaches and periorbital edema followed by tibial edema with progressive exacerbation. Patient history revealed acute pharyngotonsillitis with painful laterocervical adenopathy 2 weeks prior. On admission the patient presented with a weight of 98 kg, height 172 cm, BMI= 33,1 kg/m2. She was afebrile, with a HR=70 bpm and BP=154/100 mmHg, discrete periorbital edema, and firm pretibial edema. Pulmonary examination indicated diminished vesicular sounds in the base of the right lung, dyspnea with orthopnea, and cough. Abdominal evaluation revealed painful hepatomegaly. Renal examinations showed oliguria.

Laboratory evaluation indicated normochromic, normocytic, normosideremic anemia, nitrogen retention, dyslipidemia, inflammatory syndrome, high ASO titers, low serum C3, negative antinuclear and dsDNA antibodies. Urinalysis revealed microscopic hematuria, nephrotic proteinuria, and negative urine cultures. Throat and nose cultures and rapid streptococcal antigen testing were negative.

Figure 3 ilustrates the imagistic findings, diagnostic for polyserositis.

Taking into account both clinical and paraclinical evaluations we considered the following diagnoses: heart failure and acute glomerulonephritis. Myocarditis was highly unlikely due to normal cardiac enzymes and non-suggestive ECG. We also ruled out IgA nephropathy and Systemic lupus erythematosus nephritis. PSGN and heart failure due to volume overload diagnoses were set, checking the following criteria: oliguria, painless hematuria, hypertension, edematous syndrome, inflammatory syndrome with normal levels of CRP, low levels of serum C3, elevated titers of ASO, proteinuria, nitrogen retention syndrome.

The patient received antibiotic treatment with penicillin for 2 weeks, diuretic treatment with Furosemide for 1 week, and ACEI - Captopril for 2 weeks. The overall condition of the patient improved, with remission of dyspnea within 24 hours, progressive resolution of the edematous syndrome, normalized values of blood pressure within 1 week, and recovery of renal function within 2 weeks. Antihypertensive treatment was discontinued two weeks post-discharge.

DISCUSSIONS

Diffuse proliferative glomerulonephritis subsequent to GAS infection is the most frequent cause of acute glomerulonephritis. It generally manifests with nephritic symptoms following a latency period, ranging from 1 to 2 weeks following pharyngitis, and 3 to 6 weeks following skin infections [17]. We reported 2 cases of PSGN (corresponding to the reported peak incidence age interval: 5 and 15 years respectivelly), both cases had a latency period of about 3 weeks after a possible GAS respiratory tract infection which was not diagnosed as such.

In the evaluation of suspected cases of PSGN, it is important to take into account serological and epidemiological investigations pointing to a recent streptococcal infection. Positive streptococcal serologies demonstrate higher sensitivity (94.6%) in supporting the diagnosis compared to the sensitivity of a recent infection history (75.7%) or positive cultures (24.3%) [16]. In first patient's case, there is suggestive history of contact with group A beta-hemolytic Streptococcus infections and progressively increased titers of ASO. The second patient had also a personal history of acute pharyngotonsillitis 2 weeks before admission with progressively increasing ASO titers.

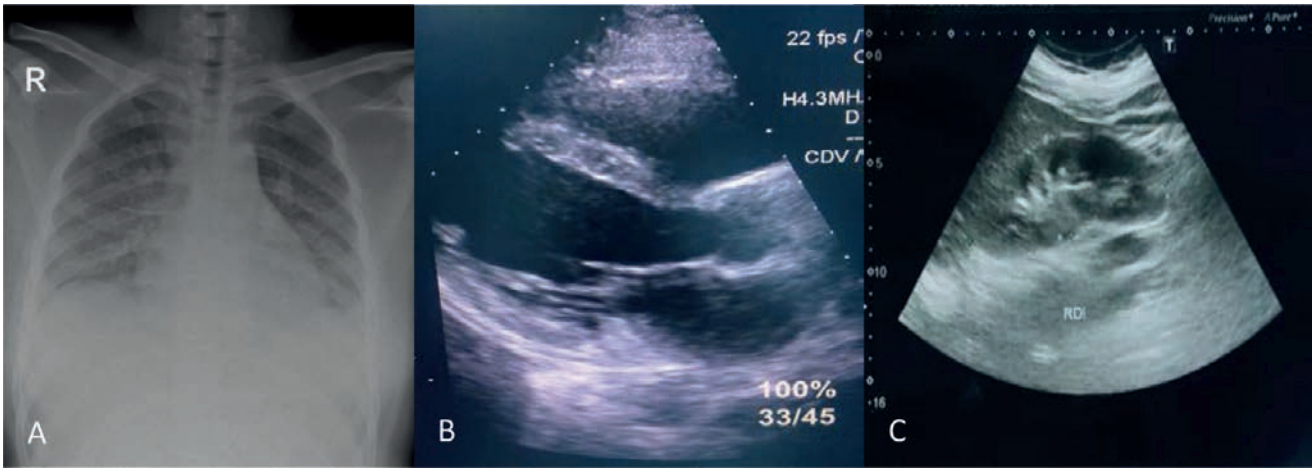

FIGURE 3. A) Chest X-ray: blunting of the left costophrenic angle, B) cardiac ultrasound: dilated left atrium and ventricle, normal systolic function, LVEF = 60%, a small circumferential pericardial effusion and bilateral pleural fluid, C) abdominal ultrasound: 15 mm of fluid in the pouch of Douglas, small bilateral pleural effusion

Gross hematuria+edema+hypertension is the characteristic clinical triad of glomerulonephritis. However, some patients may have only microscopic hematuria, normal to mildly elevated blood pressure, and the absence of noticeable edema. Consequently, these patients may not seek healthcare services. Almost all PSGN patients present hematuria as the primary symptom, although only 1/3 report gross hematuria, episode that might persist for up to 10 days. While recurrence can occur with febrile illnesses in the weeks following the acute presentation, such exacerbations are rare and should prompt consideration of alternative etiologies, particularly other forms of glomerulonephritis. Microscopic hematuria often persists for several months and may last up to a few years after the initial presentation. In our study, only the first patient presented gross hematuria that initially resolved over the course of six days of antibiotic treatment. One week post-discharge, the patient was admitted again with gross hematuria and turbid urine, which is why corticoid treatment was initiated with the subsequent improvement of urine output [17].

Edema is reported in 65-90% of cases. It primarily results from excessive retention of fluid and sodium rather than substantial protein loss in the urine, thus ascites are not commonly seen. While less frequent, pulmonary edema may occur in severe cases. Signs of congestive heart failure have been identified in up to 50% of cases when specifically investigated. Similar to gross hematuria, edema typically subsides after 7 to 10 days. Hypertension often parallels edema due to its shared origin in excessive fluid and salt retention. It affects 60% to 80% of patients with PSGN and requires treatment in approximately half of the cases. Hypertension is usually acute in duration, frequently resolving within about 10 days [17]. Both our cases presented with edema, but in the second patient it was more pronounced-periorbital and tibial edema with progressive exacerbation. Furthermore, the second case had generalized edema with polyserositis and hypertension due to fluid retention and also nephrotic range proteinuria. Congestive heart failure resulting from volume overload, presenting with characteristic symptoms such as dyspnea exacerbated by orthopnea was also identified. The overall condition of the patient improved, edematous syndrome and hypertension were remitted within 1 week under treatment.

Clinical findings play a key role in the diagnosis of PSGN, particularly when there is a documented history of recent GAS infection. Confirmation typically requires only a few laboratory tests. Ideally, identification of GAS pharyngitis during acute infectious process is achieved through throat culture or rapid streptococcal antigen testing. However, alternative methods are avialable to confirm recent GAS infection even in the absence of a positive bacteriological test [17]. Elevated serum titers against GAS proteins, notably ASO titers, have traditionally served as indicators of possible infection. ASO titers typically peak 2 to 4 weeks post-pharyngitis episode. Persistently elevated ASO levels with an increasing titer over time are diagnostically significant [17]. Serum C3 emerges as a highly valuable diagnostic test in PSGN because C3 plays a central role in the disease's pathogenesis. Decreased C3 levels are observed in over 90% cases. PSGN activates the alternate complement pathway, with C3 being predominantly consumed. While other total pathway components like C4 are typically unaffected, measuring both C3 and C4 levels may assist in distinguishing between various possible diagnoses [17]. In both instances, despite the absence of a positive pharyngeal culture, a history of illness or epidemiological exposure to GAS infection was noted. Additionally, both patients exhibited rising ASO titers. Immunologically, hypocomplementemia and specifically low C3 levels were observed in both cases, while C4 values remained within normal ranges, indicating activation of the alternative complement pathway.

Additional recommended tests, mandatory in the evaluation of any renal disorder, include complete blood cell count and electrolytes, renal function tests, urinalysis with urinary erythrocytes' microscopy. Results from urine dipstick tests frequently reveal significant quantities of blood and protein. In freshly voided specimens, red blood cells in the urine may exhibit dysmorphic features, alongside the possible presence of red blood cell casts. While the presence of red blood cell casts is not specific to PSGN, it is pathognomonic of glomerular diseases in general. The first patient's initial laboratory testing revealed urinalysis with large amounts of blood, and protein, but no nitrites, no urinary casts, and normal red blood cell morphology. Total 24h urine demonstrated nephritic proteinuria 0.02 g/kg/day. In evolution, the patient presented abnormal erythrocyte morphology. In the second case, the patient presented with microscopic hematuria and nephrotic-range proteinuria [17].

Concerning the management of PSGN, the timely administration of antibiotics for the initial GAS infection may potentially mitigate the onset of nephritis and prevent the spread of infection to susceptible individuals. Although early antibiotic therapy theoretically reduces the overall duration of exposure to GAS antigens and thus the degree of immunologic response, its efficacy in PSGN remains unsubstantiated. A Cochrane review of 27 trials examining sore

throat management indicated a trend towards antibiotic treatment protecting against nephritis development, yet the limited number of PSGN cases precluded statistical significance. Similarly, trials comparing various cephalosporins administered over a 5-day regimen with the traditional 10-day penicillin course revealed no disparity in PSGN development rates. Consequently, while GAS infections warrant timely treatment, prompt antibiotic therapy does not appear critical for PSGN prevention [1,20].

The primary management approach for PSGN, once established, involves supportive care targeting the main disease sequelae, such as hypertension, edematous syndrome, impaired renal function and potassium overload. These complications typically emerge early in the disease course and are often transient. Frequent reevaluations are necessary to monitor disease progression. Considering the common origin of edema and hypertention, the primarly therapeutic approach is based on the decrease in sodium and fluid intake alongside increased urinary excretion. Thiazide diuretics serve as first-line treatment, while loop diuretics should be reserved for patients with significant fluid retention and/or renal dysfunction [17].

ACEIs and ARBs are generally approached cautiously in PSGN. Theoretically, decreased levels of serum renin and aldosterone could potentially diminish efficacy in hypervolemia. Nevertheless, intrarenal renin levels are expected to be higher in PSGN patients with reduced glomerular capillary perfusion. Furthermore, studies have demonstrated that patients who received ACE inhibitors experienced improved blood pressure management and better cardiac outcomes compared to those treated with other antihypertensives, including loop diuretics. Nonetheless, concerns persist regarding the potential exacerbation of glomerular filtration and hyperkalemia with the use of these agents, necessitating caution [17].

The initial treatment for the first case involved the administration of Penicillin to eliminate the underlying streptococcal infection with with the temporary improvement of the laboratory parameters and normal macroscopic urinalysis. Upon the recurrence of gross hematuria, Ceftriaxone, and corticoid treatment were initiated with the subsequent improvement of clinical status and urine output. In addition to antibiotic therapy involving Penicillin, the second case demanded treatment for edematous syndrome, arterial hypertension, and heart failure due to volume overload. Treatment with Furosemide and ACE inhibitor Captopril was initiated, resulting in a favorable clinical outcome [17].

CONCLUSIONS

Despite a declining incidence in developed countries, acute post-streptococcal glomerulonephritis is resurfacing in pediatric healthcare, coinciding with the increasing cases of streptococcal infections within children's communities.

Given its diverse clinical manifestations, ranging from hematuria to heart failure, clinicians must proactively consider and investigate this condition, particularly in cases involving multi-organ impairment.

Recurrences of acute PSGN are relatively rare, but clinically significant. It is mandatory to monitor patients with a history of PSGN, ensuring prompt treatment of new streptococcal infections, and addressing any recurrent renal symptoms swiftly. Diligent assessment of renal function, along with preventive measures and patient education regarding the early signs of streptococcal infections, are essential for reducing the risk of recurrence and preserving renal function.

Patient consent:
Informed consent was obtained from all subjects involved in the study.

Conflict of interest: The authors declare they do not have any financial or personal relationships that might bias the content of this work.

Author's contributions:
Conceptualization: RMV, DP. Methodology: CV, RMV. Formal analysis: CV, RMV. Data curation: CV, RMV, IO, DP. Original draft preparation: CV. Review and editing: RMV, DP. Supervision: RMV, IO, DP. Project administration: RMV.
All authors have read and agreed to the published version of the manuscript

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