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Early Repeat Renal Biopsy in Steroid-Resistant Tubulointerstitial Nephritis: A Case of c-ANCA–Associated Vasculitis Initially Presenting as Tubulointerstitial Nephritis

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ABSTRACT

Background: ANCA-associated vasculitis (AAV) typically presents with pauci-immune crescentic glomerulonephritis. Isolated tubulointerstitial nephritis (TIN) as an initial manifestation is rare and may delay diagnosis.

Case Report: A 39-year-old man developed acute kidney injury, with a serum creatinine level of 5.11 mg/dL, after exposure to amoxicillin–clavulanate. Initial renal biopsy revealed acute TIN with eosinophilic infiltration and no crescents. Despite corticosteroid therapy and hemodialysis, renal function did not improve. Two weeks later, the patient developed massive hemoptysis and tested positive for c-ANCA. Repeat biopsy demonstrated pauci-immune crescentic glomerulonephritis, with crescents in 18 of 20 glomeruli. Intensive immunosuppressive therapy was initiated; however, the patient remained dialysis-dependent.

Conclusion: Steroid-resistant TIN may represent an early manifestation of AAV. Although acute TIN is most often drug-related, it should be kept in mind that it may be the first sign of various systemic diseases. Therefore, rebiopsy should not be delayed in treatment-resistant cases.

Keywords: Acute kidney injury, ANCA-associated vasculitis, crescentic glomerulonephritis, renal biopsy, tubulointerstitial nephritis.

INTRODUCTION

ANCA-associated vasculitis (AAV) is a systemic small-vessel vasculitis that commonly involves the kidneys, lungs, and upper respiratory tract. Renal involvement typically manifests as pauci-immune necrotizing crescentic glomerulonephritis and is a major determinant of prognosis.[1,2] Delayed recognition is associated with irreversible nephron loss and progression to end-stage kidney disease.[2] Current international guidelines emphasize early diagnosis and the prompt initiation of immunosuppressive therapy in organ-threatening AAV to prevent permanent renal damage.[3,4]

Although glomerular involvement predominates, isolated or predominant tubulointerstitial nephritis (TIN) as an initial renal manifestation of AAV is rare.[5,6] Such presentations may delay diagnosis, particularly when drug-induced acute interstitial nephritis is suspected.[7] We present a case of c-ANCA–associated vasculitis that initially manifested as isolated TIN and rapidly progressed to crescentic glomerulonephritis.

CASE REPORT

A 39-year-old previously healthy man presented to an outside center with groin pain, where laboratory evaluation revealed acute kidney injury, with a serum creatinine level of 5.11 mg/dL. He was subsequently admitted for further evaluation. Approximately 1 month before admission, he had completed a 14-day course of amoxicillin–clavulanate prescribed for ear fullness. Urinalysis demonstrated 3+ proteinuria and 3+ hematuria, corresponding to approximately 1.4 g/day proteinuria, with approximately 10 white blood cells and 400 red blood cells per high-power field. Daily urine output was approximately 2 L. No peripheral eosinophilia was detected despite marked eosinophilic infiltration on renal biopsy. The patient did not report typical hypersensitivity features, such as fever or rash.

The first biopsy contained 13 glomeruli, five of which were globally sclerotic. Histopathological examination demonstrated marked interstitial edema with dense eosinophilic infiltration and eosinophilic tubular casts, without crescent formation, consistent with acute tubulointerstitial nephritis. Intravenous methylprednisolone, 250 mg daily for 3 days, was administered, followed by oral methylprednisolone at a dose of 1 mg/kg/day for 15 days. Hemodialysis was initiated because of uremic symptoms, particularly nausea, and was continued three times weekly. Histopathological examination demonstrated marked interstitial edema with dense eosinophilic infiltration (Fig. 1a) and preserved glomerular architecture without crescent formation (Fig. 1b).

Two weeks later, the patient developed massive hemoptysis, and serological testing revealed c-ANCA positivity. Intravenous pulse methylprednisolone, 500 mg daily for 3 days, was administered, followed by cyclophosphamide, 1 g, with mesna prophylaxis, administered for a total of six doses. Although the findings of the first biopsy were consistent with tubulointerstitial nephritis, the detection of c-ANCA positivity together with concomitant pulmonary involvement raised suspicion for systemic vasculitis and prompted an early repeat renal biopsy. The repeat biopsy demonstrated 20 glomeruli, 18 of which showed cellular or fibrocellular crescents, consistent with pauci-immune crescentic glomerulonephritis.

The repeat biopsy demonstrated cellular and fibrocellular crescents (Fig. 2a), with a prominent cellular crescent

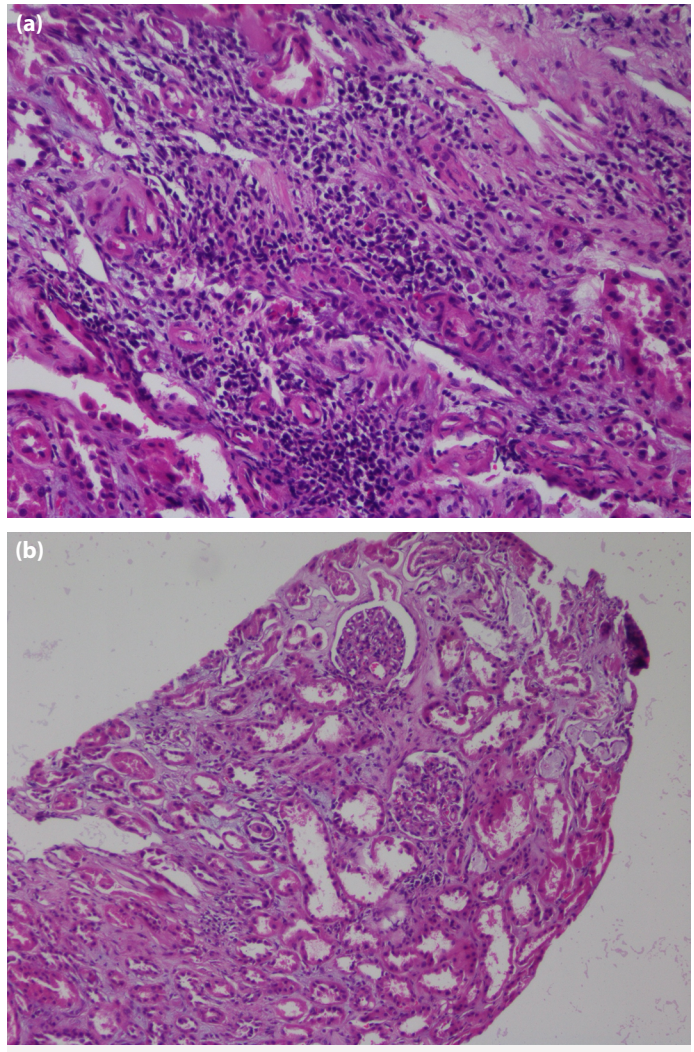

Figure 1. (a) The first renal biopsy specimen demonstrates dense mononuclear inflammatory cell infiltration containing eosinophils (H&E, ×200). **(b)** The first renal biopsy specimen shows glomerular structures within normal limits (H&E, ×100).

highlighted on PAS staining (Fig. 2b). The patient subsequently underwent six sessions of plasmapheresis. Despite intensive immunosuppressive therapy, renal function did not recover, and the patient remained on chronic hemodialysis. Follow-up chest imaging demonstrated persistence of the cavitary lesion in the left lower lobe.

DISCUSSION

Renal involvement in ANCA-associated vasculitis (AAV) is a major determinant of morbidity and long-term renal survival.[1] The classic renal lesion is pauci-immune necrotizing crescentic glomerulonephritis, and the extent of crescent formation,

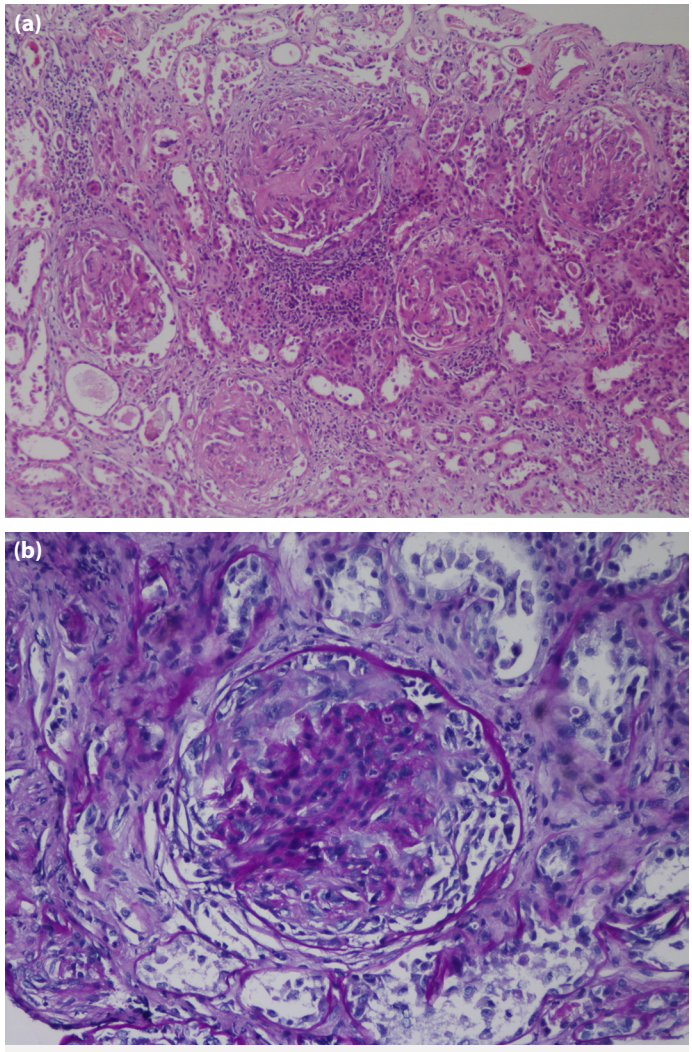

Figure 2. (a) The repeat renal biopsy specimen demonstrates cellular and fibrocellular crescent formation (H&E, ×200). **(b)** The repeat renal biopsy specimen shows cellular crescent formation (PAS stain, ×400).

together with baseline renal function, are critical predictors of outcome.[2] Delayed diagnosis may result in irreversible nephron loss and progression to end-stage kidney disease. For this reason, both KDIGO and EULAR guidelines strongly emphasize early recognition and the rapid initiation of immunosuppressive therapy in organ-threatening disease.[3,4]

Although glomerular involvement predominates, isolated or predominant tubulointerstitial nephritis (TIN) as an initial manifestation of AAV is rare.[5,6] In such cases, the absence of glomerular crescents may lead clinicians toward alternative diagnoses, most commonly drug-induced acute interstitial nephritis. This distinction is particularly challenging in patients with recent exposure to antibiotics or other potentially nephrotoxic agents.[7] The patient's initial presentation with ear fullness, initially attributed to an upper respiratory tract infection, may also have represented early upper airway involvement of ANCA-associated vasculitis, particularly in c-ANCA–positive disease.

The pathophysiological basis of isolated TIN in AAV is not fully understood. It has been suggested that early small-vessel vasculitic injury may initially affect the peritubular capillaries before overt glomerular necrosis becomes apparent. Previous reports have described cases of AAV presenting as isolated TIN, but progression to extensive crescentic glomerulonephritis within a short interval appears uncommon.[5,6] Several case reports have described ANCA-associated vasculitis initially presenting as isolated tubulointerstitial nephritis without evident glomerular involvement. In most of these cases, progression to crescentic glomerulonephritis occurred over weeks to months. However, the rapid progression observed in our patient, with the development of extensive crescent formation within a short interval, highlights the aggressive and evolving nature of the disease. This finding underscores the importance of close monitoring and early reconsideration of the initial diagnosis in atypical or treatment-resistant cases.

In our patient, the lack of response to corticosteroid therapy, followed by pulmonary hemorrhage and c-ANCA positivity, raised suspicion for systemic vasculitis and prompted repeat renal biopsy. Reviews of acute TIN emphasize that steroid resistance or atypical clinical progression should prompt reconsideration of the initial diagnosis and evaluation for systemic autoimmune disease.[7,8] The second biopsy, demonstrating extensive crescent formation, confirmed the rapidly evolving nature of the disease.

This case highlights that steroid-resistant TIN may represent an early or evolving phase of AAV rather than a separate pathological entity. Early repeat renal biopsy should therefore be strongly considered in patients with persistent renal dysfunction, emerging systemic manifestations, or ANCA positivity. Timely recognition may alter the therapeutic strategy and potentially improve renal outcomes.

Drug-induced ANCA-associated vasculitis has been increasingly recognized in the literature, with several medications implicated as potential triggers. Although antibiotics are less commonly associated with this condition than other agents, a possible link between amoxicillin–clavulanate exposure and the onset of vasculitis cannot be entirely excluded in this case. The temporal relationship between drug exposure and the initial presentation may suggest a potential triggering role, although causality cannot be definitively established.

CONCLUSION

Steroid-resistant tubulointerstitial nephritis may represent an early manifestation of ANCA-associated vasculitis. In such cases, early repeat renal biopsy is essential for timely diagnosis and the initiation of appropriate therapy, which may improve renal and systemic outcomes.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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