Tubulointerstitial nephritis as an exclusive renal manifestation of MPO-ANCA-associated vasculitis

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ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) typical presents as a pauci-immune necrotizing and crescentic glomerulonephritis (GN). Glomerular lesions are usually accompanied by a certain degree of tubulointerstitial injury. However, isolated tubulointerstitial nephritis (TIN) may be the only manifestation of renal involvement in AAV. Here, we describe a rare case of TIN associated with MPO-AAV and review the literature on pathogenesis, epidemiology, clinical presentation, and treatment. It is important to recognize this atypical renal involvement of AAV, and to consider the diagnosis of AAV-associated TIN in patients with progressive renal disease and persistent high-titer ANCA, even in the absence of GN on kidney biopsy.

Keywords: ANCA-associated vasculitis. MPO-AAV. Tubulointerstitial nephritis. Peritubular capillaritis. Tubulitis.

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a heterogeneous group of autoimmune diseases characterized by necrotizing inflammation of small and medium vessels[1]. ANCA are autoantibodies directed against cytoplasmic antigens expressed in the primary granules of neutrophils and the lysosomes of monocytes. AAV can be classified according to ANCA serotype in anti-proteinase 3 (PR3-ANCA) and anti-myeloperoxidase (MPO-ANCA). Renal involvement is common in AAV and is the most important predictor of mortality[2,3]. The typical presentation includes asymptomatic hematuria (mostly microscopic), a variable degree of proteinuria, and acute kidney injury[2]. Kidney involvement is characterized by rapid progressive glomerulonephritis (GN) due to a pauci-immune necrotizing, and often crescentic glomerulonephritis[4]. Glomerular lesions are usually accompanied by a certain degree of tubulointerstitial injury[5,6]. Tubulointerstitial lesions are thought to be secondary to rupture of Bowman's capsule and crescent formation rather than representing an independent process[7]. However, rarely, tubulointerstitial nephritis (TIN) in the absence of glomerular involvement may be found. In this report, we describe a rare case of TIN in the context of AAV without apparent glomerular involvement.

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CASE REPORT

A 71-year-old woman was admitted to the emergency department with anorexia, asthenia, and edema of the lower limbs with 4 weeks of evolution. Before the onset of complaints, the patient had started naproxen (500 mg twice a day) due to a complete tear of the left supraspinatus tendon. In the week before coming to the emergency department, she noticed a pruritic erythematous rash on the lower limbs and trunk and a decrease in urinary output. She also mentioned having started pantoprazole (20 mg once a day) that week due to complaints of heartburn. There were no complaints of epistaxis, hemoptysis, or upper respiratory tract symptoms. On initial evaluation, the patient's vital signs were notable for a body temperature of 36,2°C, respiratory rate of 15 breaths per minute, pulse rate of 79 beats per minute, and blood pressure of 137/70 mmHg. Physical examination of the lungs, heart, abdomen, and nervous system was unremarkable. Pitting edema (3+) was present in the lower extremities. No skin lesions were observed. Laboratory studies revealed hemoglobin 6,8 g/dL, white blood cell count of 17,300/µL. A chemistry panel revealed blood urea 373 mg/dL (normal range, 19-49 mg/dL), serum creatinine (sCr) 14,4 mg/dL (previous sCr value of 0,56 mg/dL 8 weeks ago), potassium 7,62 mmol/L, and normal anion gap metabolic acidemia

(pH 7,12, bicarbonate 10 mmol/L, pCO_2 25,5 mmHg). The analysis of the sediment showed 5-10 red blood cells and more than 50 white blood cells per high power field. Urine culture was negative. Less than 1% of eosinophils were found in urine. Protein-to-creatinine ratio (PCR) in a spot urine sample was 1,4 g/g, with an albumin-to-creatinine ratio (ACR) of 210 mg/g. Renal ultrasound demonstrated normal-size kidneys and no hydronephrosis. Serologic studies revealed an MPO-ANCA titer of 88 U/mL and a negative PR3-ANCA titer. Serum C3 and C4 complement levels were normal. Erythrocyte sedimentation rate was 70 mm/h and C-reactive protein (CRP) was 9,8 mg/dL. After controlling the electrolyte disturbances and uremia through hemodialysis, a kidney biopsy was performed. The preliminary histological result highlighted the presence of a tubulointerstitial inflammatory infiltrate, with fibrosis in 25% of the interstitium, without glomerular changes. Assuming an initial diagnosis of acute interstitial nephritis, on hospital day 14, oral prednisone (PDN) was initiated at a dose of 1 mg/kg/day. The definitive histological result revealed 20 glomeruli, none of them with global sclerosis nor crescentic lesions. In the tubular compartment, there were signs of tubulitis —presence of neutrophil polymorphonuclear cells and cellular debris in the tubular wall— and infiltration of the epithelium by mononuclear inflammatory cells with occasional basal membrane rupture. Focal areas of tubular atrophy were observed. In the interstitium, there was an inflammatory infiltrate composed of mononuclear cells and neutrophils. Peritubular capillaries showed lesions of neutrophilic vasculitis, with fibrinoid necrosis in one small vessel. Immunofluorescence analysis revealed no deposits of immunoglobulin or complement. Loss of CD31 labeling was observed limited to peritubular and interstitial capillaries, while remaining present in glomerular capillaries. Based on these pathological findings, a diagnosis of tubulointerstitial nephritis associated with AAV (figure 1). With the start of corticosteroid therapy, an improvement in renal function was observed, allowing dialysis independence, resolution of the rash, and regression of edema. After the biopsy results were known, rituximab was added to the ongoing immunosuppressive therapy with two doses of 1 g each, administered 14 days apart. The patient was discharged on the 34th day of hospitalization with a sCr of 3,2 mg/dL. Three months after the induction regimen, the patient was in remission with a stabilized sCr level of 2,4 mg/dL (PCR 0,6 g/g, without hematuria or leukocyturia), and the MPO-ANCA titer was negative. Rituximab was continued as maintenance therapy (500 mg × 2 at complete remission, and 500 mg at months 6, 12, and 18 thereafter). After completing the maintenance regimen, the patient remained in remission with a sCr of 1,2 mg/dL, a PCR of 0,2 g/g, and undetectable MPO-ANCA.

DISCUSSION AND CONCLUSION

TIN in the absence of glomerular involvement in patients with AAV is uncommon, with an estimated frequency of 1-4.5%[8,9].

The detailed mechanism for TIN in AAV remains unknown. Some authors suggest that tubulointerstitial lesions are a secondary phenomenon to rupture of Bowman's capsule by crescents, explaining why pauci-immune crescentic GN is usually accompanied by a certain degree of tubulointerstitial involvement[5-7]. Others authors argue that the mechanism of tubulointerstitial damage is independent of glomerular injury, attributing a primary role to damage of peritubular capillaries with consequent tubulitis[10,11]. This could explain the exclusive tubulointerstitial involvement in AAV. In our case, TIN was presumed to result from peritubular capillaritis and tubulitis, since kidney biopsy showed normal glomeruli and no existence of arteritis, arteriolitis, or venulitis.

Nakabayashi K. et al.[9] described 3 cases of tubulointerstitial nephritis without glomerular lesions in the scenario of a MPO-AAV. They presumed that TIN results from peritubular capillaritis and tubulitis. An immunohistochemical staining using various antibodies to the vascular endothelial cell surface markers in the tissue specimens obtained from kidney biopsies was performed. One of those antibodies was CD34. They found that loss of CD34 occurs in the early phase of the disease, even when capillary walls were not yet destroyed. With these observations, they presumed that MPO, bursts out from the infiltrating neutrophils and releases proteolytic enzymes and radical oxygen species, induces the antigenic loss of vascular endothelial cells (evidenced by the loss of CD34), and results in the initial damage of the peritubular capillary walls. Then, this process progresses to peritubular capillaritis, followed by the infiltration of neutrophils and mononuclear cells in the surrounding interstitium and into tubular epithelial cells, which can lead to tubular basement membrane lysis.

In our case, we used CD31, a transmembrane glycoprotein also designated as PECAM-1 (platelet endothelial cell adhesion molecule-1). In the kidney, fenestrated endothelium of the glomeruli strongly expressed CD31 with a slight lower expression in the interstitial capillaries[12]. We also observed the loss of CD31 limited to the peritubular capillaries, confirming the absence of glomerular involvement.

The reason for exclusive peritubular capillaritis involvement may be related to the affinity and epitope specificity of MPO-ANCA[13,14].

From the pathogenesis of AAV, it is known that for endothelial damage to occur, there must be binding of ANCA to MPO expressed on the neutrophil surface. This connection will result in the activation of neutrophils with consequent adhesion to the vascular endothelium. The degranulation of neutrophils leads to the release of reactive oxygen species, proteases and neutrophil extracellular traps that cause endothelial injury[2].

The ability of ANCA to induce neutrophil extracellular traps correlates with MPO-ANCA affinity[15]. The affinity of MPO-ANCA, based on ANCA affinity for MPO, can be largely categorized as high and low, irrespective of the level of MPO-ANCA titers. The higher the affinity, the greater the number of activated neutrophils that will adhere to the vascular endothelium and induce endothelial damage. The low-affinity group will only be able to activate a smaller number of neutrophils, with a consequent lower capacity for adhesion and damage to the vascular endothelium. The adhesion can be easier in the peritubular capillary

than in the glomeruli because of decreased vascular flow speed and pressure. This could explain why the low-affinity type of MPO-ANCA could induce TIN instead of rapidly progressive GN and why this type is more frequently associated with chronic kidney disease presentation[13,15,16].

Although MPO-ANCA affinity is stable during the disease course, the association between low-affinity group and histological findings of mixed/sclerotic glomerulonephritis could be explained by the increase in intravascular pressure in the upper stream, the efferent arteriolar and glomeruli due to obstruction in the peritubular capillary[13,15].

Antibodies can recognize different binding sites (epitopes) on their corresponding antigens[17]. Differences in binding specificity may influence the pathogenic potential of the antibodies[17]. Epitope specificity of MPO-ANCA can contribute to the heterogeneity of clinical features in AAV[14,17,18].

ANCA binding to MPO interferes with the binding of MPO to its physiological inhibitor, ceruloplasmin. Differences in epitope specificity can explain varying degrees of interference in the binding of MPO to ceruloplasmin, leading to more or less severe clinical phenotypes[17].

Differences in the number of epitope regions recognized in the ANCA-MPO heavy chain and the location of recognized linear epitopes may be involved in disease activity and clinical and pathological manifestations. For example, MPO-ANCA restricted to one or two major epitope regions may be associated with a worse prognosis than those recognizing three major epitope regions[17]. The same way, binding to the light chain of MPO-ANCA was associated with more severe renal dysfunction and systemic disease activity[18].

How this epitope specificity associates with exclusive tubulointerstitial involvement in AAV remains to be elucidated. Some previous studies have suggested that specific MPO-ANCA epitopes may be involved in the pathogenesis of MPO-associated TIN by controlling the binding affinity of the MPO-ANCA. However, the exact relationship between MPO-ANCA epitopes and affinity needs to be further clarified.

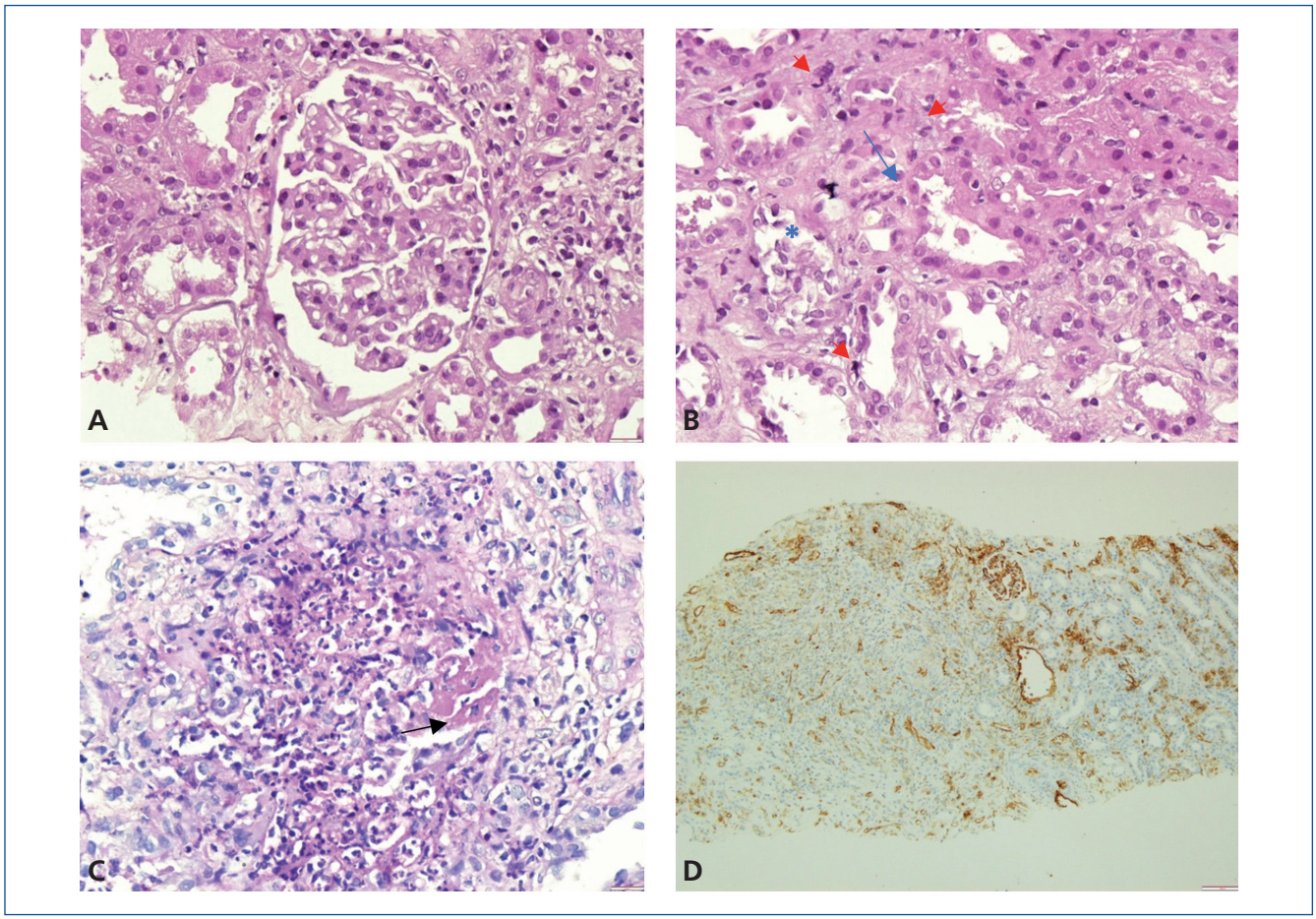

Figure 1. **A)** Hematoxylin eosin stain (magnification × 400), on light microscopy (LM): glomerulus with normal appearance. **B)** Hematoxylin eosin stain (magnification × 400), on LM: inflammatory infiltrate with neutrophils (red arrow), invading the tubules (blue arrow), causing basal membrane rupture, intratubular cellular debris (*). **C)** Periodic acid-Schiff stain (magnification × 400), on LM: area of tubular atrophy by an intense inflammatory infiltrate, with fibrinoid necrosis (black arrow). **D)** Immunohistochemical stain: Loss of CD31 labeling in interstitial capillaries; normal staining in glomerulus.

The initial belief that tubulointerstitial lesions were secondary to glomerular involvement justifies the fact that current histopathological classifications of renal involvement in AAV are based on glomerular lesions[5,6]. Unless there are remarkable findings, tubulointerstitial lesions are not mentioned in the final diagnosis[4]. However, acute and chronic tubulointerstitial lesions have been associated with renal outcome[5,6]. In fact, tubulointerstitial damage may represent the main cause of renal dysfunction, especially in cases of progressive dysfunction, due to the tubulointerstitial ischemia induced by peritubular capillaritis[10,19].

To diagnosis the cause of TIN, drug-related, infectious, and auto-immune diseases must be excluded. Systemic symptoms such as fatigue, cough, myalgia, arthralgia, weight loss, and pulmonary involvement could be key factors for suspecting of an AAV as the cause of TIN. In our patient, we initially suspected that the TIN was attributed to a hypersensitivity reaction to recently initiated medications. However, the presence of neutrophils in the inflammatory infiltrate argued against this hypothesis.

He et al.[20] reported 3 cases of AAV-associated TIN without GN. They compared these patients to a matched group of AAV patients with typical GN. These cases of isolated TIN showed significantly fewer urinary RBCs and tended to exhibit lower levels of sCr, 24 h urine protein, and MPO-ANCA titer (without significance). The degree of interstitial edema, fibrosis, inflammatory infiltrate, tubular basement membrane thickening, and tubular atrophy was also greater in the patients with isolated TIN. The authors also reviewed 18 cases of AAV-associated TIN and noted that this form of disease tends to occur in older patients (average age of 61 years) and, more commonly in women (60%). Most of them had elevated sCr levels (80%), proteinuria (73.3%) —with a few having nephrotic range proteinuria, hematuria (73.3%), MPO positivity (66.7%), and anemia (46.7%). Specific symptoms related to MPO-AAV were less frequent (fever 40%, arthralgias 40%, edema 33.3%). However, this revision included cases of PR3-ANCA-vasculitis, dual positivity for MPO and PR3, and ANCA-negative pauci-immune vasculitis. One patient had a possible pharmacological association with positive AAV, and some of them had glomerular changes.

Due to the unusual presentation of this form, no specific treatment guidelines are available. There are case reports where patients were successfully treated with PDN monotherapy[9,21,22]. In other cases, conventional immunosuppression regimens used in ANCA-associated GN (corticosteroids + cyclophosphamide and/or rituximab) were prescribed, leading to disease remission[13,20,23,24]. In our case, we used PDN + rituximab since fibrinoid necrosis was observed in only one vessel, without severe involvement of other organs.

It has been suggested that AAV-related kidney lesions may occur on a spectrum, ranging from TIN to crescentic GN[24,25]. In this spectrum, TIN is believed to represent a more mild or benign form of kidney involvement. Despite this, some reports have shown a transition from TIN to the necrotizing crescentic GN[24]. It is uncertain whether this transformation represents a natural progression of the disease or a distinct disease variant.

In summary, we describe an isolated TIN, an unusual renal presentation of AAV. We should pay attention to this phenotype of AAV, as it tends to occur more in older patients, in whom the risks of corticosteroid therapy may be greater. It is important to recognize this atypical renal involvement of AAV, and to consider the diagnosis of AAV-associated TIN in patients with progressive renal disease and persistent high-titer ANCA, even in the absence of GN on kidney biopsy. Further investigation is crucial to elucidate the underlying mechanisms, optimal treatment strategies, and clinical outcomes of ANCA-associated TIN.

Conflict of interest

The authors declare that they have no conflicts of interest.

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