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Delayed Development of Pulmonary Hemorrhage in a Patient with Positive Circulating Anti-Neutrophil Cytoplasmic Antibody: A Clinical Dilemma

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Key Words
ANCA-related nephritis and vasculitis · Pulmonary hemorrhage · Focal and segmental glomerulosclerosis · Tuberculosis

Abstract
Detection of circulating anti-neutrophil cytoplasmic antibody (ANCA) provides a powerful clue in the diagnosis of vasculitis, but the clinical interpretation of the results is difficult in some cases. Here, we describe the case of a 65-year-old man who underwent hemodialysis due to focal segmental glomerulosclerosis and abruptly developed hemoptysis 14 years after a renal biopsy. At the time of the biopsy, computed tomography (CT) showed interstitial shadows in the lungs and pleural thickening, indicating pneumoconiosis that was accompanied by tuberculosis. Circulating myeloperoxidase-ANCA (10.5–32.5 U/ml) was subsequently noted, but the significance of this observation was unclear due to the preexisting disorders in the lungs and kidneys. Potent immunosuppressive therapies were avoided because of the pulmonary lesions and decreased renal function. There were few changes noted on follow-up CT, but infiltrative shadows emerged in the bilateral lungs, consistent with hemoptysis. The hemorrhagic shadows completely disappeared shortly after initiation of steroid therapy, with normalization of the serum ANCA level. Herein, we report this case, with an emphasis on the clinical dilemma faced in deciding the appropriate treatment. The findings in the case provide deep insights into clinical management of ANCA-positive patients.

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Introduction

Myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibody (ANCA) is frequently detected in cases of microscopic polyangiitis (MPA) and renal-limited vasculitis, while those directed against proteinase 3 (PR3-ANCA) are commonly seen in granulomatosis with polyangiitis [1]. These conditions are collectively referred to as ANCA-associated vasculitis (AAV), which is a life-threatening autoimmune disease characterized by pulmonary-renal involvement. A recent nationwide survey showed that MPO-ANCA was positive in 88.1 and 91.8% of patients with renal-limited vasculitis and MPA, respectively, among rapidly progressive glomerulonephritis patients in Japan [2]. Thus, circulating ANCA is now widely used as diagnostic markers for several forms of idiopathic systemic vasculitis and rapidly progressive glomerulonephritis [1, 3]. There is also growing evidence for their pathogenicity, per se, in in vitro and in vivo studies [4]. However, paradoxically, elevation of serum ANCA titers has also been observed in diverse conditions such as rheumatic diseases [3, 5], inflammatory bowel diseases [3, 5], infectious disorders [5, 6], and drug-induced syndromes [7], which creates a clinical puzzle.

Here, we describe a hemodialysis (HD) patient who developed pulmonary hemorrhage as long as 10 years after detection of circulating MPO-ANCA. Despite our concern about AAV, the preexisting pulmonary disease (thought to be pneumoconiosis and tuberculosis; TB) and renal disease (biopsy-proven focal segmental glomerulosclerosis; FSGS) limited a definite diagnosis and administration of potent immunosuppressive therapy. This case provides deep insights into the appropriate clinical management of patients with circulating ANCA.

Case Report

A 50-year-old male visited our hospital in October 1996 because of abnormalities detected in a medical checkup. Urinary protein and occult hematuria had been documented in medical checkups over the previous few years, with marked proteinuria of up to 3.8 g/day being a prominent feature of his clinical presentation. Renal biopsy performed in December 1996 revealed segmental sclerosis in 1 of 7 glomeruli and deposition of immunoreactive substances into glomeruli, including IgM and complement. Therefore, a diagnosis of FSGS was made on the basis of the results of a renal biopsy. Also, chest computed tomography (CT) delineated interstitial changes accompanied by cystic lesions in the lung and pleural thickening (fig. 1a), along with chest X-ray abnormalities that had been noted in a past medical checkup. He had worked as a demolition worker and smoked approximately 30 cigarettes a day since he was 18 years old. Work- and smoking-related lung conditions were therefore the most likely causes of the pulmonary lesions. An annual chest CT showed little change over several years, in contrast to progression of the renal disorder. Pleural thickening strongly suggested concomitant TB based on epidemiological reports showing a strong association of TB with pneumoconiosis [8], although mycobacterium species were not detected by sputum culture tests that were repeatedly performed over a couple of years.

Cyclosporine A (CsA) was administered at doses of 50–100 mg per day under therapeutic drug monitoring (the trough level was usually around 50 ng/ml) in lieu of steroid therapy [9] to reduce the risk of excessive immunosuppression, but the serum creatinine (Cr) level showed a rapid elevation in 2000, at approximately 3 years after biopsy (fig. 2a). He had

presented with persistent microscopic hematuria, which is inconsistent with the clinical presentation of FSGS, since the first visit. By contrast, a temporary decrease in proteinuria (down to 1.3 g/day) was observed afterward, unlike with treatment-resistant FSGS. Rapidly progressive glomerulonephritis was suspected despite the biopsy findings, and circulating ANCA was measured (this test has been clinically available since 1998 in Japan). Elevation of the MPO-ANCA titer (168 EU) was found, along with an altered clinical presentation. However, potent immunosuppressive therapies such as glucocorticoids were still withheld due to the possibility of an underlying infection (TB). Apheresis was alternatively conducted in an effort to avoid decreased immune competence, but initiation of HD was required in September 2001 because of end-stage renal disease (ESRD). Thrice-weekly HD was performed uneventfully for several years, and there were also no changes in pulmonary signs. An annual CT checkup had shown little change (fig. 1b), and elevation of serum KL-6 [10] had not been documented. In contrast, circulating MPO-ANCA had ranged from 10.5 to 32.5 U/ml, even in the dialysis period, indicating possible AAV (fig. 2b). However, steroid therapy was postponed due to the unconfirmed diagnosis, presumed TB, and lack of problematic clinical events.

Abruptly, the patient developed gross hemoptysis accompanied by severe cough at night in bed and was transported to our facility by ambulance in October 2010. Chest CT showed infiltrative shadows in the bilateral lung fields (fig. 1c). Under a presumptive diagnosis of alveolar hemorrhage associated with AAV, steroid therapy comprising 3-day intravenous infusion of 500 mg methylprednisolone followed by daily oral administration of 20 mg prednisolone (PSL) was launched. A preventive dose of 100 mg isoniazid per day was also prescribed. As expected, the hemorrhagic shadows almost disappeared as early as 2 days after hospitalization (fig. 1d), and the serum MPO-ANCA titer subsequently fell to normal (fig. 2b). The patient was discharged after 17 days and has had no recurrence of hemoptysis. At present, PSL has slowly been tapered to a daily dose of 5 mg, but there has been little change over time in the serum MPO-ANCA level and follow-up CT.

Discussion

The main features of the present case can be summarized as (1) sustained elevation of serum MPO-ANCA, of which the significance was uncertain; (2) the result of a renal biopsy and presumed pulmonary disease, which were different from AAV, and (3) delayed onset of pulmonary hemorrhage.

Renal and pulmonary involvements are the principal features of AAV. However, in our case, the pathological findings of renal biopsy, including deposition of immunoreactive substances (IgM and complement) into glomeruli and a lack of glomerular crescent formation, were entirely different from those commonly observed in AAV patients (pauci-immune necrotizing crescentic glomerulonephritis) [11]. The clinical features, such as heavy proteinuria (up to 3.8 g/day), agreed well with those of FSGS, whereas interstitial changes in the inferior lobes of the lungs and the former job of the patient (demolition worker) strongly indicated pneumoconiosis [12], including asbestosis and silicosis. Incidentally, CsA might be regarded as an exacerbating factor for renal impairment. However, CsA nephrotoxicity was less likely in the present case, based on the treatment duration and the use of therapeutic drug monitoring. In fact, we have recently reported that patients who were treated for minimal change nephrotic syndrome with CsA for at least 2 years experienced no deterioration in renal function [10]. We were also concerned about subsequent infection by *Mycobacterium tuberculosis* since an increased risk of this infection has been reported in populations

with similar features to our patient [8]. Renal function was already impaired (Cr clearance 45.3 ml/min) when circulating ANCA was noted. Thus, the pre-existing lesions described above were important hurdles in defining the clinical strategy. However, based on suspicion of latent AAV, an annual CT was performed, and the serum KL-6 level, a good monitoring approach for diagnosis and follow-up of interstitial pneumonia in AAV patients as with other rheumatic diseases [13], was measured every month even after progression to ESRD. However, despite our effort at preclinical detection of AAV, no radiographic changes were observed over time, and serum KL-6 remained normal. There was also no evidence for other sites of involvement, including gastrointestinal, neural, or otological symptoms. Furthermore, there was no significant change in serum C-reactive protein or signs of possible pulmonary infection prior to the hemoptysis. The radiographic findings at the time of hemoptysis were compatible with alveolar hemorrhage, which is the most frequent manifestation of lung involvement in MPA [14]. Although other possibilities such as infectious disorders, organized pneumonia, and overt TB cannot be completely excluded, the bilaterality, rapid response to steroid therapy, and follow-up normalization of serum ANCA were eloquent indicators of AAV. It has been well described that there are some differences in characteristics of Japanese AAV patients compared with those in Europe. For instance, MPA and MPO-ANCA are more common in Japan, and granulomatosis with polyangiitis and PR3-ANCA are more common in the UK [15]. In light of the Japanese prospective multicenter study with MPO-associated vasculitis [16], the clinical practice guideline for AAV (a Japanese-language publication) was published for Japanese patients in 2011. According to this guideline, in cases of focal (<30%) lung hemorrhage (severe form), steroid therapy should be launched and combined with cyclophosphamide within 4 weeks. Hence, as a result of the rapid improvement, monotherapy of corticosteroids was conducted in the present case.

Positive ANCA test results have been reported in many diseases other than systemic vasculitis, including rheumatic diseases [3, 5], inflammatory bowel diseases [3, 5], infectious disorders [5, 6], and drug-induced syndromes [7]. With regard to antecedent infection, Flores-Suárez et al. [6] found that 18 of 45 TB patients (40%) were ANCA positive by enzyme-linked immunosorbent assay (ELISA) and concluded that a positive ANCA test must be carefully interpreted as indicative of systemic vasculitis, especially when there are no signs of extrapulmonary involvement. Andersen-Ranberg et al. [17] also highlighted the high prevalence of autoantibodies among very old people (centenarians) in whom MPO- and PR3-ANCA were positive in 10.8 and 7.2%, respectively. Mandl et al. [18] found that the positive predictive value was only 54% for ANCA testing, indicating that a positive result on an ANCA test (ELISA) is not a definitive diagnostic indicator of AAV. This diversity sometimes hampers the diagnosis of AAV. However, in the present case, clinical manifestation of these autoimmune diseases was not observed and antithyroid agents had not been used.

The studies described above suggest that circulating ANCA is not only a diagnostic clue for AAV but also a critical issue in clinical practice. Knight et al. [5] found that 18 of 74 subjects with a positive test for cytoplasmic- or PR3-ANCA did not present with clinical evidence supportive of or insufficient to support a diagnosis of systemic vasculitis, but presented with a range of other diseases including ankylosing spondylitis, sarcoidosis, and ulcerative colitis. In particular, it was concluded that ANCA-positive subjects with no vasculitis at the time of the test had only a small risk of subsequent development of vasculitis, since none of the 18 patients developed vasculitis during a mean follow-up period of 6.8 years [5]. In the present case, alveolar hemorrhage occurred at 10 years after an initial positive ANCA test. Thus, our experience strongly suggests that long-term care should be

provided to patients with positive circulating ANCA, even in a case with an undetermined diagnosis.

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References

1 Hagen EC, Daha MR, Hermans J, Andrassy K, Csernok E, Gaskin G, Lesavre P, Lüdemann J, Rasmussen N, Sinico RA, Wiik A, van der Woude FJ: Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. Kidney Int 1998;53:743–753.
2 Koyama A, Yamagata K, Makino H, Arimura Y, Wada T, Nitta K, Nihei H, Muso E, Taguma Y, Shigematsu H, Sakai H, Tomino Y, Matsuo S: A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity. Clin Exp Nephrol 2009;13:633–650.
3 Schönermarck U, Lamprecht P, Csernok E, Gross WL: Prevalence and spectrum of rheumatic diseases associated with proteinase 3-antineutrophil cytoplasmic antibodies (ANCA) and myeloperoxidase-ANCA. Rheumatology (Oxford) 2001;40:178–184.
4 Gómez-Puerta JA, Bosch X: Anti-neutrophil cytoplasmic antibody pathogenesis in small-vessel vasculitis: an update. Am J Pathol 2009;175:1790–1798.
5 Knight A, Ekbom A, Brandt L, Askling J: What is the significance in routine care of c-ANCA/PR3-ANCA in the absence of systemic vasculitis? A case series. Clin Exp Rheumatol 2008;26:S53–S56.
6 Flores-Suárez LF, Cabiedes J, Villa AR, van der Woude FJ, Alcocer-Varela J: Prevalence of antineutrophil cytoplasmic autoantibodies in patients with tuberculosis. Rheumatology (Oxford) 2003;42:223–229.
7 Gao Y, Chen M, Ye H, Yu F, Guo XH, Zhao MH: Long-term outcomes of patients with propylthiouracil-induced anti-neutrophil cytoplasmic auto-antibody-associated vasculitis. Rheumatology (Oxford) 2008;47:1515–1520.
8 teWaternaude JM, Ehrlich RI, Churchyard GJ, Pemba L, Dekker K, Vermeis M, White NW, Thompson ML, Myers JE: Tuberculosis and silica exposure in South African gold miners. Occup Environ Med 2006;63:187–192.
9 Korbet SM: Treatment of primary focal segmental glomerulosclerosis. Kidney Int 2002;62:2301–2310.
10 Inoue M, Yumura W, Morishita Y, Ito C, Hamano Y, Ando Y, Muto S, Kusano E: Patients with adult minimal change nephrotic syndrome treated with long-term cyclosporine did not experience a reduction in their eGFR. Clin Nephrol 2013;79:101–106.
11 Jennette JC: Rapidly progressive crescentic glomerulonephritis. Kidney Int 2003;63:1164–1177.
12 Wade WA, Petsonk EL, Young B, Mogri I: Severe occupational pneumoconiosis among West Virginian coal miners: one hundred thirty-eight cases of progressive massive fibrosis compensated between 2000 and 2009. Chest 2011;139:1458–1462.
13 Iwata Y, Wada T, Furuichi K, Kitagawa K, Kokubo S, Kobayashi M, Sakai N, Yoshimoto K, Shimizu M, Kobayashi K, Yokoyama H: Serum levels of KL-6 reflect disease activity of interstitial pneumonia associated with ANCA-related vasculitis. Intern Med 2001;40:1093–1097.
14 Manganelli P, Fietta P, Carotti M, Pesci A, Salaffi F: Respiratory system involvement in systemic vasculitides. Clin Exp Rheumatol 2006;24:S48–S59.
15 Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DR, Scott DG, Hashimoto H, Nunoi H: Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the UK. Rheumatology (Oxford) 2011;50:1916–1920.
16 Ozaki S, Atsumi T, Hayashi T, Ishizu A, Kobayashi S, Kumagai S, Kurihara Y, Kurokawa MS, Makino H, Nagafuchi H, Nakabayashi K, Nishimoto N, Suka M, Tomino Y, Yamada H, Yamagata K, Yoshida M, Yumura W, Amano K, Arimura Y, Hatta K, Ito S, Kikuchi H, Muso E, Nakashima H, Ohsone Y, Suzuki Y, Hashimoto H, Koyama A, Matsuo S, Kato H: Severity-based treatment for Japanese patients with MPO-ANCA-associated vasculitis: the JMAAV study. Mod Rheumatol 2012;22:394–404.
17 Andersen-Ranberg K, HØier-Madsen M, Wiik A, Jeune B, Hegedus L: High prevalence of autoantibodies among Danish centenarians. Clin Exp Immunol 2004;138:158–163.
18 Mandl LA, Solomon DH, Smith EL, Lew RA, Katz JN, Shmerling RH: Using antineutrophil cytoplasmic antibody testing to diagnose vasculitis: can test-ordering guidelines improve diagnostic accuracy? Arch Intern Med 2002;162:1509–1514.

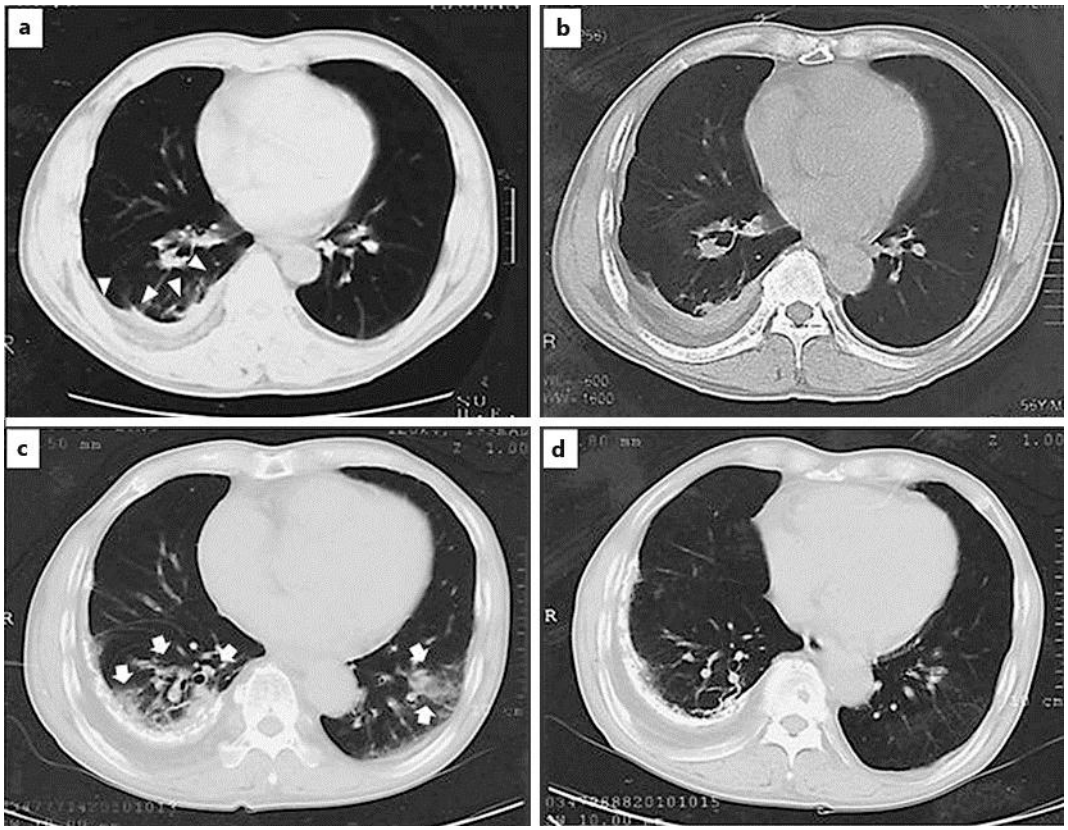

Fig. 1. Time course of pulmonary lesions in our patient. **a** In a kidney biopsy performed in December 1996, interstitial changes of the lungs and pleural thickening (arrowheads) were the principal findings. **b** Chest CT from September 2001 shows little change. **c** Chest CT from October 2010 shows infiltrative shadows (arrows) in bilateral inferior lobes, simultaneously with hemoptysis. **d** Chest CT 2 days later in October 2010 shows disappearance of the hemorrhagic shadows shortly after initiation of steroid therapy.

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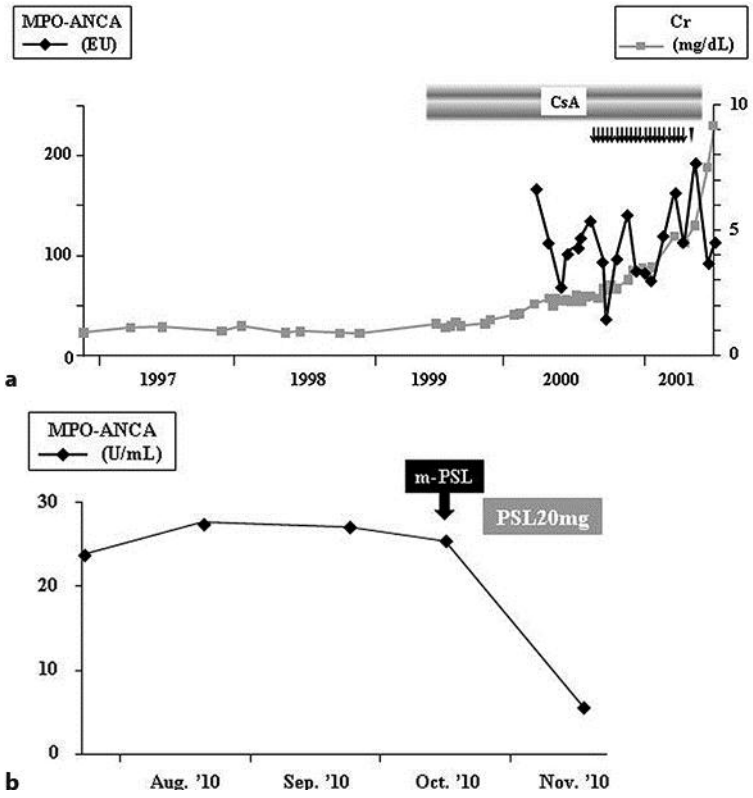

Fig. 2. **a** Course of serum Cr levels and MPO-ANCA titers from the time of renal biopsy until initiation of HD. Arrows indicate plasma exchange therapy; inverted triangle indicates granulocytapheresis. **b** Normalization of circulating MPO-ANCA following steroid therapy against alveolar hemorrhage. m-PSL = 3-day infusion of 500 mg methylprednisolone.