

## CASE REPORT

# Tubulointerstitial nephritis without glomerular crescent formation as an underestimated subgroup of renal involvement among microscopic polyangiitis patients: A case report

Se Hee Kim<sup>1</sup>  | Hae-Rim Kim<sup>2</sup>  | Sang-Heon Lee<sup>2</sup>  | Hong Ki Min<sup>1</sup> 

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Konkuk University Medical Center, Gwangjin-gu, Korea

<sup>2</sup>Division of Rheumatology, Department of Internal Medicine, Research Institute of Medical Science, Konkuk University Medical Center, Konkuk University School of Medicine, Gwangjin-gu, Seoul, South Korea

## Correspondence

Hong Ki Min, Department of Rheumatology, Department of Internal Medicine, Konkuk University Medical Center, 120-1 Neungdong-ro (Hwayang-dong), 05029 Gwangjin-gu, Seoul, Korea.  
Email: alsghdr11921@naver.com

## Abstract

Although extra-glomerular involvement of microscopic polyangiitis is not regarded as a characteristic finding of the disease, tubulointerstitial nephritis should be considered as a new subclass of renal involvement.

## KEYWORDS

interstitial, microscopic polyangiitis, nephritis

## 1 | INTRODUCTION

Microscopic polyangiitis (MPA) is an anti-neutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which mainly involves the small vessels without granulomatous changes. More than 70% of MPA patients have renal involvement.<sup>1</sup> Renal biopsy is the gold standard to confirm the renal manifestation of MPA. Rapid progressive glomerulonephritis (RPGN) with a crescent formation in the glomeruli and pauci-immune nephritis are typically found in glomerulonephritis associated with MPA. However, several case reports documented MPA patients without these typical glomerulus pathologies. These suggested that tubulointerstitial nephritis without crescentic glomerulonephritis pertained to a new subgroup of renal manifestation in MPA. We describe a case of MPA with tubulointerstitial nephritis without a crescentic change in the glomeruli.

## 2 | CASE REPORT

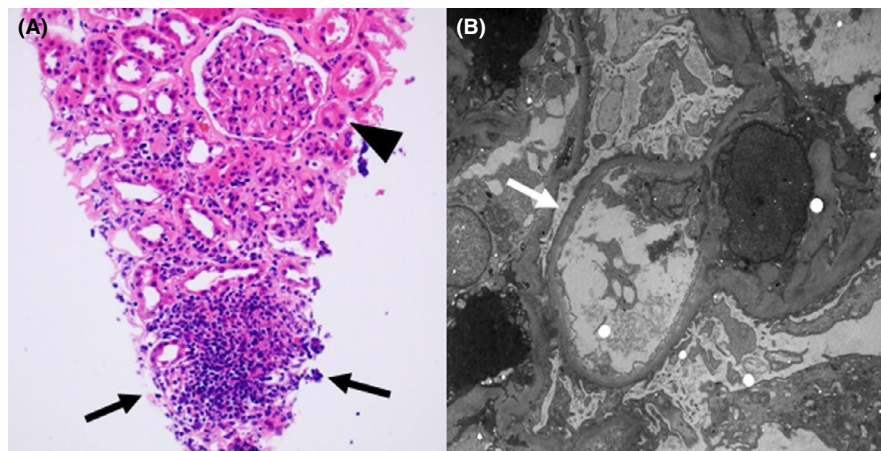
A 70-year-old woman with underlying hypertension was admitted for complaints of intermittent fever, backache, bilateral shoulder and leg pain, and left-sided foot drop for 2 months. On admission, her blood pressure was 136/61 mm Hg, and her heart rate was 99 bpm. On the next day, she had a fever of 40°C. On neurologic examination, the deep tendon reflex of the left ankle was negative. The initial laboratory findings are presented in Table 1. A urine analysis showed microscopic hematuria (red blood cells [RBCs]: 10-19 cells/HPF) and proteinuria [spot urine protein/creatinine ratio, 907.4 mg/g, albumin 16.8%, alpha 1 globulin 15.3%, alpha 2 globulin 21.1%, beta globulin 27.8%, and gamma globulin 19.0%] without RBC cast. The result of the respiratory viral panel was negative. Chest computed tomography showed multiple ground-glass opacities and

This is an open access article under the terms of the Creative Commons Attribution NonCommercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non commercial and no modifications or adaptations are made.

© 2021 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

Laboratory test	Interpretation	Reference range
White blood cell	$11.50 \times 10^3/\mu\text{L}$	$4 \times 10^3 \sim 10 \times 10^3$
Hemoglobin	9.2 g/dL	11.5 ~ 14.5
Platelet	Platelets, $608 \times 10^3/\mu\text{L}$	$140 \times 10^3 \sim 400 \times 10^3$
Erythrocyte sedimentation rate	>120 mm/h	0 ~ 20
HbA1c	7.1%	4.3 ~ 5.6
High-sensitivity C-reactive protein	14.76 mg/dL	0.01-0.03
Blood urea nitrogen	31.7 mg/dL	8-22
Creatinine	1.50 mg/dL	0.5-0.9
Glomerular filtration rate	34 mL/min/1.73 m <sup>2</sup>	
Rheumatoid factor	154 IU/mL	3-18
Complement 3	178.2 mg/dL	86-160
Complement 4	32.5 mg/dL	17-47
Anti-nuclear antibody	+ (speckled pattern, 1:80)	
Myeloperoxidase antibody	+ (antibody index 3.70)	0-0.90
Proteinase-3 antibody	+ (antibody index 1.96)	0-0.90

**TABLE 1** Laboratory findings at initial visit



**FIGURE 1** Renal biopsy finding. A, (light microscopy [LM],  $\times 20$ ) Tubules reveal focal moderate atrophy and loss with infiltration of mononuclear cells (black arrows) and fibrosis in interstitium (black arrowhead). Mild arteriosclerosis is also seen. B, (Electron microscopy [EM],  $\times 5000$ ) Glomerular basement membrane measures normal in thickness having relatively smooth contours. No electron-dense deposits are found in epithelial cell; foot processes are widely effaced (white arrow)

mosaic attenuation in both lungs. The patient experienced difficulty urinating. Urodynamic studies revealed a bladder muscle dysfunction. Magnetic resonance imaging (MRI) of the whole spine showed mild disk protrusion at the C4-C5 level without spondylitis. A nerve conduction study (NCS) showed left peroneal neuropathy, bilateral lumbosacral radiculopathy (L4-S1), and bilateral distal median neuropathy at the wrist level. The MRI findings did not correlate with the patient's clinical symptoms or NCS findings. These findings, along with ANCA positivity, elevated acute phase reactants, polyneuropathy, and hematuria with proteinuria, suggested AAV. Thus, a renal biopsy was performed. The renal biopsy included 14 glomeruli and showed no immune complex deposits or crescent formation. However, segmental mesangial

cell proliferation, focal atrophy and loss of tubules, and mononuclear cell infiltration with fibrosis were noted in the interstitium (Figure 1A). On electron microscopy, foot process effacement was observed. However, electron-dense deposits were not found (Figure 1B). In the immunohistochemical examination, staining of immunoglobulin G (IgG), IgM, IgA, complement 3, C4, C1q, kappa light chain, or lambda light chain was not noted. The patient did not have any allergic disorders, peripheral eosinophilia, upper respiratory involvement, or granulomatous changes. Hence, granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) were excluded.<sup>2</sup> The clinical and laboratory findings were compatible with a diagnosis of MPA. Ceftriaxone, azithromycin, and piperacillin/tazobactam were

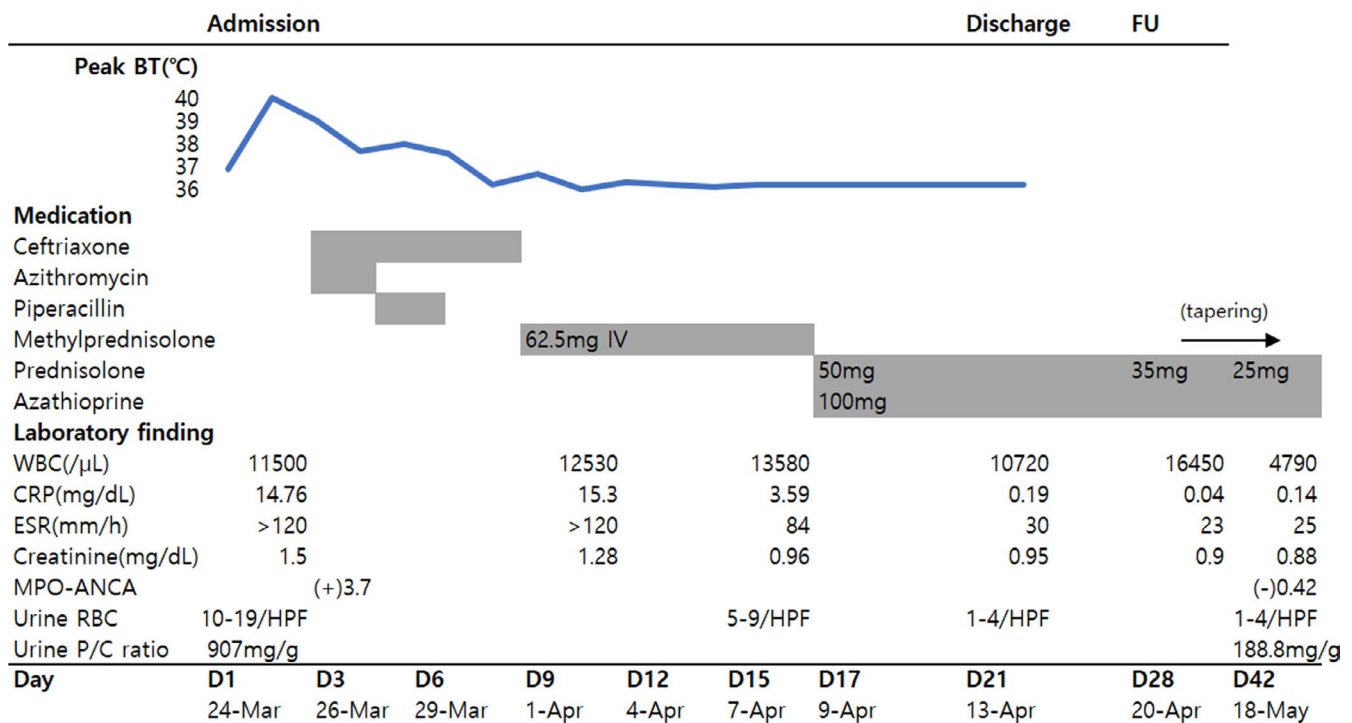
administered after admission for 6 days. However, the clinical and laboratory findings did not improve. Antibiotic treatment was terminated, and high-dose glucocorticoid therapy was initiated (1 mg/kg methylprednisolone; body weight, 60 kg). Her back pain and difficulty in urination improved. After 8 days of high-dose glucocorticoids, we added azathioprine, and the glucocorticoid dose was tapered. Foot drop improved after a week of treatment. The deep tendon reflex of her left ankle normalized after 6 weeks of medication. Mycophenolic mofetil was not prescribed due to insurance problems in Korea. Methotrexate was also not administered because the patient exhibited interstitial lung disease. Instead of two drugs, we chose azathioprine. After 1 month of glucocorticoid therapy, her follow-up laboratory findings improved (WBC level,  $4.79 \times 10^3/\mu\text{L}$ ; ESR, 25 mm/h; hs-CRP, 0.14 mg/dL; BUN, 33.4 mg/dL; creatinine, 0.88 mg/dL; GFR, 64 mL/min/1.73 m<sup>2</sup>; negative ANCA [MPO-Ab 0.42, PR3-Ab 0.67]). Urine analysis showed no protein or RBCs (Figure 2). There were no adverse events during glucocorticoid therapy, and the patient was satisfied with the current therapy because the previous symptoms improved.

### 3 | DISCUSSION

Rapid progressive glomerulonephritis is a typical renal manifestation of MPA.<sup>3</sup> Typical pathological findings of AAV nephritis include glomerular necrosis and crescent

formation with no immune complexes deposition. This is also known as pauci-immune glomerulonephritis.<sup>4</sup> In 2010, Berden et al proposed a pathologic classification for ANCA-associated glomerulonephritis. The classification consisted of four categories: focal ( $\geq 50\%$  of normal glomeruli), crescentic ( $\geq 50\%$  glomeruli with cellular crescents), sclerotic ( $\geq 50\%$  with globally sclerotic glomeruli), and mixed, which was defined as a combination of  $< 50\%$  of normal, crescentic, and sclerotic glomeruli. The extent of crescentic glomerulonephritis in MPA is essential because it predicts the prognosis of renal manifestations in AAV.<sup>5</sup> The renal biopsy of our patient had pauci-immune findings. However, contrary to the typical presentation, glomerular crescent formation was absent. Only foot process effacement and tubulointerstitial nephritis were noted in the present case.

The foot processes of podocytes form the filter of the glomerular basement membrane, and changes in foot processes can be observed in various kidney diseases at an early stage.<sup>6</sup> In a typical MPA renal biopsy, the changes in podocytes are not apparent because MPA features advanced crescentic glomerulonephritis. Tubulointerstitial changes are also observed in the renal biopsy of patients with MPA. However, this histologic feature is considered a secondary change following crescent formation and consequent rupture of the Bowman's capsule.<sup>7</sup> A recent study discussed the importance of tubulointerstitial damage in the long-term prognosis of AAV-associated nephritis. It associated a specific tubulointerstitial biomarker (*EGF* mRNA expression) with the severity of



**FIGURE 2** Clinical course, treatment schedule, and laboratory findings. On the day of initiating methylprednisolone 62.5 mg intravenously, fever was subsided, and antibiotics were stopped. After administration of methylprednisolone for 8 d, it was switched to prednisolone tablet 50 mg and azathioprine 100 mg was added. On D14, kidney biopsy was done. BT, body temperature; P/C, protein/creatinine

renal function loss.<sup>8</sup> In our case, renal histology showed foot process effacement without glomerular crescent formation. This indicated that podocyte changes may be an early-stage pathologic finding in MPA. Furthermore, tubulointerstitial nephritis may occur in MPA independently of crescent formation, and these may form a unique subgroup of MPA-associated nephritis.

Distinguishing MPA nephritis from other alternative causes is essential because hypertension and diabetes mellitus can cause chronic kidney disease. The present case's findings differed from those seen in hypertensive nephropathy cases (characterized by arterial nephrosclerosis, renal arterial hyalinization, and thickening of the arterial wall).<sup>9</sup> In addition, the patient was newly diagnosed with diabetes mellitus after admission. Diabetic retinopathy, which occurs before diabetic nephropathy, was absent. Pathologic findings of diabetic nephropathy include glomerulosclerosis and Kimmelstiel-Wilson lesions,<sup>10</sup> which were not noted in the present case. Other possible causes of nephritis, such as allergic reactions or nephrotoxic drugs, were excluded. The absence of a history of allergy and systemic eosinophilia excluded the diagnosis of EGPA. GPA usually involves the upper and lower respiratory tracts. Moreover, cavitory lesions or nodules are typically seen on chest radiography. In contrast, a diffuse ground-glass appearance without a cavitory lesion is more common in patients with MPA.<sup>11</sup> Distinguishing between GPA and MPA is sometimes difficult. However, the clinical findings in the present case were closer to MPA than GPA.

There have been few similar documented cases of MPA and nephritis without crescentic glomerulonephritis.<sup>12,13</sup> Nakabayashi et al revealed that patients with an intact cluster of differentiation (CD)34, the surface marker for glomerular endothelial cells had tubulointerstitial nephritis-dominant pathology rather than crescentic glomerulonephritis. This suggested that the loss of CD34 was related to the glomerular damage found in MPA.<sup>13</sup> Gou et al found that the MPO antibody was able to bind to several epitopes of MPO. Moreover, a higher portion of normal glomeruli and a lower portion of cellular crescents were found in MPA patients whose MPO antibodies were bound to the H4 fragment (a part of the C-terminal epitope of MPO) than in those with MPO antibodies unresponsive to the H4 fragment.<sup>14</sup> In addition, levels of interleukin-1 $\beta$ , toll-like receptor-4, and nod-like receptor family pyrin domain-containing-3 in the tubulointerstitium correlated with the severity of tubulointerstitial injury in ANCA-associated nephritis. This indicated that the mechanism behind tubulointerstitial injury was independent of glomerular injury.<sup>15</sup> Previous studies have suggested that a specific cell surface marker, MPO epitope, or receptors were involved in the pathogenesis of MPA-associated tubulointerstitial nephritis by controlling the binding affinity of the MPO antibody.

## 4 | CONCLUSIONS

In conclusion, the present report described a patient with MPA and atypical nephritis, which dominantly demonstrated tubulointerstitial nephritis with podocyte changes. These histologic changes in the present case suggested a specific subcategory or an early change in MPA-associated nephritis. Physicians should consider MPA as a possible diagnosis, even if crescentic glomerulonephritis is absent on renal biopsy.

## ACKNOWLEDGMENTS

We thank Hyunsoon Lee, from Hankook Renal pathology laboratory, for investigating and analyzing the results of kidney biopsies. Published with written consent of the patient.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## AUTHOR CONTRIBUTIONS

HKM: involved in conceptualization the study, interpreting data, and writing the manuscript. HRK and SHL: involved in interpretation of the clinical data. SHK: involved in collecting clinical data and writing the manuscript.

## ETHICAL APPROVAL

The present case report was approved by institutional review boards or local ethics committees.

## ORCID

Se Hee Kim  <https://orcid.org/0000-0002-9987-7480>

Hae-Rim Kim  <https://orcid.org/0000-0002-1911-6236>

Sang-Heon Lee  <https://orcid.org/0000-0002-7539-9330>

Hong Ki Min  <https://orcid.org/0000-0003-1147-1046>

## REFERENCES

1. Kronbichler A, Shin JI, Lee KH, et al. Clinical associations of renal involvement in ANCA-associated vasculitis. *Autoimmun Rev*. 2020;19(4):102495.
2. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65(1):1-11.
3. Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum*. 1999;42(3):421-430.
4. Binda V, Moroni G, Messa P. ANCA-associated vasculitis with renal involvement. *J Nephrol*. 2018;31(2):197-208.
5. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol*. 2010;21(10):1628-1636.
6. Reiser J, Sever S. Podocyte biology and pathogenesis of kidney disease. *Annu Rev Med*. 2013;64:357-366.

7. Kriz W, LeHir M. Pathways to nephron loss starting from glomerular diseases—insights from animal models. *Kidney Int.* 2005;67(2):404-419.
8. Bulanov N, Chebotareva NV, Novikov PI, Moiseev SV. Role of tubulointerstitial injury in ANCA-associated vasculitis is underestimated. *Ann Rheum Dis.* 2019;78(10):e111.
9. Wang XC, Liu CH, Chen YJ, et al. Clinical and pathological analysis of the kidney in patients with hypertensive nephropathy. *Exp Ther Med.* 2013;6(5):1243-1246.
10. Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol.* 2010;21(4):556-563.
11. Thickett DR, Richter AG, Nathani N, Perkins GD, Harper L. Pulmonary manifestations of anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis. *Rheumatology.* 2006;45(3):261-268.
12. Plafkin C, Zhong W, Singh T. ANCA vasculitis presenting with acute interstitial nephritis without glomerular involvement. *Clin Nephrol Case Stud.* 2019;7:46-50.
13. Nakabayashi K, Sumiishi A, Sano K, et al. Tubulointerstitial nephritis without glomerular lesions in three patients with myeloperoxidase-ANCA-associated vasculitis. *Clin Exp Nephrol.* 2009;13(6):605-613.
14. Gou SJ, Xu PC, Chen M, Zhao MH. Epitope analysis of anti-myeloperoxidase antibodies in patients with ANCA-associated vasculitis. *PLoS One.* 2013;8(4):e60530.
15. Tashiro M, Sasatomi Y, Watanabe R, et al. IL-1 $\beta$  promotes tubulointerstitial injury in MPO-ANCA-associated glomerulonephritis. *Clin Nephrol.* 2016;86(10):190-199.

**How to cite this article:** Kim SH, Kim H-R, Lee S-H, Min HK. Tubulointerstitial nephritis without glomerular crescent formation as an underestimated subgroup of renal involvement among microscopic polyangiitis patients: A case report. *Clin Case Rep.* 2021;9:e04123. <https://doi.org/10.1002/ccr3.4123>