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IgA Nephropathy Flare-Up Mimicking Staphylococcus Post-Infection Glomerulonephritis in Patient with *Staphylococcus Aureus* Infection Treated with Cefazolin: A Case Report and Brief Review of the Literature

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 81
Final Diagnosis: IgA nephropathy flare up
Symptoms: Fever
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare disease

Background: Glomerulonephritis (GN) associated with post staphylococcus infection (PSIGN) and high serum immunoglobulin A (IgA) has been reported recently. Patients with GN after infection with underlying IgA nephropathy create a challenge to determine the etiology of GN. Therefore, treatment should be accordingly, with steroids used if the IgA nephropathy flare-up is determined to be the etiology. The aim of this case report was to shed light on the difference between PSIGN and IgA nephropathy flare-ups in patients with a history of IgA nephropathy, and how to treat patient cases accordingly.

Case Report: An 81-year-old male presented to our Emergency Department complaining of increasing pain, swelling, and redness of his left knee since 2 days ago. He had a history of recent methicillin sensitive *Staphylococcus aureus* (MSSA) left knee arthroplasty infection that was treated with cefazolin, and he had a history of IgA nephropathy diagnosed 1 year ago.

Conclusions: In our patient case, renal biopsy studies were not enough to differentiate between PSIGN and IgA nephropathy flare-ups, thus, clinical presentation was important. PSIGN was found to have a delayed onset compared to IgA nephropathy. Lower serum complement 3 (C3) level, heavier proteinuria, and acute renal failure are common with PSIGN compared to IgA nephropathy. Identifying the etiology and treating our patient accordingly with immunosuppressive therapy had a positive impact on the patient, restoring renal function without further damage.

MeSH Keywords: Glomerulonephritis, IGA • *Staphylococcus Aureus* • Vasculitis

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Background

Glomerulonephritis (GN) associated with predominant immunoglobulin A (IgA) deposition includes IgA nephropathy, Henoch-Schönlein nephritis, lupus nephritis, and rarely post-infectious glomerulonephritis (PIGN) [1]. The most prevalent IgA GN is immunoglobulin A nephropathy, particularly in the Asia-Pacific region. Approximately one-third of patients with IgA will develop end-stage kidney disease. Risk factors associated with IgA GN are persistent proteinuria, diminished kidney function, and hypertension [2]. Streptococcal, staphylococcal, and gram-negative bacterial infections have been found to be related to 28–47%, 12–24%, and 22% of PIGN cases, respectively [3]. Post staphylococcus infection glomerulonephritis (PSIGN) creates a challenge in patients with a history of IgA nephropathy. The prevalence of PSIGN is well describe in the literature, however, IgA nephropathy flare-up after staphylococcus infection is not well studies or documented.

Treatment of IgA consists of angiotensin converting enzyme inhibitors (ACEIs) and/or steroids for persistent proteinuria. PSIGN is often treated with antibiotics to ensure preventing staphylococcus antigen dissemination to different areas of the body [3,4]. The challenge for clinical practitioners is to differentiate between PSIGN and IgA nephropathy in order to treat the patient properly. Wen et al. compared IgA predominant PSIGN and idiopathic IgA based on kidney biopsies taken from patients and found that IgA nephropathy was statistically significantly associated with lower microscopic hematuria, normal serum C3 complement, serum creatinine 2.2±2 mg/dL, and increased serum IgA [1].

Henoch-Schönlein purpura (HSP) is an immune-complex mediated vasculitis that characterized by palpable purpura, diffuse abdominal pain, and arthritis (arthralgia) [5]. It occurs in 10 to 22 persons in 100 000 each year in children more than adults do. This version of vasculitis is under-diagnosed due to low prevalence and difficult diagnosis. We reported a case of a patient with rapid decline in renal function and lower extremities vasculitis after MSSA left knee infection has been treated with cefazolin, who has a history of IgA nephropathy. The aim of this case report was to discuss the challenges of differentiating between IgA nephropathy flare-up and PSIGN with a brief literature review. To our knowledge, this is the first case report that discussed a clinical scenario in which PSIGN and IgA nephropathy flare-up along with HSP are suspected.

Case Report

An 81-year-old male presented to the Emergency Department complaining of shortness of breath, fever, nausea, vomiting, increasing pain, swelling, and redness of the left knee since 2 days ago. The patient had a left knee arthroplasty done in 2000, which was explanted in February 2017 due to MSSA infection and re-implanted early in 2018. On October 2018, he had an incision and drainage procedure due to infection; the drainage culture grew MSSA again. The patient's spouse reported that he had decreased urine output with bilateral petechial rash on the lower extremities, extending to the thighs. The patient had significant medical history of IgA nephropathy confirmed on kidney biopsy last year, multiple myeloma that was in remission, atrial fibrillation with a pacemaker, hypertension, and congestive obstructive pulmonary disease. Home medications include cefazolin 1 g intravenous (IV) q12h, rifampin 600 mg orally daily, warfarin 3 mg orally daily, metoprolol succinate 50 mg orally daily, atorvastatin 10 mg orally daily, and gabapentin 300 mg orally daily. Laboratory test results on admission were WBCs 11 000 with 85% segments, hemoglobin and hematocrit were 8.8 g/dL and 26% respectively, platelet count 239, BUN 44, and creatinine 2.14 mg/dL (baseline=2 mg/dL). Microscopic urine analysis was positive for blood and had >500 mg/dL protein. The Infectious Disease Team was consulted, and cefazolin was switched to vancomycin. The orthopedic surgeon had performed an incision and drainage procedure and found a large area of purulent material and necrotic tissue; tissue sample was sent for further microbiological analysis, which turned out to be negative. Later on, an antibiotic spacer was placed when the patient became clinically stable. On day 3 of hospital admission, serum creatinine and BUN had trended up to 2.94 mg/dL and 54 respectively. The patient had increased petechial rash, and he became hypertensive and developed acute respiratory distress. The patient was found later to have volume overload that induced hypertension and atrial blood gas tests revealed severe respiratory acidosis. Renal ultrasound showed bilateral renal atrophy. The patient's family refused hemodialysis, so furosemide IV was started. The 24-hour protein urine collection showed 857 mg/dL and the immunofixation test on urine showed IgA monoclonal protein with lambda light chain specifically. Serum C3 complement was within normal range and serum IgA was high. Pulse dose methylprednisolone was started after ruling out PSIGN (1 g IV×1, then 40 mg oral prednisone daily). Furosemide and oral steroid doses were tapered down during the hospital stay to 40 mg and 20 mg orally daily respectively. Serum creatinine trended up to 3.1 mg/dL, however, gentle hydration, diuretic therapy, and oral steroid helped in serum creatinine reduction to 2.25 mg/dL on discharge. His petechial rash was diminished and improved through the hospital stay after starting steroid IV therapy and switching cefazolin to vancomycin. His rash looked similar to HSP; however, no skin biopsy was obtained. So, the final diagnosis was not confirmed.

Discussion

Post infection GN represent a challenge in patients with staphylococcus infection. Prevalence of PSIGN is well described in

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the literature. The cornerstone treatment is to eradicate the infection since super antigens induce the disease and resulted in increased production of inflammatory mediator such as cytokines, immunoglobulins IgG and IgA, and subsequently, formation of immune-complexes (ICs) consisting of IgA and IgG in the circulation. These ICs can cause glomerulonephritis and vasculitis [6].

Treatment becomes tricky in patients with underling autoimmune kidney diseases such as IgA nephropathy. Our patient had IgA nephropathy that was under-control with a baseline serum creatinine of 2 mg/dL prior to the index event. GN and bilateral lower extremities vasculitis occurred within a few days after an incision and drainage procedure was performed due to MSSA left knee infection, and the initiation of cefazolin. Determining if GN was secondary to MSSA infection or IgA nephropathy flare-up was crucial to appropriate treatment. It is important not to treat patients with PSIGN with immunosuppressive therapy (steroids) since it will delay/hinder infection eradication. Therefore, efforts to differentiate between PSIGN and IgA nephropathy, as in our case, may be necessary.

Renal biopsies studies are not enough to differentiate between PSIGN and IgA nephropathy flare-up, thus, clinical presentation is important. Satoskar et al. studied the differences between PSIGN and IgA nephropathy by comparing renal biopsy results and clinical presentation of 16 patients in the United States [7]. They found that PSIGN had a delayed onset compared to IgA nephropathy (5 weeks versus 1 to 2 days post infection); serum complement 3 (C3) level was low or low normal and IgA was normal. Additionally, heavier proteinuria was associated with PSIGN usually in the nephrotic range, acute renal failure was common upon presentation compared to IgA that was uncommon, and serum cryoglobulins may be present in PSIGN compared to IgA that is usually absent. These findings were similar to those found by Wen et al. [1] mentioned earlier.

Unfortunately, we were unable to obtain a kidney biopsy in our case to confirm IgA disposition, however, the clinical presentation of our patient correlated with IgA nephropathy more than PSIGN. Our patient had very high serum IgA, normal serum C3, onset index was 2 days, there was no gross proteinuria (nephrotic range), and no acute renal dysfunction on presentation. In this particular case, we were leaning toward IgA nephropathy flare-up since our patient had an established diagnosis of IgA nephropathy. A methylprednisolone pulse dose was started due to aggressive deterioration of serum creatinine during his hospital stay (3 mg/dL on day 5) and progressive vasculitis that extended bilaterally to both thighs. So, methylprednisolone at 1000 mg was given, then oral prednisone at 20 mg daily, continuously.

Another issue encountered in our patient was the petechial purpura rash that looked similar to vasculitis (palpable purpura). We had excluded HSP (IgA vasculitis) since no abdominal pain or arthritis existed. Normal thrombocyte counts excluded thrombocytopenia purpura. Serum anti-neutrophil cytoplasmic antibodies (ANCA) were negative and by this ANCA vasculitis was excluded as well. That lead us to believe that it could be leukocytoclastic (hypersensitivity) vasculitis, and based on that, cefazolin was switched to vancomycin. The infection or cefazolin or both could induce the rash. One case reported in the literature described cefazolin-induced leukocytoclastic vasculitis which was similar to our patient, however, the diagnosis was confirmed by skin biopsy which we do not have.

Overall, the patient's renal function continued to improve over his hospital stay. His serum creatinine upon discharge was 2.25 mg/dL, his vasculitis had completely resolved, and the patient had no signs or symptoms of systemic infection. We switched from vancomycin to daptomycin for ease of administration (q48hrs for creatinine clearance <30 mL/min) and equal efficacy for treatment of MSSA infection.

Conclusions

In this case report, we shed light on different etiologies of GN associated with IgA disposition. We discuss the importance of identifying the etiology to initiate appropriate treatment with immunosuppressive agents (steroids) in patients with underlying active infection process. Patients with a history of IgA nephropathy with an active *S. aureus* infection should be monitored closely during hospitalization and in the outpatient arena.

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