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Unusual Form of Kidney Injury without Glomerulonephritis in Microscopic Polyangiitis

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Abstract

ANCA test has diagnostic significance on AAV. The Immunofluorescence Assay (IFA) usually has a perinuclear staining pattern (P-ANCA), and Enzyme-Linked Immuno Sorbent Assays (ELISA) detect antibodies to Myeloperoxidase (MPO-ANCA) in MPA. Kidney involvement is noted in approximately 80-100 percent of patients with MPA cases, and the clinic spectrum range from microscopic hematuria to severe kidney injury with dialysis requirement. Pulmonary involvement is noted in approximately 25-55 percent of patients with MPA. Several observations and presumptions have been noted about TIN accompanying crescentic glomerulonephritis. This diversity may be considered as only a simple histological elaboration. However, it is a significant clinical entity for guiding the treatment.

Keywords: Microscopic polyangitis • Tubulointerstitial nephritis • Dialysis

Introduction

Antineutrophil Cytoplasmic Autoantibody (ANCA)-Associated Vasculitis (AAV) is a group of disorders that affect small sized vessels predominantly and have similar histopathological features in kidney involvement [1]. Microscopic Polyangiitis (MPA), a kind of AAV, is a significant cause of pulmonary-renal syndrome [2]. Although MPA has been reported at all ages, intensive and severe clinics generally occur in older adults [3]. Clinical manifestations are various in MPA; most of the patients present with constitutional symptoms including; fatigue, fever, arthralgia, or weight loss at diagnosis or months prior to diagnosis [4]. ANCA test has diagnostic significance on AAV. The Immuno Fluorescence Assay (IFA) usually has a Perinuclear Staining Pattern (P-ANCA), and Enzyme-Linked Immuno Sorbent Assays (ELISA) detect Antibodies to Myeloperoxidase (MPO-ANCA) in MPA. Kidney involvement is noted in approximately 80-100 percent of patients with MPA cases, and the clinic spectrum range from microscopic hematuria to severe kidney injury with dialysis requirement [5]. Kidney involvement of MPA presents with evident Glomerulonephritis (GN) in almost all cases. Pauci-immune necrotizing and crescentic GN is the typical histological feature in AAV [6]. Tubulointerstitial lesions may occur and mostly form with inflammatory cell infiltration in the interstitium [7]. However, a few cases were reported, a purely tubulointerstitial injury without glomerular lesions in patients with MPA [8-10]. We present anunusual kidney involvement of MPA, which resulted in dialysis requirements.

Case Presentation

A 70-year-old male patient was admitted to the emergency department with confusion and vomiting. Any chronic disease diagnosis or medication was not detected in medical history. The onset of complaints was two weeks ago; a neurologist regarding headaches and insomnia had examined him. The central nervous system imaging did not determine any significant abnormality, and serum creatinine level was 0,8 mg/dl in laboratory assessment. Only a salt-free diet was recommended to him for new-onset hypertension. However, his general condition deteriorated over time. On physical examination, he was confused, tachypneic (24/minute), tachycardic (96/minute), and hypertensive (170/95 mmHg). The mouth was dry; a respiratory sound decreased on the lower right side, the abdominal examination was usual, and palpable purpura with edema was detected on the lower extremities. The laboratory results were as follows; BUN:154 mg/dl, creatinine: 19,2 mg/dl, sodium: 138 mEq/L, potassium: 6,2 mEq/L, calcium: 9,5 mg/dl, phosphorus: 9,9 mg/dl, uric acid: 12 mg/dl, glucose: 82 mg/dl, protein: 5.6 g/dl, albumin: 2,8 g/dl, ALT: 25 IU/L, AST:13 IU/L, LDH: 201 IU/L, bilirubin: 0,4 mg/dl, CRP: 164 mg/L, leucocyte:14.2 10^3/µl, hemoglobin: 8.2 g/dl, platelet: 390 10^3/µl. The urinary protein-to-creatinine ratio was 0.8 mg/g.

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The urine sediment analysis detected isomorphic erythrocytes, pyuria, granular cast, and leukocyte cast. On ultrasonographic examination, kidney size and echogenicity were normal. The ophthalmologic examination has not shown signs of hypertensive retinopathy. Dialysis was performed promptly due to hyperkalemia and uremic symptoms. Afterward, etiological investigation and treatment were maintained in the nephrology service.

The immunoassay laboratory resulted in as follows; anti-Glomerular Basal Membrane (GBM) antibody was negative, Anti-Nuclear Antibodies (ANA) was positive with 1/100 titer (granular pattern), anti-double-stranded DNA antibody was negative, anti-SSA/anti-SSB were negative, C_3/C_4 levels were in the normal range, C-ANCA was negative, P-ANCA was positive (formaline resistance). The ELISA test confirmed the positivity of MPO-ANCA (>200 RU/ml). Lastly, monoclonal gammopathy was not detected on serum protein electrophoresis, and a serum-free light chain ratio (K/λ) was in a normal range.

Hemoptysis occurred on the third day of hospitalization; minimal pleural effusion and interstitial fibrosis were detected on thoracic Computed Tomography (CT). These radiological findings were considered pulmonary involvement of vasculitis attack, CT image is shown in Figure 1.

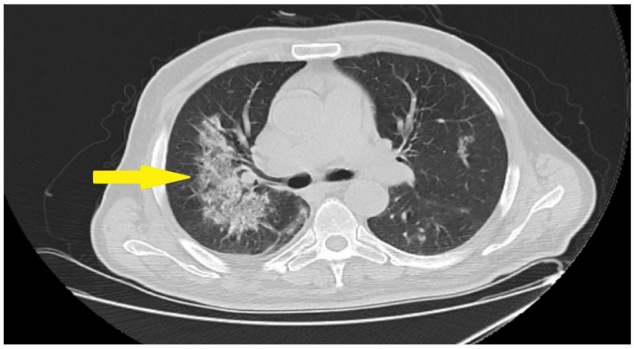

Figure 1. Thoracic computerized tomography image shows interstitial inflammation and fibrosis due to pulmonary involvement of vasculitis.

Bronchoscopy was planned; however, the patient refused the intervention to the lung. A kidney biopsy was performed several dialysis sessions afterward. The six glomeruli have been determined in light microscopy. The two glomeruli have been globally sclerotic, and the others have appeared intact. The damaged tubular epithelial cells and tubular atrophy have been observed. Also, erythrocytes have been observed in tubular lumens. Hyaline arteriosclerosis has been detected in the vessel wall. Interstitial areas have been infiltrated with inflammatory cells, including neutrophil, eosinophil, lymphocyte, and plasma cells. The glomerular staining has not been shown in the immunofluorescence examination. Only tubular cast material has been stained abundantly with IgA, IgM, Kappa, and Lambda. Congo Red staining has resulted in negative. The biopsy was reported as acute tubulointerstitial nephritis, and the biopsy sections are shown in Figures 2 and 3.

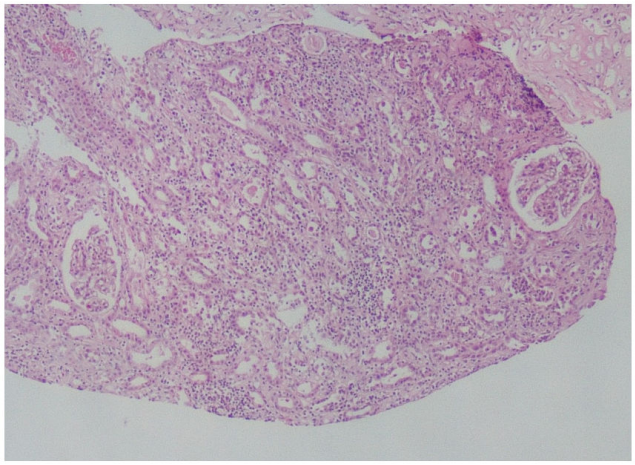

Figure 2. The kidney biopsy specimen shows interstitial inflammation and intact glomeruli.

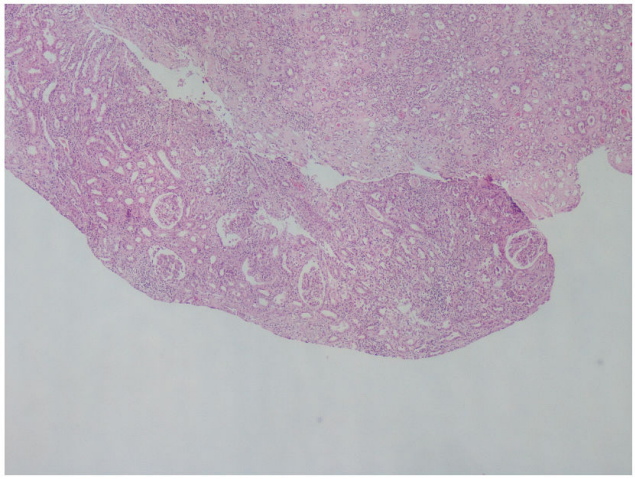

Figure 3. The kidney biopsy specimen shows interstitial inflammation and intact glomeruli.

Consequently, we have considered the diagnosis as MPA, and we have planned to treat him like crescentic glomerulonephritis. Due to the life-threatening involvement of vasculitis, aggressive induction therapy was preferred. Pulse steroid therapy was administered (500 mg methylprednisolone for three days) and continued with an oral dose of 1 mg/kg/day. The parenteral cyclophosphamide (15 mg/kg) therapy was administered, and plasmapheresis was performed. The clinical and radiological improvement was observed in the lung and skin lesions after induction therapy, although the dialysis requirement has remained. Dialysis therapy continued three times a week after being discharged home. The patient has infected with SARS-CoV-2 subsequently after the third administration of cyclophosphamide. He was admitted to the intensive care unit for respiratory failure and then died.

Results and Discussion

We have presented a case of pulmonary-renal syndrome due to MPA, a kind of AAV. MPA has exhibited kidney involvement *via* purely Tubulointerstitial Nephritis (TIN) in this case. This circumstance is unusual and rare during AAV. The onset of dialysis requirements due to this injury mechanism is quite interesting. Renal manifestations

have been reported in 80–100% of patients with MPA. Severe kidney injury characterized mainly by Rapidly Progressive Glomerulonephritis (RPGN) is the essential clinical feature of MPA. Despite significant changes demonstrated in the glomerular apparatus, damage to tubular and interstitial can be part of the kidney involvement. The kidney involvement of AAV consisting of the only TIN without glomerular injury is atypical. However, several cases have been reported [11,12].

Acute interstitial nephritis is characterized by an inflammatory infiltrate in the kidney interstitium. It is most often induced by drugs or systemic diseases such as Sjögren's syndrome, sarcoidosis, and Systemic Lupus Erythematosus (SLE). Our patient took only one paracetamol tablet one day before the emergency admission. This duration (one day) is too short for the predicted onset of a drug-induced TIN. Also, constitutional symptoms have already occurred before taking paracetamol.

The diagnosis of AAV is based upon the combination of characteristic clinical findings, pathological evidence, laboratory tests, and imaging studies. In the presented case, MPA diagnosis was established with of positive MPO-ANCA test, acute kidney injury, radiological lung lesions, and skin lesions. The conventional treatment of acute TIN has not been preferred for patient. Due to life-threatening lung and kidney involvement, we administered AAV induction therapy [13].

The lack of histological evidence of vasculitis may conflict with the diagnosis. However, several laboratory and radiological evidence were essential in diagnosing AAV. Especially ANCA assays are a very reliable biomarker for AAV diagnosis. The relationship between ANCA with vasculitides was well established. Approximately 90 percent of patients with MPA have ANCA positivity in widely used types of ANCA assessments. P-ANCA pattern results from a staining pattern around the nucleus on IFA. Most MPA patients have MPO-ANCA, but a small part has PR3-ANCA on ELISA [14]. Both MPO-ANCA and P-ANCA positivity has high specificity for MPA (P-ANCA 81-96% and MPO-ANCA 96-99%) [15]. ELISA should be performed to determine the specific antibody and subsequently positive IFA detection. In this case, formalin-fixed staining and high titer of MPO-ANCA on ELISA have been confirmed to the positivity of P-ANCA.

Pulmonary involvement is noted in approximately 25-55 percent of patients with MPA. Clinical manifestations include; alveolar hemorrhage, infiltrates, pulmonary edema, pleuritis, and interstitial fibrosis. Common presenting symptoms are dyspnea, cough, hemoptysis, and chest pain. The most common radiological finding is ground-glass attenuation, which corresponds to alveolar hemorrhage, chronic interstitial inflammation of the alveolar septa, and capillaritis [16]. CT evaluation revealed interstitial pneumonitis and septal thickening in this presented case.

MPA often has cutaneous signs scattered over the lower extremities. The skin lesions are mainly palpable purpura or histologically leukocytoclastic vasculitis induced by necrotizing capillaries [17]. The purpuric lesions were observed on the legs initially; these rashes disappeared after steroid therapy in this case.

We had planned to repeat the kidney biopsy in this case due to the remaining dialysis requirement. However, we could not perform because patient survival was too short. The low quantity of glomeruli in biopsy might have obscured glomerular injury. Also, the lack of electron microscopic examination is another deficiency of our approach.

In literature screening, we encountered a few cases that resemble this patient. Wen et al. have reported pulmonary-renal involvement of MPA; kidney biopsy showed all intact 25 glomeruli and infiltration of inflammatory cells in the tubular epithelium. The initial therapy has failed and consisted of only low-dose glucocorticoids. The clinical remission has attained subsequently after the administration of pulse steroid plus cyclophosphamide therapy. In another case with MPA, the first kidney biopsy has shown TIN without glomerular injury. After six years, the active glomerular injury has not shown again in the second biopsy. Only the evidence of chronical alterations have been detected, such as glomerulosclerosis, mild interstitial fibrosis, and tubular atrophy in the latter specimen. In another case of drug-associated MPA, the patient had a positive MPO-ANCA test and a positive drug-induced lymphocyte stimulation test for cimetidine. Kidney biopsy has shown alterations consistent with acute TIN and intact 11 glomeruli. The kidney biopsy has been repeated after drug discontinuation, and only persistent TIN has been observed again. Furthermore, isolated interstitial nephritis has been reported in Granulomatosis Polyangiitis (GPA) [18].

Several observations and presumptions have been noted about TIN accompanying crescentic glomerulonephritis. For example, the rupture of Bowman's capsule subsequently causes inflammation involves in the interstitial area. Also, the interstitial region-specific antigen's avid affinity to autoantibodies has been proposed as a possible mechanism for originating TIN in MPA without glomerular injury [19]. The spillover of peritubular capillaritis and interstitial granuloma formation are other suppositions [20].

Conclusion

The pathogenesis of this atypical process in MPA is not elucidated currently, despite the increasing number of reported cases. This diversity may be considered as only a simple histological elaboration. However, it is a significant clinical entity for guiding the treatment. Furthermore, this case emphasizes the presence of vasculitides in the etiology of TIN. We presented an unusual kidney involvement of MPA, so physicians should be alert regarding atypical vasculitis presentations.

Conflict of Interest

The authors have no conflict of interest to declare.

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