AP-VAS 2012 case report: an atypical case of microscopic polyangiitis presenting with acute tubulointerstitial nephritis without glomerular change

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Abstract Renal involvement in myeloperoxidase–antineutrophil cytoplasmic antibody (MPO–ANCA)-associated vasculitis is frequently characterized by focal segmental crescentic and/or necrotizing glomerulonephritis. However, a few cases of only tubulointerstitial nephritis (TIN) involvement without any apparent glomerular lesions have been reported. Here we report just such a case. A 74-year-old woman was admitted to a nearby hospital with a 2-week history of pitting edema, fever and anemia. She developed acute renal failure without proteinuria and microscopic hematuria. The urinary excretion of *N*-acetyl-beta-D-glucosaminidase and beta2-microglobulin concentration were 30.3 U/ml and 42270 µg/ml, respectively. Gallium-67 scintigraphy revealed abnormal concentrations on both sides of her kidneys. Her MPO–ANCA titer was 92 EU (normal range <10 EU). Skin and renal biopsies demonstrated fibrinoid vasculitis, necrotizing angiitis and TIN without glomerular change. Microscopic polyangiitis was diagnosed based on clinical and pathological criteria. No other factor that could induce TIN was detected. This case illustrates an unusual renal presentation of acute renal failure due to necrotizing arteritis and TIN, consistent with MPO–ANCA-associated vasculitis lacking crescentic glomerulonephritis. The pathogenesis is currently unclear, but the low-affinity type of MPO–ANCA was identified.

Keywords Myeloperoxidase (MPO)–antineutrophil cytoplasmic antibody (ANCA) · Acute renal failure · Affinity of MPO–ANCA · Tubulointerstitial nephritis

Introduction

Renal involvement in myeloperoxidase–antineutrophil cytoplasmic antibody (MPO–ANCA)-associated vasculitis is frequently characterized by focal segmental crescentic and/or necrotizing glomerulonephritis and is usually associated to some extent with tubulointerstitial (TI) lesions. Most of the TI lesions presenting in this disease are thought to be due to secondary phenomena resulting from the rupture of Bowman's capsule in association with crescent formation, arteriolitis/arteritis and venulitis in the interstitium, tubulitis or the release of cytokines by the infiltrated inflammatory cells in the interstitium [1]. However, a few cases have been reported that have only tubulointerstitial nephritis (TIN) without any apparent glomerular lesions.

In this report, we describe a rare case of TIN without any glomerular lesion abnormality accompanied by microscopic polyangiitis (MPA).

Case report

A 74-year-old Japanese woman who had been treated with levothyroxine sodium 75 µg/day for chronic thyroiditis was admitted to hospital on 12 October 2011 with a 2-week history of fever (38–39 °C), pitting edema of her legs and purpura of her extremities. She was admitted to the hospital on 12 October. Increased levels of C-reactive protein (CRP; 12.0 mg/dl) and leukocytosis (9660/µl) were found. The baseline serum creatinine concentration (s-Cr) was 0.7 mg/dl on admission, but it increased to 1.3 mg/dl during the following 2 weeks. She was transferred to our hospital on 28 October for further investigation. Upon admission, the laboratory findings were as follows: white blood cell (WBC)

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Fig. 1 Renal biopsy findings. **a** Light microscopy examination revealed almost normal glomeruli [Periodic acid–Schiff (PAS) stain, $\times 400$]. **b**, **c** Focal infiltrate of inflammatory cells, composed of lymphocytes, monocytes, neutrophil, eosinophil and plasma cells with fibrosis, was observed in the interstitial compartment: **b** tubulitis and peritubular capillaritis (arrows), **c** fibrinoid vasculitis in interlobular artery and arteriole. **b** PAS stain, $\times 400$, **c** Masson's trichrome stain, $\times 40$

count, $12100/\mu\text{l}$; hemoglobin, 8.0 g/dl ; platelets, $478 \times 10^3/\mu\text{l}$; serum total protein, 7.0 g/dl ; serum albumin, 2.1 g/dl ; blood urea nitrogen, 25.0 mg/dl ; s-Cr, 1.31 mg/dl ; CRP,

13.07 mg/dl ; MPO–ANCA, 92 EU ; rheumatoid factor, 74 IU/ml ; anti-nuclear antibody, $40\times$; anti-Sjogren antigen A, 33.1 index ; proteinase 3-ANCA, anti-glomerular basement membrane antibody and anti-Sjogren antigen B were negative. Her serum immunoglobulin levels were: immunoglobulin (Ig)G, 2511 mg/dl ; IgA, 199 mg/dl ; IgM, 106 mg/dl ; IgG4, 7.0 mg/dl . Urinalysis showed negative proteinuria and red blood cells (RBC) at $1\text{--}4/\text{high power field}$ in the sediment. In addition, urinary β_2 -microglobulin (β_2 -MG) and urinary *N*-acetyl-beta-D-glucosaminidase levels were increased to 42270 mg/l and 30.3 U/l , respectively. The 24-h creatinine clearance was $31\text{ ml/min/1.73 m}^2$ and urinary protein excretion was 0.3 g/24 h . Gallium-67 scintigraphy revealed abnormal concentrations on both sides of her kidneys. There was no symptoms of dry eye and dry mouth, and salivary gland scintigraphy findings were normal.

The patient underwent renal biopsy and skin biopsy to facilitate diagnosis.

The skin biopsy showed that the subcutaneous small artery was affected by fibrinoid vasculitis. A renal biopsy was performed 7 days after admission to evaluate the cause of the acute renal failure. Examination of the renal biopsy specimen by light microscopy revealed 19 glomeruli, one of which was globally sclerotic. The other glomeruli showed an almost normal appearance except for collapsing capillary loops (Fig. 1a). Tubulitis and peritubular capillaritis were also noted (Fig. 1b). The extent of TI injury was approximately 10 % of the cortex. Fibrinoid vasculitis was observed in the interlobular artery and arteriole and there was diffuse infiltration of inflammatory cells composed of mainly lymphocytes around it (Fig. 1c). Immunofluorescence showed no depositions of immunoglobulin and complements. The diagnosis based on kidney biopsy findings was necrotizing arteritis and TIN, consistent with MPO–ANCA-associated vasculitis lacking crescentic glomerulonephritis.

The clinical course of our patient is outlined in Fig. 2. Based on the renal biopsy findings, we concluded that the acute renal failure was primarily due to the TIN. She was given orally prednisolone 50 mg/day and intravenous pulse cyclophosphamide 500 mg/body , which resulted in a gradual decrease in her s-Cr level and urinary excretion of β_2 MG.

After 1 month, her WBC and platelet counts had decreased and she began to have epigastralgia. Simultaneously, cytomegalovirus (CMV) antigen (C7-HRP) became positive at 6 cells per 50000 cells. Multiple erosive gastritis and ulcers on the vestibular portion, which had not been observed before treatment, were revealed by esophagogastroduodenoscopy (EGD) on 7 December. The CMV-infected cells were found in the gastric tissue biopsy sample removed by endoscopy. We diagnosed CMV gastroenteritis and treated the patient with ganciclovir 800 mg/day

Fig. 2 The patient's clinical course. A renal biopsy was performed 7 days after admission to hospital. She was given prednisolone (PSL) 50 mg/day and intravenous pulse cyclophosphamide (IVCY), which resulted in a gradual decrease in her serum creatinine level and urinary excretion of β_2 -microglobulin (β_2 -MG). After 1 month, she was diagnosed with cytomegalovirus (CMV) gastroenteritis and treated with ganciclovir and consecutively with valganciclovir

hydrochloride. Her symptoms gradually improved, and she was discharged on 28 December. CRP C-reactive protein, *div* daily/intervenous, EGD esophagogastrroduodenoscopy, *eGFR* estimated glomerular filtration rate, *Hb* hemoglobin, CMV (C7-HRP) CMV antigen, *Ga* gallium, MPO-ANCA myeloperoxidase-antineutrophil cytoplasmic antibody, *Plt* platelets, *po* orally, *u-Cr* urinary creatinine, WBC white blood cell

intravenously for 2 weeks and consecutively with oral valganciclovir hydrochloride 900 mg/1 × daily for 4 weeks. Her symptoms gradually improved, and she was discharged from our hospital on 28 December.

Discussion

We describe a case of acute renal failure due to necrotizing arteritis and TIN, consistent with MPO-ANCA-associated vasculitis lacking crescentic glomerulonephritis. When the pathogenesis of TIN is considered, a few other pathogenic mechanisms must be addressed. This patient had not taken any drugs known to cause renal toxicity and had no systemic infections and no systemic autoimmune diseases, such as systemic lupus erythematosus, Sjogren's syndrome, IgG4-related disease or TIN-uveitis syndrome.

Renal involvement in MPO-ANCA-associated vasculitis is frequently characterized by focal segmental crescentic and/or necrotizing glomerulonephritis. However, a few cases have been reported to involve only TIN without any apparent glomerular lesions, such as in our case. In an analysis of 232 renal biopsy specimens from patients with ANCA-positive pauci-immune renal disease evaluated at

the University of North Carolina Nephropathology Laboratory, 75 % were found with both glomerular necrosis and crescent formation. The frequency of TIN in the absence of glomerulonephritis was only 1 % [1]. In another study, only three (4.5 %) of 66 renal biopsy specimens from patients with MPO-ANCA-associated nephritis showed TIN without any apparent glomerular lesions [2]. On the other hand, TI injury in ANCA-associated vasculitis is generally thought to be secondary to crescentic glomerulonephritis, arteritis or arteriolitis [3]. In a recent report, Sato et al. [4] suggested that peritubular capillary injury is the pathogenesis of tubulointerstitial changes in ANCA-associated vasculitis. Peritubular capillary injury (peritubular capillaritis) has been emphasized in renal allograft nephropathy and results in interstitial fibrosis [5]. TI damage rather than glomerular changes represents the major cause of renal dysfunction [6]. In particular, ischemia in the tubulointerstitium due to peritubular capillaritis leads to progressive renal failure [5]. In our case, ischemia due not only to peritubular capillaritis in tubulointerstitial changes but also to fibrinoid vasculitis in the interlobular artery and arteriole led to increases in the creatinine level of up to 2 mg/dl. Because of the focal involvement, it is possible that we underestimated the real extent of the

interstitial lesion due to the biased samples of the renal biopsy.

The affinity of MPO–ANCA from patients with MPO–ANCA-associated vasculitis can be largely categorized as high and low affinity, irrespective of the level of MPO–ANCA titers [7]. This categorization may be helpful for the assessment of vasculitis activity affecting mainly the kidney and the lung. The high-affinity group ($n = 14$) included mainly cases of severe vasculitis disease activity (i.e. rapidly progressive glomerulonephritis, 57 %; acute respiratory distress syndrome, 36 %), while the low-affinity group ($n = 13$) included mainly cases of mild vasculitis activity (i.e. chronic renal failure, 77 %; chronic interstitial pneumonitis, 54 %). The difference between the renal pathological findings of the high-affinity group and low-affinity group was not described [7]. We investigated the affinity of MPO–ANCA in our patient and determined it was of the low-affinity type. This is consistent with the findings of Yoshida et al. [7] as the BVAS of our patient was relatively low (14 points at diagnosis, with fever, purpura, s-Cr increase of >30 %). The high-affinity type of MPO–ANCA may be able to activate a large number of neutrophils and stimulate neutrophil-induced cytotoxicity toward endothelial cells in coincidentally peritubular capillary and glomeruli and also in the other organs. On the other hand, in the case of the low-affinity type MPO–ANCA, there may be only weak activation of the neutrophils and only a small number of adhesion molecules may be induced. Therefore, one of the few activated neutrophils may be able to adhere to the endothelial cells easier in the peritubular capillary than in the glomeruli because of decreased vascular flow speed and pressure. The obstruction in the peritubular capillary would subsequently increase the intravascular pressure in the upper stream, the efferent arteriolar and glomeruli.

Previous studies have reported that the severity of the diseases in crescentic glomerulonephritis associated with MPO–ANCA is correlated with particular epitopes of MPO–ANCA that recognize the N- or C-terminus of the MPO heavy chain [8–10]. This difference in MPO–ANCA epitopes may also explain the pathologic features. We did not investigate the epitope of our patient. Nakabayashi et al. [2] reported three cases of TIN but without glomerular lesions in MPO–ANCA-associated vasculitis and early loss of CD34 antigenicity in the peritubular capillary. This early loss of CD34 antigenicity due to MPO and tubulitis played important roles in the pathogenesis of peritubular capillaritis and lysis of tubular basement membrane and induced TIN. However, similar processes were not observed in the glomeruli, which showed preservation of CD34 staining. The reason why MPO–ANCA affects mainly the TI lesion without glomerular lesions is not easily explained. It is

possible that differences in the affinity of the MPO–ANCA may be associated with differences in each specific antigen. In this context, the low-affinity type of the MPO–ANCA would possibly recognize some antigens specific to a TI area.

Further studies are needed to define the difference between high- and low-affinity MPO–ANCA in terms of pathogenesis.

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Conflict of interest The authors have declared that no conflict of interest exists.

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