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Diagnostic Challenges of Infection-Related Glomerulonephritis: A Case of Progressive AKI in the Setting of Osteomyelitis Clarified through Renal Biopsy

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Abstract

Acute kidney injury (AKI) and glomerulonephritis have diverse causes and pathophysiology. Infection-related glomerulonephritis varies in presentation and pathology depending on the pathogen and severity. Classically, exudative glomerulonephritis results from the infiltration of neutrophils; however, this is complicated by multifactorial glomerular injury, including medical comorbidities and nephrotoxic agents [1]. A 73-year-old female presented with worsening renal function following treatment for a soft tissue infection of the left third toe. The patient developed uremic symptoms during a course of sulfamethoxazole-trimethoprim, which was subsequently discontinued given concerns for drug-induced AKI. Despite discontinuation of the medicine and conservative treatment for suspected osteomyelitis, renal dysfunction progressed. Renal biopsy revealed exudative glomerulonephritis consistent with an infectious process and acute tubular necrosis (ATN). Subsequently, definitive source control was achieved through surgical intervention for the osteomyelitis. This case emphasizes the importance of source control for cases refractory to parenteral antibiotics and emphasizes the importance of renal biopsy histopathology for management.

Keywords

Infection-Related Glomerulonephritis, Osteomyelitis, Acute Kidney Injury, Post-Infection-Related Glomerulonephritis, Renal Biopsy

1. Introduction

Acute kidney injury (AKI) has a broad differential diagnosis and range of patho-

physiology. The presentation and pathology of infection-related glomerulonephritis (GN) vary depending on the severity of infection, the pathogen itself, and the overall infectious course. Infection-related GN presents with non-specific symptoms that can often mimic other conditions, leading to potential delays in diagnosis [2]. Exudative GN is classically characterized by the infiltration of neutrophils, resulting in glomerular injury. Additionally, C3 deposition in the mesangium and capillary walls (with or without immunoglobulin) is also consistent with exudative GN; however, it is not exclusive to this pathophysiology, given that these can be present in complement glomerular pathologies [1]. Moreover, this is often complicated by multifactorial glomerular injury with medical comorbidities and nephrotoxic agents, which can overall mask the initial etiology and renal injury can progress. The complexity of the pathology requires maintaining a broad differential diagnosis and a multidisciplinary discussion to approach these cases for optimal patient outcomes.

This case demonstrates an atypical presentation of exudative GN associated with an infectious process despite culture negativity and conservative treatment with antimicrobials. Previous literature has noted the diagnostic challenges of culture-negative pauci-immune GN [3]. Additionally, this emphasizes the crucial role of renal biopsy in elucidating underlying pathology and subsequent management for complex AKI management. A multidisciplinary approach allotted guidance on IV antibiotics, volume expansion, and ultimately, source control was pursued through surgical intervention for definitive osteomyelitis management. Depending on the initial patient presentation, an appropriate diagnosis can be delayed.

Infection-related GN, previously called post-infectious GN, is increasing within adults and elderly populations. It contains a spectrum of inflammatory-mediated glomerular injury resultant from bacterial, viral or fungal pathogens [1]. Infection-related GN classically presents with hematuria, proteinuria and declining renal function. Diagnostic challenges occur given common features between other glomerular injuries, including drug-induced renal injury and acute tubular necrosis (ATN). Management involves supportive care and treatment of the underlying infection; however, renal biopsy is often necessary for definitive diagnosis and guidance of therapy. Raising awareness of atypical presentations of infection-related GN can improve recognition, guide therapy, and ultimately improve patient outcomes.

2. Case Report

A 73-year-old female with a past medical history of valvular atrial fibrillation on warfarin, severe aortic stenosis, heart failure with preserved ejection fraction, hypertension, hypothyroidism, gout, and obesity. She was diagnosed with a soft tissue infection of the foot and treated with antibiotics on an outpatient basis who presented with complaints of abdominal pain and nausea and was admitted to the inpatient service for acute renal failure and for IV antibiotics.

The patient was diagnosed with a soft tissue infection involving the middle digit of her left foot in an outpatient setting. She was started on a course of sulfamethoxazole-trimethoprim. Shortly after initiating treatment, she developed symptoms of nausea and abdominal pain, with associated arm spasms, intermittent vomiting, and uremic symptoms. The patient was anticoagulated on warfarin and additionally noted to have intermittent hematuria but denied dysuria or flank pain. However, she denied fever, chills, dysuria, chest pain, orthopnea, or dyspnea. On presentation, the patient was afebrile and hemodynamically stable. Laboratory findings were notable for a serum creatinine of 4.86 mg/dL (baseline approximately 0.8 mg/dL the month prior). Additional laboratory findings included nephrotic-range proteinuria (4 - 5 g/day), anemia (hemoglobin 8.4 g/dL), and elevated inflammatory markers, including C-reactive protein (CRP) of 2.0 mg/dL and erythrocyte sedimentation rate (ESR) of 111 mm/h. Diagnostics notable for renal ultrasound with multiple cysts, however, without hydronephrosis. MRI findings of subtle abnormal marrow signal within the distal half of the third digit distal phalanx, suggestive of osteomyelitis given the proximity to skin ulcer (Figure 1).

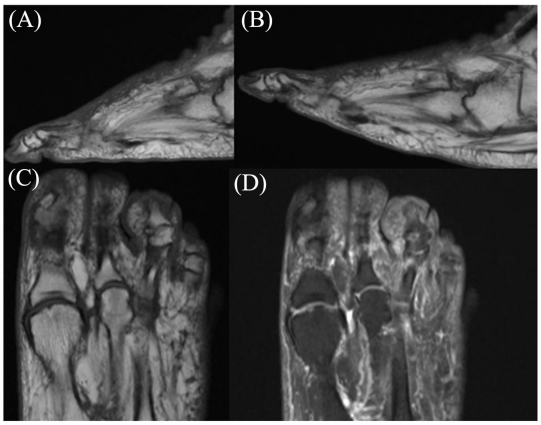

Figure 1. MRI of the left lower extremity consistent with osteomyelitis. MRI of extremity with subtle abnormal marrow signal within distal half of third digit distal phalanx, suggestive of osteomyelitis given proximity to skin ulcer. T1 sagittal (A) and sagittal STIR imaging (B) cross referenced with axial T1 imaging (C) and axial proton density fat-suppressed view (D).

The patient was diagnosed with renal failure suspected in the setting of sulfamethoxazole-trimethoprim and admitted for IV antibiotics in the setting of osteomyelitis. The initial choice of sulfamethoxazole-trimethoprim was provided, given outpatient suspicion of uncomplicated soft tissue infection. Given the significant increase in serum creatinine level during sulfamethoxazole-trimethoprim administration, the antibiotic was discontinued. Upon admission, given the renal function and concern for drug-induced nephrotoxicity, the patient was transitioned to ceftriaxone and vancomycin for broader coverage; this regimen was continued for five days. Given rise in creatinine to 5.9 mg/dL, vancomycin was discontinued in favor of daptomycin for its lower nephrotoxic profile while maintaining gram-positive coverage, and the patient was continued on ceftriaxone. Management included

volume expansion, Nephrology and Infectious Disease consultation, and avoidance of nephrotoxic agents. The creatinine level initially improved after ten days to 3.59 mg/dL. The patient was discharged to a skilled nursing facility with a planned course of 6 weeks of parenteral antibiotics.

Over a course of 5 days, the abdominal pain and nausea worsened, and creatinine continued to climb to 4.1 mg/dL. Additional workup was ordered given the progressive renal failure, which was notable for normal serum C3, elevated serum C4, serum protein electrophoresis did not show monoclonal protein, and serum-free light chain ratio was 0.99. Urine protein to creatinine ratio was 4 g/g. Antinuclear antibody and anti-double-stranded DNA studies were negative. Antimyeloperoxidase, antiproteinase-3, anti-glomerular basement membrane, and cryoglobulinemia studies were negative.

Given progressive renal failure, a renal biopsy was pursued. The progression and clinical course are summarized in **Table 1**. Renal biopsy revealed exudative GN associated with an infectious process and acute tubular necrosis (**Figure 2**). IV antibiotics were continued at that time, however, definitive management of osteomyelitis through surgical intervention was pursued given progressive renal dysfunction. The patient underwent left third toe amputation, followed by ten days postoperative parenteral antibiotics. At two weeks postoperatively, the creatinine level was 2.16 mg/dL. Prior to publication of this case report and images, written informed consent was obtained from the patient.

Table 1. A detailed chronological summary of the patient's presentation, diagnostic workup, treatment interventions, and response to therapy.

Hospital Day	Clinical Course		
	Key Events	Labs	Intervention
Day −10	Started TMP-SMX[a] for foot infection (outpatient)	Creatinine 0.8[b]	-
Day 0	Admitted with abdominal pain, nausea	Creatinine 4.86, CRP 2.0[c], ESR 111[d]	Discontinued TMP-SMX, started IV ceftriaxone + vancomycin
Day 5	Worsening renal function	Creatinine 5.9	Switched to daptomycin + ceftriaxone
Day 10	Renal improvement	Creatinine 3.59	Discharged to SNF[e]
Day 15	Worsening nausea, rising creatinine	Creatinine 4.1	Ordered further serologies
Day 17	Biopsy performed	Biopsy: Exudative GN[f], ATN[g]	Planned surgical source control
Day 19	Left toe amputation	-	Continued IV[h] antibiotics
Day 33	Post-op improvement	Creatinine 2.16	-

[a]TMP-SMX: sulfamethoxazole-trimethoprim, [b]Creatinine Values in mg/dL, [c]CRP: C-reactive protein in mg/dL, [d]ESR: Erythrocyte sedimentation rate in mm/h, [e]SNF: Skilled nursing facility, [f]GN: Glomerulonephritis, [g]ATN: Acute tubular necrosis, [h]IV: Intravenous.

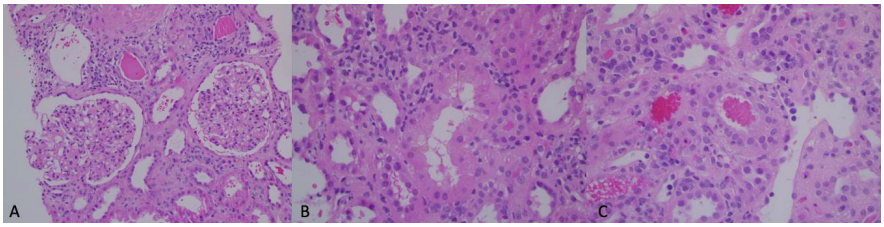

Figure 2. Renal histopathology results consistent with infection-related glomerulonephritis. Renal biopsy yielding exudative glomerulonephritis (A), tubular necrosis (B) and red cell casts (C).

3. Discussion

This case highlights the complex and diverse pathophysiology of AKI in the setting of infection-related GN, and emphasizes the importance of renal biopsy and subsequent source control through surgical intervention. The AKI was initially attributed to drug-induced ATN, given the recent exposure to medications. Sulfamethoxazole-trimethoprim has been associated with renal injury, including ATN and acute interstitial nephritis [4]. However, despite the discontinuation of the suspected offending medications and conservative management, the renal function continued to decline, prompting further evaluation and ultimately source control with surgical intervention.

Clinicians must remain vigilant for deeper infectious processes, including insidious infection resulting in renal failure, especially given an increased incidence of infection-related GN within adults over time [5] [6]. The current suggested pathophysiology of infection-related GN involves a combination of circulating pathogen antigens and the subsequent immune response. Bacterial antigens may localize within the glomeruli, activating complement pathways and recruiting neutrophils, which results in exudative glomerular injury [6]. This process aligns with mechanisms observed in post-streptococcal and staphylococcal GN. In this case, the sustained inflammatory response from the osteomyelitis likely played a contributory role in the development of glomerular pathology.

A significant diagnostic challenge in this case was the delayed recognition of an underlying glomerular process, given the treatment of the infection with antibiotic therapy on an outpatient basis, resulting in negative cultures and subsequently, despite treatment with alternative antibiotics, the renal function continued to decline. The provision of antibiotics on an outpatient basis is common practice for soft tissue infections, despite guidelines recommending delaying treatment for cultures if the patient is clinically stable [7]. Prior outpatient antibiotic therapy likely masked the initial presentation with inflammatory markers as well. Specific inflammatory markers have been shown to increase the likelihood of osteomyelitis if ESR is >60 mm/h and CRP level is >7.9 mg/dL [8]. However, like in this case, the CRP was marginally elevated, and the ESR was noted to be 111 mm/h, raising suspicion for osteomyelitis. Moreover, current literature supports that these are non-specific and have been demonstrated to be elevated and positively correlated with renal interstitial inflammatory cell infiltration in drug-

induced acute tubulointerstitial nephritis [9]. Prior studies have emphasized culture-negative pauci-immune GN, and this case additionally emphasizes the need for comprehensive evaluation given the diagnostic challenges [3]. Infection-related GN was lower on the differential diagnosis initially due to the subacute, nonspecific presentation and absence of positive cultures or classic signs of systemic infection. Additionally, the patient's recent exposure to known nephrotoxic agents biased the differential toward drug-induced injury and ultimately, the patient had been receiving appropriate antimicrobial therapy treating the infection. There is a clear role in maintaining a broad differential diagnosis and if progression of renal failure despite conservative measures, therefore renal biopsy and histopathology are crucial for navigating these complex cases of renal failure.

Renal biopsy and histopathology played a key role in the definitive diagnosis and ultimately pursuit of source control with surgical resection. Biopsy was notable for acute tubular injury, neutrophilic infiltrate consistent with exudative GN. A multidisciplinary approach was employed, including Nephrology, Infectious Disease, and surgical specialties. This collaboration led to a kidney biopsy, which led to the diagnosis of infection-related GN. Subsequently, the confirmation of diagnosis with histopathology led to definitive source control with surgical intervention. AKI represents a dynamic relationship between hemodynamic compromise, toxin exposure, and immune activation. Early recognition and intervention have been shown to reduce morbidity and mortality [10]. Similarly, perioperative AKI has been associated with poor surgical outcomes, emphasizing the importance of timely diagnosis and multidisciplinary approach [11]. In complex cases like ours, where multiple insults coexist, histopathology remains the cornerstone for targeted management. Increased awareness among healthcare providers for infection-related GN is necessary, given the multifactorial nature of renal pathophysiology. Challenging components of this presentation included the initial indolent infectious presentation. Additionally, this highlights the importance of maintaining a broad differential diagnosis and not anchoring to a single etiology, given that the cause of infection-related GN can often be masked on presentation.

4. Conclusion

This case demonstrates the importance of source control if persistent renal decline despite parenteral antibiotics and the importance of renal biopsy, given the initial masking of infection-related GN. The accurate and prompt identification of atypical presentations enables targeted treatment and can ultimately lead to improved patient outcomes through collaborative efforts.

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Informed Consent

Patient information was de-identified to protect privacy and informed consent for the publication of this case report was obtained in accordance with institutional guidelines.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

AKI	Acute Kidney Injury
ATN	Acute Tubular Necrosis
GN	Glomerulonephritis
ESR	Erythrocyte Sedimentation Rate
CRP	C-Reactive Protein