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Case Report

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Is Staphylococcus Infection-Associated Glomerulonephritis Overlooked? A Case Report and Literature Review

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ABSTRACT

Staphylococcus infection-associated glomerulonephritis is an immune complex-mediated glomerulonephritis seen with active Staphylococcal infection. Kidney injury usually occurs within 4 weeks of the onset of Staphylococcal infection. Long-time prognosis of Staphylococcus infection-associated crescentic glomerulonephritis despite therapy against the infectious pathogen is usually poor for the adult patients. A 59-year-old diabetic male patient was admitted to our nephrology outpatient clinic with the complaints of fatigue, oliguria, edema, and erythema on the left leg. The diagnosis of our patient was considered as crescentic Staphylococcus infection-associated glomerulonephritis by excluding other causes of glomerulonephritis due to the history of skin infection, decreased C3 level, renal biopsy, and clinical findings. Treatment of Staphylococcus infection-associated glomerulonephritis focuses on eradicating infection with the use of antibiotic therapy. The role of steroids is still unclear in the treatment. The present case was treated with high-dose methylprednisolone successfully. Staphylococcus infection-associated glomerulonephritis must be distinguished from IgA-dominant or -codominant immune complex-mediated Staphylococcus infection-associated glomerulonephritis depending on the prognosis and treatment differences.

Keywords: Glomerulonephritis, methylprednisolone, Staphylococcus

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INTRODUCTION

The incidence of Staphylococcus-associated glomerulonephritis (SAGN), caused by the immunological response of the kidney to Staphylococcus superantigens, is gradually increasing due to the rise in the frequency of drug-resistant Staphylococcus strains, community- and hospital-acquired *Staphylococcus aureus* infections, elderly population, and comorbidities such as diabetes mellitus (DM) and morbid obesity. The clinical manifestations may include nephritic syndrome with severe renal failure (acute or rapidly progressive), microscopic hematuria, oliguria, edema, hypocomplementemia, hypertension, and nephrotic (21-48%) or non-nephrotic proteinuria.[1,2] We presented a case of crescentic SAGN which was successfully managed with intravenous (i.v.) pulse methylprednisolone.

CASE PRESENTATION

A 59-year-old male patient with normal basal creatinine level was hospitalized in our nephrology clinic to investigate the etiology of acute kidney injury and to treat hypervolemia. He had fatigue, oliguria, bilateral lower extremity edema, and erythema on the left leg, which had begun 10 days ago. Oral ciprofloxacin and amoxicillin were given to the patient for cellulitis at another hospital. He was diabetic for 4 years and was taking oral antidiabetics. On the physical examination, high blood pressure of 160/90 mm Hg and tachycardia were detected. Grade 2/6 systolic mitral murmur and rales were heard on the auscultation of heart and right lung, respectively. Bilateral pretibial pitting 2+ edema and cellulitis were observed on his left leg. The laboratory findings of the patient were summarized in Table 1.

Evaluation of the initial laboratory parameters showed white blood cell (WBC) count of 17,600/µL (neutrophils 78.1%), hypoalbuminemia, mild hyponatremia, and high levels of urea, creatinine, phosphorus, uric acid, erythrocyte sedimentation rate, C-reactive protein (CRP), and HbA1c 7.9%. The other biochemical and hematological parameters were within normal limits. In urinalysis, 28 leukocytes/high power field (HPF), red blood cells (45/HPF), protein 3+, and leukocyte esterase 2+ were present. Predominantly right-sided bilateral pleural effusion was observed on chest x-ray. Echocardiography revealed an ejection fraction of 65% and mild mitral and tricuspid valve regurgitations. Urinary ultrasonography was normal. Ocular examination revealed neither diabetic nor hypertensive retinopathies. The level of C4, IgG, IgA, IgM, and anti-streptolysin O were all normal except decreased level of C3 0.14 (0.79-1.52 g/L). Antinuclear antibody, anti-dsDNA, anti-neutrophil cytoplasmic antibody (MPO-ANCA, PR3-ANCA), and anti-glomerular basement membrane antibodies were all negative. Urinary protein excretion was 6.6 g/day, and urine cultures were negative. Because of cellulitis and a high level of CRP, linezolid (2× 600 mg, i.v.) was given with the suggestion of the department of infectious diseases. There was no growth in blood cultures taken before the antibiotic treatment. Despite the i.v. administration of furosemide in addition to fluid and salt restriction, the patient was still oliguric and hypervolemic. Levels of urea and creatinine increased to 171 mg/dL and 5.1 mg/dL, respectively. Three sessions of the hemodialysis and ultrafiltration were performed due to hypervolemia and the presence of uremic symptoms. Rapid deterioration of kidney functions continued during the antibiotic therapy. Renal biopsy was performed for the possibility of rapidly progressive glomerulonephritis (RPGN) (Figures 1 and 2).

Cellular crescent was seen in 50% of glomeruli in light microscopy. During the immunofluorescence (IF) examination, IgA deposition in diffuse-global form with 2+ intensity and C3 deposition in diffuse-segmental form with 1+ intensity, mostly in the mesangium and locally in the peripheral capillary walls, were detected. Once the infection was under control, 500 mg pulse

Table 1. Laboratory Findings on Admission and Follow-Up of the Patient

	Admission	First Month	Third Month
White blood cell (/µL)	17 600	8500	7800
Hemoglobin (g/dL)	14	13.6	14.2
Platelet (10^3/µL)	170	180	220
Total protein (g/dL)	5.1	6.5	7
Albumin (g/dL)	2.62	3.3	3.54
Urea (mg/dL)	94	62	54
Creatinine (mg/dL)	2.49	1.3	1.26
e-GFR (CKD-EPI) (mL/min/1.73 m^2)	27	60	62
Sodium (mEq/L)	134	139	141
Potassium (mEq/L)	4.25	4	4.3
Phosphorus (mg/dL)	5.02	4.3	–
Uric acid (mg/dL)	8.6	7	–
ESR (mm/h)	48	22	18
CRP (mg/L)	163	4.37	2.31
C3 (g/L) (0.79-1.52)	0.14	1.2	1.3
C4 (g/L) (0.16-0.38)	0.16	0.18	0.2
Proteinuria (mg/day)	6600	2100	880

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; e-GFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate.

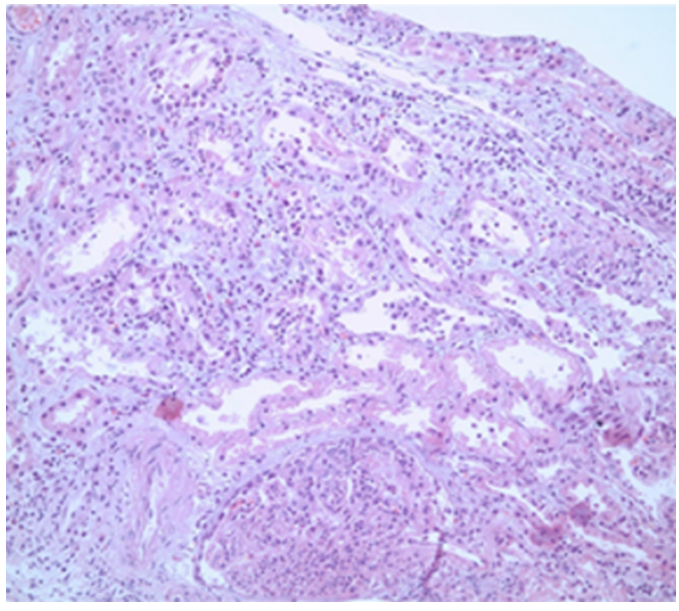

Figure 1. Diffuse exudative endocapillary and extracapillary glomerulonephritis. Note accompanying tubulitis and acute interstitial inflammation.

MAIN POINTS

- The frequent IgA-dominant glomerular immunoglobulin staining is mostly seen on kidney biopsy in Staphylococcus infection-associated glomerulonephritis (SAGN).
- Clinicians should consider SAGN in the presence of new findings of acute kidney injury on the basis of active Staphylococcus infection, hematuria, proteinuria, hypocomplementemia (the typical pattern is low C3 and normal C4 levels), development of rapidly progressive glomerulonephritis, culture positivity (not essential), and underlying risk factors.
- Clinicians should be careful in differentiating SAGN from primary IgA nephropathy, Henoch–Schönlein purpura nephritis, and C3 glomerulonephritis.

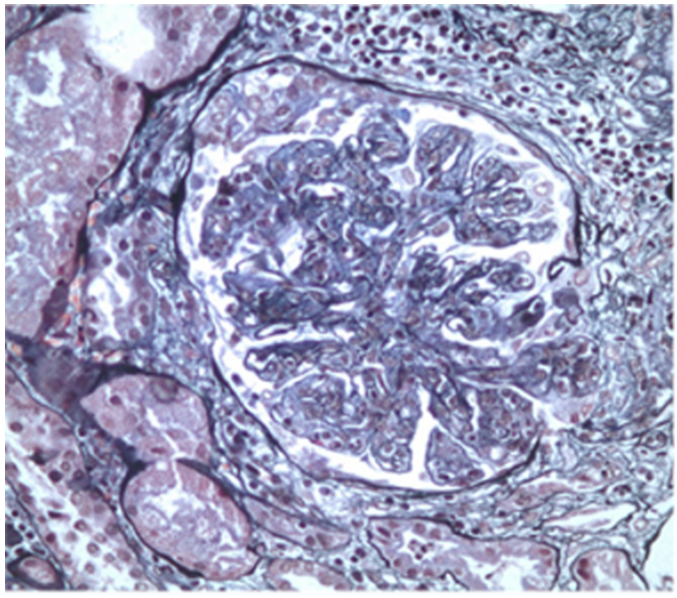

Figure 2. Silver stain emphasizing diffuse endocapillary and segmental extracapillary proliferation.

methylprednisolone treatment was given i.v. to the patient for 3 days due to crescentic GN. Oral methylprednisolone was continued at a dose of 64 mg/day and a dose reduction was planned after 1 month. Creatinine level was 1.3 mg/dL, hematuria and proteinuria (2.1 g/24 h) decreased, and C3 (1.2 mg/L) returned to normal level during the follow-up at the first month of steroid treatment. After 3 months, serum creatinine and proteinuria improved to 1.26 mg/dL and 880 mg/24 h, respectively (Table 1).

Informed consent was obtained from the patient.

DISCUSSION

Unlike the post-infectious GN (PIGN), SAGN occurs due to ongoing active Staphylococcal infections. Therefore, it is not recommended to use the term "post-Staphylococcal GN" for GN caused by *Staphylococcus aureus*.[3] Typical microscopic findings of SAGN in the renal biopsy are inflammatory infiltration with neutrophils and endocapillary and/or mesangial proliferative immune complex GN with crescentic formation, which is seen in 30-40% of the patients. Accompanying mild but active interstitial inflammation is common.[2] Immunofluorescence examination mostly reveals glomerular IgA and C3 (codominant) staining.[4] IgA nephropathy (IgAN), IgA-dominant Henoch–Schönlein Purpura nephritis, and C3 glomerulonephritis (C3GN) are important for differential diagnosis of the pathological findings of SAGN.[5,6] Besides, pathological and clinical findings should be evaluated together during differential diagnosis. IgAN in IF examination is characterized by predominant global mesangial IgA deposition, whereas hypocomplementemia is not a characteristic of IgAN.[1,7,8] IgAN affects younger individuals. SAGN is widespread among elderly diabetic patients and is typically associated with Staphylococcal infections.[8] The presence of an exudative proliferative response with polymorphonuclear leucocytes can support the diagnosis of SAGN over IgAN. Subepithelial hump-like deposits can be seen in electron microscopic (EM) examination in 31-45% of the SAGN cases, whereas such depositions are not present in usual IgAN.[2,4,9] The presence of membranoproliferative GN in kidney biopsy and prolonged hypocomplementemia are more expected to occur in C3GN compared to SAGN. C3 deposition with no significant immunoglobulin deposition is present in IF examination of C3GN. EM examination is indicative of differential diagnosis. However, EM examination could not be performed in our renal biopsy material. In a study of Nasr et al.[10] 82% of the 39 patients with SAGN had hypocomplementemia and 56% had low C3 levels. Our patient also had low C3 level. The diagnosis of our patient was considered as crescentic SAGN due to the history of skin infection, decreased C3 level, negative immunological and viral markers, kidney biopsy, and clinical findings.

Treatment of SAGN is based on antibiotics for the underlying infection. Although the treatment with immunosuppressive agents such as corticosteroids has been reported to be successful in a few studies,[5,11-13] this approach is generally not suggested due to the risk of uncontrolled infection and insufficient level of evidence.[2,3] 2019 Glomerular Disease Consensus Report recommended that SAGN should be considered in the presence of IgA dominance in biopsy and that effective antibiotherapy should be given.[14] It has been suggested that the steroid therapy can be a possible alternative for the cases of IgA-dominant acute PIGN with no improvement in the renal functions after antibiotic treatment.[7,9] The study by Koo et al[8] analyzed clinical data of 7 patients, whose renal biopsy results were compatible with IgA-dominant acute PIGN. The crescentic GN patient with methicillin-resistant *Staphylococcus aureus* (MRSA)-positive culture did not respond to antibiotics but responded to high-dose prednisolone treatment, resulting in complete recovery of renal function and decreased proteinuria. In a study of Eswarappa et al,[12] serum creatinine increased from normal levels to 10.29 mg/dL in a patient with IgA-dominant SAGN. The patient was required intermittent hemodialysis and received pulse i.v. methylprednisolone, which was followed by narrowed dose of oral prednisone. Serum creatinine after 3 months decreased to 1.2 mg/dL. Similar to our case, Kapadia et al[13] reported a patient with psoas abscess and MRSA isolated in blood culture who developed RPGN during antibiotic therapy and was started on hemodialysis. After renal biopsy revealed IgA-dominant crescentic postinfectious GN, the patient received pulse doses of steroids followed by oral steroids. On follow-up after 2 weeks of treatment, the patient was removed off hemodialysis. Negative cultures in our case may be explained by antibiotics given to the patient at another hospital before hospitalization.

Sakthirajan et al[15] evaluated the clinical profiles of 47 patients with crescentic infection-related GN. The most common pathogen and region of infection in the study were MRSA and skin,

respectively. Oral steroid regimen given after pulse steroid treatment had no significant effect on the renal outcomes during the follow-up period.

The long-term prognosis of SAGN is not very good, the disease has progressed to end-stage renal disease at a rate of 41%. Advanced age, high serum creatinine level, tubulointerstitial scarring, DM, and hypertension are the risk factors of poor renal outcome.[2,6]

Although there are insufficient data for the efficacy of immunosuppressive treatment in the patients with crescentic SAGN, methylprednisolone treatment was administered to our patient. The clinical status and laboratory findings of the patient were recovered during follow-up period.

In conclusion, immunosuppression with corticosteroids may be considered in the treatment after the control of infection if there is progression in kidney disease. Therefore, there is a need for further studies with more extensive patient series to improve treatment.

Informed Consent: Informed consent was obtained from the patient.

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