Disparate effects of methicillin-resistant Staphylococcus aureus infection on renal function in IgA-dominant infection-associated glomerulonephritis and menstrual toxic shock syndrome: a case report and literature review

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Abstract
The sudden outbreak of severe acute respiratory syndrome coronavirus 2 pneumonia posed a significant challenge to medical professionals because treatment of critically ill patients requires the efforts of a multidisciplinary team. To highlight this principle, we examined acute kidney injury (AKI) in IgA-dominant infection-associated glomerulonephritis (GN) and menstrual toxic shock syndrome (mTSS). Both GN and mTSS are rare diseases caused by staphylococcal infection, and

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renal function is frequently impaired. The resulting AKIs are disparate pathological entities driven by distinct immune mechanisms. We begin by describing the case of a diabetic man with pyopneumothorax following methicillin-resistant *Staphylococcus aureus* (MRSA). He had endocapillary proliferative GN with *in situ* IgA-dominant immune-complex formation in the mesangium accompanied by complement C3 deposition in the glomerular capillary wall. By contrast, acute tubular necrosis was observed in a case of mTSS; the patient’s immune response was stimulated differently by MRSA enterotoxin and exotoxin resulting in aberrant IgA deposition, complement activation, and insufficient antibody production. As a multidisciplinary communication covering the fields of nephrology, immunology, and pathology, this report may help clinicians to understand these distinct renal lesions and make optimal therapeutic decisions expeditiously.

**Keywords**
Acute kidney injury, infection-associated glomerulonephritis, IgA, menstrual toxic shock syndrome, *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, renal pathology

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**Introduction**

The sudden outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia in Wuhan caught the majority of the medical community off guard.\(^1\) Our previous work reported another *de novo* zoonotic viral disease recently found to be transmissible in humans and cautioned against potential spread.\(^2\) Among critically ill patients who died from coronavirus disease 2019 (COVID-19), 67.0%, 29.0% and 13.5% had acute respiratory distress syndrome, acute kidney injury (AKI) and nosocomial infections, respectively.\(^3\) In the face of this grim situation, Chinese medical staff, clinicians and researchers alike, formed a multidisciplinary team (MDT) under the leadership of prominent academician Nan-Shan Zhong.\(^4\) In the spirit of the MDT concept, we describe two pathologically disparate cases of AKI in serious pulmonary infection and a rare form of severe sepsis. Both cases were caused by *Staphylococcus aureus*. We begin by discussing postinfectious glomerulonephritis (GN).
histologically exhibit endocapillary hypercellularity and neutrophil infiltration. In affected patients, these changes may predispose to AKI. Indeed, Haas et al.\textsuperscript{11} found that only 2% of patients in their cohort had a peak serum creatinine (Scr) within the normal range. Alternatively, \textit{S. aureus} may also cause a severe infection called menstrual toxic shock syndrome (mTSS) in which AKI is almost unavoidable.\textsuperscript{12}

AKI may be an active participant in the infection rather than a consequence. We consistently found that compromised renal function may expose immunosuppressed patients with kidney disease to higher risk of severe infection.\textsuperscript{13,14} Hence, clinicians should be familiar with the bidirectional interactions between infection and AKI, a lesson learned in the recent battle against COVID-19.\textsuperscript{3} The roles of staphylococcal superantigens and immune-mediated injuries in AKI are also discussed.\textsuperscript{15} Hopefully, our report will promote multidisciplinary collaboration and enable comprehensive treatment by providing a central source of information.

**Case 1**

A 47-year-old diabetic man was referred to our facility with fever, pneumonia, pyopneumothorax and AKI (Figure 1). He had been taking oral prednisone for Sjögren syndrome for 6 months; the dose was tapered to 10 mg daily prior to admission. Upon arrival, his temperature was 39.3°C and he was experiencing hemoptysis and dyspnea. Laboratory tests showed white blood cells (WBCs) of $11.3 \times 10^{9}$/L with 94.8% neutrophils, a T-lymphocytes of $320/\mu$L (reference 690–1760/\mu$L), hemoglobin 110 g/L (130–150 g/L), platelets $127 \times 10^{9}$/L (100–300 $\times 10^{9}$/L), plasma albumin 32.1 g/L (40–55 g/L), Scr 155.6 \mu mol/L (88.4–132.6 \mu mol/L) that was normal 1 month \textit{ex ante}, fasting blood sugar 8.7 mmol/L (3.9–6.1 mmol/L), total triiodothyronine 1.0 pmol/L (1.3–3.1 pmol/L), IgG 4.1 g/L (7.2–16.5 g/L), IgA 0.97 g/L (0.69–3.28 g/L), complement C3 1.02 g/L (0.85–1.93 g/L) and C4 0.22 g/L (0.12–0.36 g/L), C-reactive protein 470.9 mg/L (<10 mg/L), procalcitonin 1.89 ng/mL (<0.05 ng/mL), and (1,3)-\beta-D-glucan 23.7 pg/mL (<10 pg/mL). Urinalysis showed 3+ occult blood and 1+ protein. Further diagnostic workup was negative for antistreptolysin O, antinuclear, antglomerular basement membrane and antineutrophil cytoplasmic antibodies. Serum immunofixation electrophoresis was also negative. Methicillin-resistant \textit{S. aureus} (MRSA) was isolated from both blood and purulent thoracic drainage. During his hospital stay, the patient was placed under stringent glycemic control, administered intravenous vancomycin and oral fluconazole, and underwent bronchoscopy and pleural washout. Accordingly, his AKI was mitigated but not fully recovered in tandem with his pulmonary infection. Until then the patient reluctantly accepted the renal biopsy that was previously declined. The result confirmed a diagnosis of IgA-dominant infection-associated GN. The patient’s Scr eventually returned to normal range (77.7–mol/L).

**Case 2**

A previously healthy 16-year-old menstruating girl was rushed to our emergency room with fever and hypotension. She had neither vaginal discomfort nor abnormal discharge. Upon admission, her temperature was 37.5°C with a pulse of 137 beats/minute, a respiratory rate of 37 breaths/minute, and a blood pressure of 70/33 mmHg. Extensive skin ecchymosis was visible throughout the body (Figure 2). Subsequent laboratory tests showed WBCs of $90.3 \times 10^{9}$/L with 91.6% neutrophils, hemoglobin 71 g/L, platelets 18 $\times 10^{9}$/L, plasma albumin 58.2 g/L, Scr 132.0 \mu mol/L, complement C3
0.60 g/L, C-reactive protein 195.5 mg/L, and procalcitonin >100 ng/mL. Liver function test results were abnormal with no specific pattern of abnormalities. Bedside chest plain film and blood cultures yielded negative findings. Furthermore, biopsy of the bone marrow and skin lesions revealed grossly normal hyperplasia and leukocytoclastic vasculitis, respectively. Methicillin-sensitive *S. aureus* was identified from cultures of purulent secretions from buttock skin lesions and palmoplantar desquama-
tions that occurred during her hospital stay. All lines of evidence confirmed a diagnosis of mTSS and treatment included intravenous piperacillin and tazobactam and supportive measures. Her Scr once surged to 800.0 μmol/L with anuria and hypoxemia, requiring renal replacement therapy and mechanical ventilation, respectively. The patient’s condition stabilized after intensive care and her urine volume began to recover. Nonetheless, renal biopsy was performed and expectedly showed acute tubular necrosis with ischemic injury. After 45 days, the patient showed near-complete recovery except for an Scr of 141.2 μmol/L.

**Discussion**

The development of modern medical science has been greatly specialized within...
each discipline, resulting in great depth but narrow focus. This fine division may create invisible barriers among individual medical branches, rendering clinicians less familiar and knowledgeable beyond their field of specialty. Delayed nephrology consultation for patients with acute renal failure was associated with increased mortality. We found that a multidisciplinary therapeutic approach was vital in managing critically ill cancer patients with AKI. More recently, the survival of patients with severe COVID-19 pneumonia reportedly depended on a similar approach.
To further highlight the MDT concept, we describe two cases of AKI in patients with GN and mTSS.

MRSA infection is still prevalent in developing countries\(^{19}\) and *Staphylococcus* is now three times more common than *Streptococcus* as the causative agent of acute postinfectious GN in the elderly population.\(^{20}\) The situation is more precarious in hemodialysis patients in whom MRSA accounts for the majority of bacterial infections.\(^{21}\) The high prevalence of staphylococcal infection may result in increased incidence of IgA-dominant infection-associated GN. However, this is sometimes overshadowed by the systemic manifestations of infection itself and thus easily overlooked. Therefore, attending clinicians should be more aware of this disease in all aspects, especially its mechanisms, glomerular abnormalities, differential diagnosis and prognosis of renal function.

IgA-dominant infection-associated GN exhibited a male predominance of roughly 4:1, higher than the male-to female ratio of 2:1 reported for poststreptococcal glomerulonephritis.\(^{22}\) In addition, 55% of diagnosed patients had underlying diabetes.\(^{19}\) The principal pathologic mechanisms are now thought to be *in situ* IgA-dominant immune-complex formation and direct activation of plasmin by bacterial antigens, which may lead to complement activation and inflammation within the glomerulus.\(^{23}\) Interestingly, intense C3 deposition as shown in Figure 1 is a hallmark of this disease and can help distinguish it from IgA nephropathy or IgA vasculitis.\(^{24}\) In MRSA-associated cases, staphylococcal enterotoxin may act as a superantigen, which during inflammatory cascades binds to antigen-presenting cells promoting massive T cell activation, production of proinflammatory cytokines and secretion of IgA.\(^{25,26}\) The advanced glycation end-products in diabetic patients were speculated to be responsible for decreased IgA clearance and/or increased synthesis.\(^{27}\) Because of aberrant IgA deposit and complement activation, the major pathological changes in the glomeruli are endocapillary (63.3%), mesangial (31.8%) and crescent GN (4.9%).\(^{9}\)

Based on these pathological changes, the clinical renal presentations of IgA-dominant infection-associated GN may include AKI, hematuria, proteinuria, and hypertension; these overlap considerably with the presentation of general postinfectious GN. In our experience, this disease should be suspected in patients who present with acute GN in the setting of infection, especially in those with known susceptibility to *S. aureus* and/or diabetes. In this context, the main differential diagnoses consist of poststreptococcal GN, systemic lupus erythematosus, Goodpasture’s syndrome, antineutrophil cytoplasmic antibody-associated vasculitis and monoclonal gammopathy.\(^{28}\) This undertaking requires recognition of subtle risk factors, monitoring for occult clinical symptoms and careful attention to laboratory results.\(^{14}\)

The kidney is one of the most affected organs during multiple organ failure associated with sepsis.\(^{29}\) and mTSS places renal function in dire jeopardy.\(^{30}\) In an early report, full-swing acute renal failure was observed in all nine fatal cases of mTSS.\(^{31}\) Unlike IgA-dominant infection-associated GN, *S. aureus* exotoxin rather than enterotoxin is responsible for mTSS and associated multiple organ failure. Because bacterial invasion of the blood is minimal\(^{31}\) and antibody responses against exotoxin are weak,\(^{12}\) AKI is mainly caused by hemodynamic perturbances, direct injury caused by the exotoxin or both. Thus, staphylococcal superantigens may play a role by enhancing the deleterious actions of the exotoxin and deficiencies in the host’s immune system are implicated.\(^{32}\) Therefore, acute tubular necrosis is predominantly observed in comparison with the glomerular injury in
immune-mediated GN (Figure 2). Perplexingly, a number of children with COVID-19 were found to have features in common with TSS according to a recent BMJ report.33 Hence, clinicians need to be aware of any existing and emerging evidence related to this syndrome.

Treatment of IgA-dominant infection-associated GN is primarily focused on achieving control of the precipitating infection and giving supportive measures. Vancomycin has been the cornerstone for treatment of MRSA infections.34 However, this agent may also cause AKI35 and Scr-dependent fine dose adjustment is recommended.36 Glucocorticoids are presumably of little help according to previous reports.37,38 About half of patients may regain initial renal function, whereas end stage renal disease developed in approximately 20% of patients.39 Our report found that recovery of renal function may lag behind recovery from pulmonary infection. Clearance of immune complexes from the glomeruli is a function of time.40 Nonetheless, any protracted recovery of renal function warrants the participation of nephrologists to rule out persistent injury within the glomeruli by renal biopsy. The safety of this procedure was recently questioned in immunocompromised patients or patients with unbridled infection because of the potential risk of sepsis41 or perinephric abscess.42

Figure 3. Chest CT evolution of a patient with COVID-19, who initially presented with incident proteinuria and showed no signs of respiratory disease. A and B. The first CT scan showed patchy ground-glass opacity and a negative nucleic acid test conducted on the same day. C and D. Corresponding slices of the second CT scan 5 days later showed progressive pulmonary lesions. Two more nucleic acid tests between the two scans remained negative and the fourth one, conducted 2 days after the second scan was positive. We speculate that proteinuria was likely a renal involvement of COVID-19.
We believe that renal biopsy is preferable for cases with uncertain diagnosis or prognosis and should be handled with discretion in cases with bacteremia or septicemia, such as mTSS, in which the etiology of AKI is less ambiguous.

Today we are engaged in containing COVID-19, which requires that we are clinicians first and specialist physicians second. Though conceived in the view of nephrology, we tried to convey an important message that latent diseases associated with a *prima facie* renal injury should be carefully considered in light of the MDT concept. Thus, we prepared this report as a review instead of a case series. As such, inflammatory cascades such as those induced by staphylococcal superantigens may evolve into cytokine storms. In this regard, the mechanism of cardiac, pulmonary and renal injury in COVID-19 is believed to be a systemic cytokine storm syndrome and/or direct cellular injury caused by the virus. A patient with SARS-CoV-2 fulminant myocarditis in moribund condition was successfully saved following treatment with glucocorticoids and human immunoglobulin. In February we successfully identified an asymptomatic patient with pneumonia (Figure 3) who initially presented with incident proteinuria. He received four nucleic acid tests for SARS-COV-2 within 7 days while in preemptive isolation, with only the last being positive. Supporting our rationale, a more recent report found that 34% of patients with COVID-19 developed massive albuminuria on the first day of admission. We aim to share this frontline knowledge with fellow medical staff fighting the current pandemic.

Using evidence from a variety fields of expertise, we re-examined two cases of AKI in patients with IgA-dominant infection-associated GN and mTSS from the perspective of the underlying immune responses, mechanisms of damage, structural changes of the nephron and timing of biopsy. Our experience may be of help to clinicians in general and infectious disease specialists in particular when combating intractable and sometimes inexorably lethal disease such as COVID-19.

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Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Ethical approval
The study was approved by the Ethics Committee of Hebei General Hospital and written informed consent was obtained from patient (case 1) or the guardians (case 2).

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