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Clinical Manifestation Patterns and Trends in Poststreptococcal Glomerulonephritis

Kee Hyuck Kim, M.D.

Department of Pediatrics, National Health Insurance System Ilsan Hospital

Corresponding author:
Kee Hyuck Kim, M.D.
Department of Pediatrics, National Health Insurance System Ilsan Hospital, 1232 Baikseok1-dong, Ilsandong-gu, 10444, Goyang, Korea
Tel: +82-31-900-0265
Fax: +82-31-900-0343
E-mail: kkim@nhimc.or.kr

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Poststreptococcal glomerulonephritis (PSGN) is one of the most recognized diseases in pediatric nephrology. Typical clinical features include rapid onset of gross hematuria, edema, and hypertension, and cases are typically preceded by an episode of group A β-hemolytic streptococcus pharyngitis or pyoderma. The most common presenting symptoms of PSGN are the classic triad of glomerulonephritis: gross hematuria, edema, and hypertension . However, patients with PSGN sometimes present with unusual or atypical clinical symptoms that often lead to delayed diagnosis or misdiagnosis of the disease and increased morbidity. Additionally, the epidemiology of postinfectious glomerulonephritis (PIGN), including PSGN, has changed over the past few decades. This paper reviews atypical clinical manifestations of PSGN and discusses the changing demographics of PIGN with a focus on PSGN.

Key words: Poststreptococcal, Glomerulonephritis, Postinfectious

Case 1. A 10-year-old boy presented with acute headache, altered mental state, and generalized seizure. He had hypertension and microscopic hematuria, and MRI showed lesions suggestive of Posterior Reversible Encephalopathy Syndrome (PRES). Analysis indicated that the antistreptolysin-O (ASO) titer was increased and complement C3 titer was decreased. The patient was diagnosed with PRES-related hypertensive poststreptococcal glomerulonephritis (PSGN).

Case 2. A 9-year-old boy was transferred from another hospital with dyspnea, and plain chest film indicated alveolar infiltrates and bilateral pleural effusions. Urinalysis and blood pressure measurements showed microscopic hematuria and hypertension. The elevated serum ASO titer and decreased serum complement C3 level confirmed the diagnosis of PSGN.

The clinical manifestations of the two cases differed from typical clinical features of PSGN. The most common presenting symptoms of PSGN are the classic triad of glomerulonephritis: gross hematuria, edema, and hypertension. However, PSGN can present with unusual or atypical clinical symptoms that often lead to delayed diagnosis or misdiagnosis, which increases morbidity[1,2].

In addition, the epidemiology of postinfectious glomerulonephritis (PIGN), including PSGN, has changed over the past few decades[3-5].

This is a review of atypical clinical PSGN manifestations and a discussion of the changing PIGN demographics, with focus on PSGN.

Atypical Clinical Features of Post-streptococcal Glomerulonephritis (PSGN)

A number of patients with PSGN may only have subclinical involvement, with microscopic hematuria, normal to mildly elevated BP, and no obvious edema. These patients may not seek medical attention, but the incidence can be detected during school urine screening tests. Hypertension and its accompanying symptoms, such as headaches or seizures, without typical urinary findings at presentation, can also be misdiagnosed, which causes a delay of treatment[1,2]. In some cases, diagnosis is confirmed by renal biopsy and presence of a typical Henoch-Schönlein purpura (HSP) rash with acute nephritis[6,7].

A delay in the diagnosis of PSGN is more common in children that do not have a history of antecedent group A β-hemolytic streptococcus (GAS) infection and have microscopic hematuria. Most patients present with findings due to volume overload, which include hypertension, edema, and pulmonary edema[1].

Dr. Watanabe classified atypical PSGN manifestation into three categories: Concurrence of immune-mediated diseases, non-immune-mediated conditions, and atypical clinical manifestations or courses[8].

1. Concurrence of immune-mediated disease

The co-occurring immune-mediated diseases include acute rheumatic fever, vasculitis, and immune thrombocytopenic purpura (ITP).

Acute rheumatic fever is an immune mediated disease that can follow a GAS infection along with PSGN. However, the epidemiology and immunology of the two diseases are different, and co-occurrence of the two diseases in the same patient is rare[9]. Gibney et al. first reported a case with simultaneous acute rheumatic fever and biopsy-proven PSGN[10]. Since then 17 patients with co-occurrent acute rheumatic fever and PSGN have been reported[11]. It is not clear why simultaneous PSGN and acute rheumatic fever are rare. One explanation may be that only about 15 of the more than 80 known M serotypes of GAS have both nephritogenic and rheumatogenic antigenic features[9].

Vasculitis is not a frequent disorder correlated with GAS infection. However there have been several articles of HSP [6] or Henoch-Schönlein purpura with nephritis (HSPN)[7]. Despite the complete pathogenic part of GAS infection that devotes to the evolution of vasculitis is not clear, an immune complex-mediated mechanism caused by GAS infection has been speculated[12].

Childhood ITP, an autoimmune disease with antibodies detectable against platelet surface antigens, often occurs after a viral infection, such as influenza, Epstein-Barr, varicella zoster, rubella virus[13] but may also be preceded by a bacterial infection[14]. Since the first reported ITP cases in two patients with PSGN[15], several cases of thrombocytopenia in patients with PSGN have also been reported[13,14]. Muguruma et al. postulated about the pathogenesis of correlated diseases based on development of antibodies that were cross-response against GAS and platelets[14].

2. Non-immune-mediated conditions

Non-immune-mediated conditions of PSGN include posterior reversible encephalopathy syndrome (PRES) and thrombotic microangiopathy.

Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), is a recently-described brain disorder with typical radiological findings of bilateral gray and white matter abnormalities in the posterior regions of the cerebral hemispheres and cerebellum[16,17]. The clinical symptoms include headache; decreased alertness; mental abnormalities such as confusion and diminished spontaneity of speech; behavior changes that range from drowsiness to stupor, seizures, vomiting; and visual perception abnormalities, such as cortical blindness[18]. The causes of PRES can vary, but it is commonly attributed to acute increase in blood pressure, renal failure, fluid retention, and treatment with immunosuppressive drugs[17]. Although the pathophysiology of PRES is not completely understood, it is believed that severe hypertension or other causes of PRES induce breakdown in cerebral autoregulation, which leads to leakage of fluid into the brain parenchyma. The leakage of fluid into the brain parenchyma is detected as vasogenic edema on neuroimaging studies[19]. The prognosis of PRES

is generally benign, but delay in diagnosis and treatment can result in permanent sequelae to the affected brain tissues[17].

Thrombotic microangiopathy (TMA) is a pathological process that involves thrombocytopenia, microangiopathic hemolytic anemia, and microvascular occlusion. TMA is common in hemolytic uremic syndrome (HUS) associated with shiga toxin or invasive pneumococcal infection, atypical HUS (aHUS), thrombotic thrombocytopenic purpura (TTP), and other disorders including malignant hypertension[20]. Histologic features of TMA include vessel wall swelling, thickening and separation of the endothelial cell from the basement membrane, aggregation of substance in the subendothelial space, intraluminal platelet thrombosis, partial or complete vascular luminal occlusion, and red blood cell fragmentation[21].

There have been at least 10 cases describing TMA associated with PSGN[22-24]. All patients exhibited hypertension, and renal replacement therapy was performed in 3 patients. Renal pathology revealed the appearance of both PSGN and TMA in 3 patients and showed PSGN features without characteristics of TMA in 7 patients. The outcome in all patients was good.

Although the precise pathogenesis of TMA in patients with PSGN is not clear, 2 causes have been speculated: serious hypertension and streptococcal neuraminidase[22,23]. HUS has been reported as a consequence of severe hypertension, regardless of the cause. If severe hypertension is temporary, histological features of TMA are not present. But hypertension becomes malignant, pathologic lesions show characteristics of TMA[22]. Another available explanation of TMA in PSGN is adjustment of vascular endothelial cells by streptococcal neuraminidase. Circulating neuraminidase triggers antigen-antibody interaction and may injure the vascular endothelial cells, leading to the clinical manifestations of HUS[23].

3. Atypical clinical manifestations or courses

Atypical clinical manifestations or courses of PSGN are acute nephritis without definite urinary abnormalities and relapse of the illness.

Patients with PSGN usually show hematuria and proteinuria. But there are several reports of histologically proven PSGN patients with minimal or no urinary abnormalities [25-27]. Most patients showed edema and hypertension, and some of them exhibited pulmonary congestion or edema. All patients improved completely without any residue. The reasons for the normal or minimal urinary abnormalities during the course of PSGN is not clear[26,27].

Recurrence of PSGN is a rare occurrence, probably because of the relatively limited number of nephritogenic strains of streptococci and the acquirement of protective immunity against a nephritogenic streptococcal antigen after an initial episode of PSGN[28]. Although incidences of recurrent PSGN have been reported to range from 0.7% to 7.0% in several clinical studies, and a few cases of recurrent PSGN have been reported[28-30], the exact pathophysiological mechanisms that cause recurrence of PSGN remain unclear[28]. Relapse of PSGN in some patients probably caused by defect of a natural immune response against nephritogenic streptococcal components such as NAPlr[28]. Recently, a patient with selective IgA deficiency exhibited two episodes of PSGN[30]. It might suggest that a failure of IgA defenses may also lead to streptococcal re-infection and cause recurrent PSGN. Because unusual or atypical features of PSGN can lead to diagnostic delays or misdiagnosis of the disease, early perception is important to ensure that the patient receives acceptable treatment.

Changing Trends of Poststreptococcal Glomerulonephritis

Poststreptococcal glomerulonephritis (PSGN) is one of the oldest recognized renal diseases. More than 200 years ago, Wells described the clinical features of dark and scanty urine after scarlet fever, and this postscarlatinal disorder was termed acute glomerulonephritis. In the 1920s, it was discovered that scarlet fever was caused by an infection with β-hemolytic streptococcus, and PSGN became the etiologically correct term[31]. It is widely acknowledged that the incidence of PSGN has decreased in the past few decades. In addition, changing patterns in the occurrence of PSGN over the last few decades have been described in studies from many countries, including the United States, Singapore, and China[32-34].

The reasons for the decreased incidence of PSGN have not been clearly defined. Some possible reasons include

the widespread use of antibiotics, changes in etiological pathogens, altered susceptibility of the host, better health care, and improved socioeconomic and nutritional conditions[32-35]. In addition, in Korea, several single-center studies from different areas showed declining incidence and sporadic outbreaks[4,5,36].

Despite the reduction in the worldwide incidence of PSGN, epidemics and clusters of cases continue to appear in several regions of the world, and the burden of PSGN ranges between 9.5 and 28.5 new cases per 100,000 individuals per year[3,37]. Sporadic cases of PSGN account for 21% (4.6-51.6%) of children admitted to the hospital with acute renal failure in developing countries[3]. In these developing countries, PSGN occurs primarily in children[38] and young adults[39].

In comparison, patients in western countries tend to be elderly[40]. An epidemiological evaluation from Italy showed an incidence of PIGN in elderly patients that was more than twice that of the pediatric population[41]. This shift is likely due to increased life expectancy and increased severity of infections in the elderly population with predisposing factors (diabetes, malignancy, and vasculopathy)[42].

The bacteriology of adult PIGN differs from the typical childhood disease. Currently, non-streptococcal infections, including staphylococcal and Gram-negative bacilli infections, are known to cause PIGN, particularly in western adults who are immunocompromised. Staphylococcus has become as common as Streptococcus in developed countries, and it is 3-fold more common in elderly patients. Diabetes is a major risk factor of Staphylococcus-related GN, reflecting the increased skin and mucosal colonization in diabetics[43].

The pathogenesis of PIGN requires additional study to determine distinguishing characteristics that differentiate it from classic PSGN; currently, various clinical and pathologic profiles have been described, including abundant IgA deposits and aggressive progression to ESRD[44].

PIGN should always be considered in the differential diagnosis of elderly patients with acute renal failure and active urinary sediment. Additionally, familiarity with its atypical presentations and evolution is crucial for a correct diagnosis and prompt treatment.

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