AP-VAS 2012 case report: two patients with rheumatoid arthritis suspected of relapsed microscopic polyangiitis after initiation of dialysis

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Received: 28 August 2012 / Accepted: 27 April 2013 / Published online: 4 July 2013
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Abstract We report two patients with rheumatoid arthritis (RA) who were suspected of microscopic polyangiitis during maintenance dialysis. Case 1 was a 52-year-old woman with RA diagnosed at the age of 38 years and treated successfully with gold compounds. At the age of 43 years, she presented with progressive renal dysfunction and abnormal urine sediments, and a renal biopsy revealed crescentic nephritis with advanced glomerular sclerosis. Myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) was not measured on that occasion. She reached end-stage renal failure within 4 months and started peritoneal dialysis. Eight years later, soon after she was switched to hemodialysis, she developed fever of unknown origin. MPO-ANCA was elevated to 37 EU, although there were no other signs or symptoms suggestive of vasculitis. After taking prednisolone orally (10 mg/day), her fever withdrew, and MPO-ANCA became undetectable. Case 2 was a 71-year-old woman with RA diagnosed at the age of 60 years and treated with gold compounds. She developed renal failure of unknown cause (no biopsy was performed), and started hemodialysis at the age of 69 years. One year later, she presented with fever and subsequently developed cough with hemoptysis. MPO-ANCA was elevated to 62 EU. Treatment with azathioprine 50 mg and prednisolone 35 mg daily brought remarkable clinical improvement, and MPO-ANCA became undetectable. These cases highlight

the importance of measuring ANCA even in RA patients on dialysis who present with fever of unknown origin or with underlying kidney disease of uncertain etiology.

Keywords Microscopic polyangiitis · Rheumatoid arthritis · Hemodialysis · Myeloperoxidase antineutrophil cytoplasmic antibody

Introduction

Microscopic polyangiitis (MPA) is a necrotizing vasculitis that typically involves the kidneys and the lungs [1]. Affected patients frequently present with glomerulonephritis that is often rapidly progressive and results in end-stage renal failure. In typical cases, MPA can be diagnosed easily soon after initial presentation, but there have also been some patients who were diagnosed with MPA years after initiation of chronic dialysis [2–4]. Here we report two patients with rheumatoid arthritis (RA) who were suspected of MPA during maintenance dialysis.

Case 1

In August 2001, a 52-year-old woman was referred to our hospital due to fever of unknown origin after each dialysis session. Her past medical history included rheumatoid arthritis diagnosed at the age of 38 years and treated with gold compounds for 6 months. She had no history of allergic disease. At the age of 43 years, she underwent a renal biopsy due to progressive renal dysfunction. The serum creatinine concentration deteriorated from 1.2 to 3.5 mg/dl over 6 months. At the biopsy, laboratory evaluations demonstrated hemoglobin 8.6 g/dl, serum creatinine

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Fig. 1 Approximately half of the glomeruli were globally sclerotic. Fibrocellular crescents with segmental sclerosis were observed in the remaining glomeruli (periodic acid Schiff staining, original magnification $\times 400$)

Fig. 2 Clinical course of Case 1

3.7 mg/dl, blood urea nitrogen 36 mg/dl, CRP 0.2 mg/dl, rheumatoid factor 9 IU/ml (<7 IU/ml) and antinuclear antibody negative. She fulfilled the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA [5]. Her Steinbrocker's differentiation was class II and stage IV [6]. Her RA was thought to be inactive, and no disease-modifying antirheumatic drugs (DMARDs) were prescribed at that time. Urinalysis showed hematuria (3+) and the 24-h urinary protein was 4–6 g/day. On the biopsy specimen, 9 out of 20 glomeruli (45 %) were globally sclerotic and the remaining glomeruli revealed fibrocellular crescents with segmental sclerosis (Fig. 1). Neither glomerular necrosis nor necrotizing vasculitis was observed. There was trace staining for C1q, C3, C4, IgA, IgG and IgM in the mesangial area in immunofluorescence staining. ANCA was not measured on that occasion, and the cause of crescentic glomerulonephritis was uncertain. She was treated conservatively, because

renal histological damages were advanced and seemed unlikely to respond to immunosuppressive therapies. She reached end-stage renal failure within 4 months and started peritoneal dialysis. Anemia improved with erythropoiesis stimulating agent.

Eight years later, soon after she was switched to hemodialysis, she developed fever of unknown origin at the end of each dialysis session. Her temperature was 36.5°C before hemodialysis, and rose to $38\text{--}39^{\circ}\text{C}$ at the end of each dialysis session. Several different dialyzers were tried, but there was no improvement. Physical examination revealed no abnormal findings. Laboratory tests showed white blood cells $10,400/\mu\text{l}$ (neutrophil 74.8 %, lymphocyte 15.3 %, eosinophil 7.2 %, monocyte 1.0 %), hemoglobin 9.6 g/dl, CRP 8.8 mg/dl, and MPO-ANCA 37 EU (<20 EU) (This was the first time MPO-ANCA was measured). There were no signs or symptoms suggestive of infectious disease or malignancy. The positive value of MPO-ANCA suggested MPA, thus treatment with oral prednisolone 10 mg/day was started. Her fever withdrew within days, and MPO-ANCA also became undetectable. Oral prednisolone was gradually reduced to 5 mg/day and tacrolimus 3 mg/day was later added to treat RA. There has been no recurrence of fever or re-elevation of MPO-ANCA. The clinical course of Case 1 is summarized in Fig. 2.

Case 2

A 71-year-old woman presented with fever, hemoptysis and systemic arthralgia. Her past medical history included RA diagnosed at the age of 60 years. Laboratory data and Steinbrocker grading at the time of diagnosis were unknown. She was treated with gold compounds for 5 years and the treatment was withdrawn because of proteinuria. She then started taking actarit which also had to be discontinued because of renal failure of unknown cause. Her renal function did not recover, and she started hemodialysis at the age of 69 years. She did not undergo renal biopsy, and MPO-ANCA was not measured on that occasion.

In January 2004, she presented with persistent cough. Bronchitis was suspected, but antibiotics were ineffective. In March, she complained of continuous fever and hemoptysis, and was admitted to the hospital in April. She did not take any antirheumatic drugs at that time. On admission, her temperature was 37.5°C , and the other vital signs were within normal range. Physical examinations revealed bilateral fine crackles. Laboratory tests showed white blood cells $12,400/\mu\text{l}$, hemoglobin 9.8 g/dl, CRP 14.2 mg/dl, rheumatoid factor 37.3 IU/ml, antinuclear antibody positive (titer 1:160), and MPO-ANCA 62 EU (<20 EU). The

chest radiogram showed bilateral ground opacity. She was tentatively diagnosed with MPA based on the MPO-ANCA positivity and suspected pulmonary bleeding, although bronchoscopic examination was not performed. Treatment with azathioprine 50 mg and prednisolone 35 mg daily brought remarkable clinical improvement, and MPO-ANCA became undetectable. After 3 weeks, azathioprine was withdrawn because of bone marrow suppression. Prednisolone was gradually reduced to 6 mg/day orally, and no recurrence has been observed.

Discussion

We present two patients with rheumatoid arthritis who were suspected of MPA during maintenance dialysis. According to the Japanese diagnostic criteria for MPA, these cases were categorized as probable MPA [7]. There had been previous case reports of similar clinical courses. Horai et al. [2] reported a case of 62-year-old man who presented with hemoptysis and was diagnosed with MPA a year after initiation of hemodialysis. The underlying kidney disease was unknown, but it was possible that MPA was the cause of end-stage renal failure. Goto et al. [3] reported a case of 26-year-old woman who was diagnosed with MPA 9 years after initiation of hemodialysis. The patient presented with acute renal failure at the age of 17 years, and her renal biopsy revealed crescentic glomerulonephritis of unknown etiology. Seven years after initiation of hemodialysis, chronic anemia unresponsive to erythropoiesis stimulating agent developed. The laboratory test showed elevated MPO-ANCA, and bronchoscopy revealed alveolar hemorrhage, both of which were compatible with MPA. In this case reported by Goto et al. crescentic glomerulonephritis might have been a renal manifestation of MPA.

The patient in Case 1 lacked typical symptoms suggestive of vasculitis, and this might be due to the co-existence of RA. We previously reported that MPO-ANCA associated crescentic glomerulonephritis in RA patients developed in middle-aged or young adult women and was accompanied by little extrarenal manifestations [8]. Patient 1 was indeed a relatively young woman and the only symptom compatible with vasculitis was fever of unknown origin. Her temperature rose to 38–39 °C at the end of each dialysis session, which rather suggested allergy to dialyzers. However, trying several different dialyzers did not improve her symptom and the absence of marked eosinophilia or history of allergic disease suggested mechanisms other than simple allergy. The other common causes of fever, such as infectious disease and cancer, were also improbable. The screening test revealed MPO-ANCA positivity, which suggested the presence of vasculitis.

Dialysis has been associated with acute changes in the complement activation status [9], granulocyte markers [10, 11], macrophage function [12], T cell activation [13, 14] and the release of various proinflammatory cytokines [15]. These immune responses might have been responsible for revealing symptoms of vasculitis after each dialysis session.

The renal biopsy of Patient 1 demonstrated pauci-immune crescentic glomerulonephritis, and it suggested the possibility that MPA had already been present before initiation of dialysis, and was the actual cause of end-stage renal failure. The common renal disorders in patients with RA include amyloid A amyloidosis, membranous nephropathy, mesangial proliferative glomerulonephritis, and drug-induced nephropathy [16]. Although less common, there have been several case reports on MPO-ANCA associated glomerulonephritis in patients with RA [17–23]. We previously reported that renal dysfunction of MPO-ANCA associated crescentic glomerulonephritis in RA patients showed slower progression compared to typical rapidly progressive glomerulonephritis without RA [8]. The duration from onset to initiation of dialysis in Case 1 was indeed more than 1 year. Although 24-h urinary protein exceeding 4 g/day was relatively uncommon for MPA, a previous report showed that MPA could present as nephrotic syndrome [1]. In Case 2, the underlying kidney disease was uncertain, but it is possible that MPA might have been present before initiation of dialysis and caused renal failure. Measuring ANCA may be useful in dialysis patients with underlying kidney disease of uncertain etiology, because MPA might be the cause of renal failure.

In summary, we report two RA patients who were suspected of MPA after initiation of dialysis. These cases highlight the importance of measuring ANCA even in RA patients after initiation of dialysis, since MPA might be the origin of fever or the actual cause of end-stage renal failure.

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

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