Case Report

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Aortic aneurysm as a complication of myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract: Myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis (MPO-AAV) does not usually involve large vessels, such as the aorta. However, we experienced three cases having an aortic aneurysm as a complication of MPO-AAV with renal insufficiency. In one patient it involved the onset of descending aortic dissection during treatment for MPO-AAV; another two patients had an abdominal aortic aneurysm at the time of our diagnosis of MPO-AAV. Although we found no pathological evidence in our patients, MPO-AAV might result in large vessel inflammation. Therefore, we suggest that patients with MPO-AAV should be examined by computed tomography scan to check for the presence of an aortic aneurysm.

Keywords: antineutrophil cytoplasmic antibody-associated vasculitis (ANCA-associated vasculitis), myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA), microscopic polyangiitis (MPA) aortic aneurysm, connective tissue disease

1 Introduction

Microscopic polyangiitis (MPA) is a systemic autoimmune vasculitis that affects small and medium-sized blood vessels (namely, capillaries, venules, or arterioles) and involves the kidneys, lungs, nerves, and skin. Antineutrophil cytoplasmic antibodies are autoimmune antibodies that are usually associated with cytoplasmic proteins (proteinase3 and myeloperoxidase) expressed in the cytoplasm of neutrophils. According to a proposal from the Chapel Hill Consensus Conference in 2012 [1], antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized pathologically by necrotizing vasculitis without an immune complex. Therefore, ANCAs have not been used to further characterize large vessel vasculitis. AAV exhibits a variety of clinical manifestations, such as renal diseases (rapidly progressive glomerulonephritis, hematuria, proteinuria), lung diseases (alveolar hemorrhage, interstitial pneumonia), and others (purpura, subcutaneous bleeding, digestive tract hemorrhage, mononeuritis multiplex).

We recognize giant cell arteritis and Takayasu's arteritis as large vessel vasculitides [2, 3]. Other large vessel vasculitides are known to occur in Cogan's syndrome [4-6], Behçet disease [7], polymyositis, and a variety of infections [8]. In the absence of other systemic diseases, aortic inflammation might be seen in atherosclerosis [9]. Generally, myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis (MPO-AAV) does not involve large vessels, such as the aorta.

We herein report that we have experienced three cases of aortic aneurysm as a complication of MPO-AAV with renal insufficiency.

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2 Cases

2.1 Case 1

A 75-year-old Japanese man was treated for hypertension and hyperuricemia with renal insufficiency.

His serum creatinine level was 1.37 mg/dL (normal range: 0.65–1.07 mg/mL) one year before, 1.49 mg/dL at 6 months before, and 11.41 mg/dL at his first visit to our hospital. He was admitted to our hospital because of elevated serum creatinine with microhematuria. He had been smoking 20 cigarettes per a day for 55 years before hospitalization. After the hospitalization, he stopped smoking.

Laboratory evaluation revealed that MPO-ANCA, serum creatinine, and serum C-reactive protein levels were elevated to 480 U/mL (normal range: <3.5 U/mL), 12.17 mg/dL (normal range: 0.65–1.07 mg/mL), and 12.50 mg/dL (normal range: <0.30 mg/mL), respectively. The estimated glomerular filtration rate (eGFR) had decreased to 4 mL/min/1.73m^2 and the CH 50 level was 49 U/mL (normal range: 30–45 U/mL). Results of various antinuclear antibody tests, including anti-double stranded DNA antibody, were negative, except that for MPO-ANCA. Urinary red blood cells were 100↑/high power field. The urine protein-to-creatinine ratio was 5.30 g/g · creatinine. Physical examination on admission revealed purpura on both lower extremities. The patient was diagnosed as having MPO-AAV with renal insufficiency. An aortic aneurysm had not been apparent on a computed tomography (CT) scan at admission (Figure 1A).

We started hemodialysis therapy, and treatment with 500 mg intravenous methyl-prednisolone pulse therapy was administered for 3 consecutive days. After methyl-prednisolone pulse therapy, 40 mg prednisolone per day was administered. Under the treatment with prednisolone, almost all laboratory findings had improved, except those for renal function. Therefore, hemodialysis therapy was continued three times a week. We had to taper prednisolone carefully to avoid recurrent activity of MPO-AAV. After the treatment for MPO-AAV had continued for 4 months, he developed a continuous dry cough, high fever, and lung air space consolidation in both middle lung fields. As his sputum smear was graded Gaffky 8 and the result of the polymerase chain reaction test of his sputum specimen for *Mycobacterium tuberculosis* was positive, he was diagnosed with pulmonary tuberculosis. Treatment for pulmonary tuberculosis was begun, and the patient's condition improved. He had been taking the tuberculosis medicines and MPO-AAV medicines for about 11 months after the start of treatment for MPA-AAV: rifampicin 450 mg per day, isoniazid 300 mg per day, ethambutol 0.5 g after each hemodialysis, and pyrazinamide 750 mg after each hemodialysis procedure (ethambutol and pyrazinamide were administered only for the first 2 months after the diagnosis of tuberculosis); medications for MPO-AAV consisted of prednisolone 15 mg per day and azathioprine 50 mg per day. Blood pressure was in the range of 130–150 / 70–90 mmHg without a medication for hypertension during treatment for MPA-AAV. He experienced pain in the upper back during the 11th month after he was admitted to our hospital. The chest CT image revealed an aortic aneurysm.

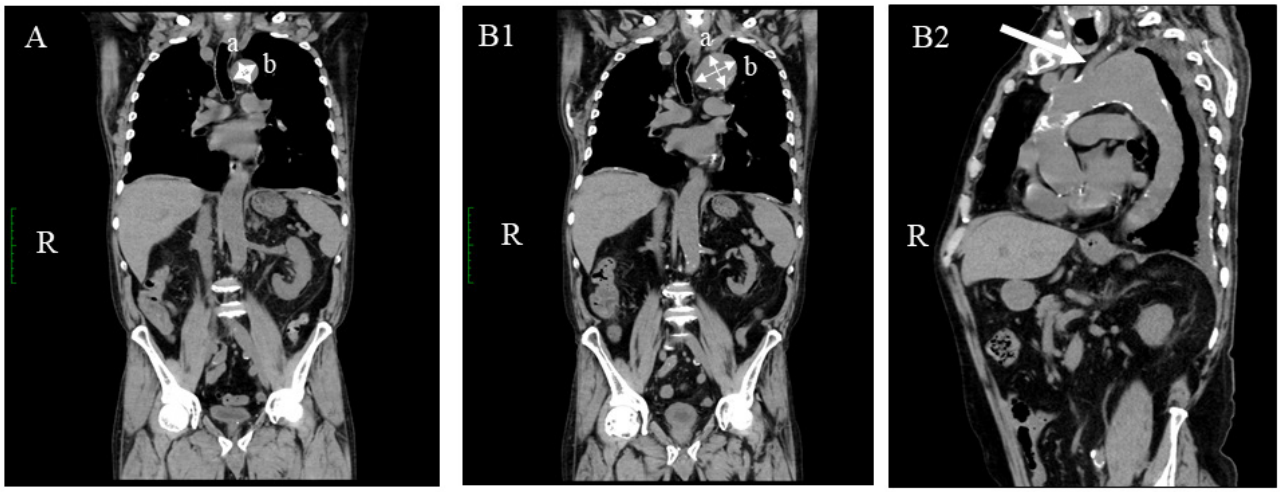

Figure 1. Plain CT images in coronal section and sagittal oblique reformation from the chest to the abdomen in Case 1.

The aortic arch at admission to our hospital (A) and after 11 months (B1) was 33 mm × 34 mm (A: a×b) and 45 mm × 48 mm (B: a×b), respectively. The size of the aortic arch at admission was nearly normal, and after 11 months was aneurysmic. The sagittal oblique CT image of the aorta showed a dissection with beginning distal to the left subclavian artery (white arrow in B2).

The size of the aortic arch at his initial admission (Figure 1A) had been 33 mm × 34 mm, which was nearly normal in size, but after 11 months the aneurysm had expanded to 45 mm × 48 mm (Figure 1 B1). The sagittal oblique CT image of the aorta showed a dissection beginning with the distal to the left subclavian artery (Figure 1 B2). We diagnosed Stanford type B descending aortic dissection. As his aneurysm on CT image had enlarged causing chest discomfort, he underwent aortic arch replacement therapy with open stent-graft for an aortic arch aneurysm. He had no major complications from the operation. He currently does not have been relapsing MPO-AAV and pulmonary tuberculosis. As he is presently treated with an amlodipine 5 mg tablet, a telmisartan 40 mg tablet, a doxazosin 1 mg, and a bisoprolol 2.5 mg tablet per day, his blood pressure is usually in the range of 100–120 / 50–80 mmHg.

2.2 Case 2

A 67-year-old Japanese man who had been treated for hypertension in a general hospital underwent a check-up for nausea and poor appetite with weight loss. He had experienced a 15-kg weight loss in the previous 2 months. His smoking history was 10 cigarettes per day for 40 years, from age 20 to 60 years. In the previous 7 years, he had stopped smoking. Blood pressure was usually in the range of 140–160 / 60–100 mmHg; he was being treated with an amlodipine 5 mg tablet per day only. Upper gastrointestinal endoscopy and colonoscopy revealed no abnormalities. An abdominal aortic aneurysm (AAA) was noted on coronal and axial CT scans (Figure 2A, B). The AAA at the admission to our hospital was 53 mm × 50 mm, which suggested aneurysm. A board-certified surgeon in cardiovascular surgery indicated the need for surgery for this AAA. Laboratory evaluation revealed that the serum creatinine and serum C-reactive protein levels were elevated to 2.66 mg/dL (normal range: 0.65–1.07) and 11.70 mg/dL (normal range: <0.30 mg/mL), respectively. The serum creatinine level 3 years previously had been 0.95 mg/dL without hematuria and proteinuria, and one week previously it had been 1.72 mg/dL with hematuria and proteinuria.

Laboratory evaluation revealed that MPO-ANCA was elevated to 29.3 U/mL (normal range: <3.5 U/mL). The eGFR was decreased to 20 mL/min/1.73m^{2,} and the CH 50 level was 47 U/mL (normal range: 30–45 U/mL). Various antinuclear antibody tests, including anti-double stranded DNA antibody, were negative, except for MPO-ANCA. Urinary red blood cells were 100↑/high power field, and urinary protein was 147 mg/dL. Physical examination on admission revealed purpura on both lower extremities. This patient was diagnosed as having MPO-AAV with renal insufficiency.

The patient was treated with 40 mg prednisolone per day. With this treatment, almost all laboratory findings improved: MPO-ANCA, creatinine level, and C-reactive protein were reduced to 1.0 U/mL, 1.59 mg/dL, and 0.21 mg/dL, respectively. Urinary red blood cells were 0–1/high power field. Care must be taken in tapering prednisolone to avoid recurrent activity of MPO-AAV. Therefore, we reduced the dosage of prednisolone from 40 mg to 15 mg per day over 2 months, step by step. Though his abdominal aneurysm on CT images had not enlarged,

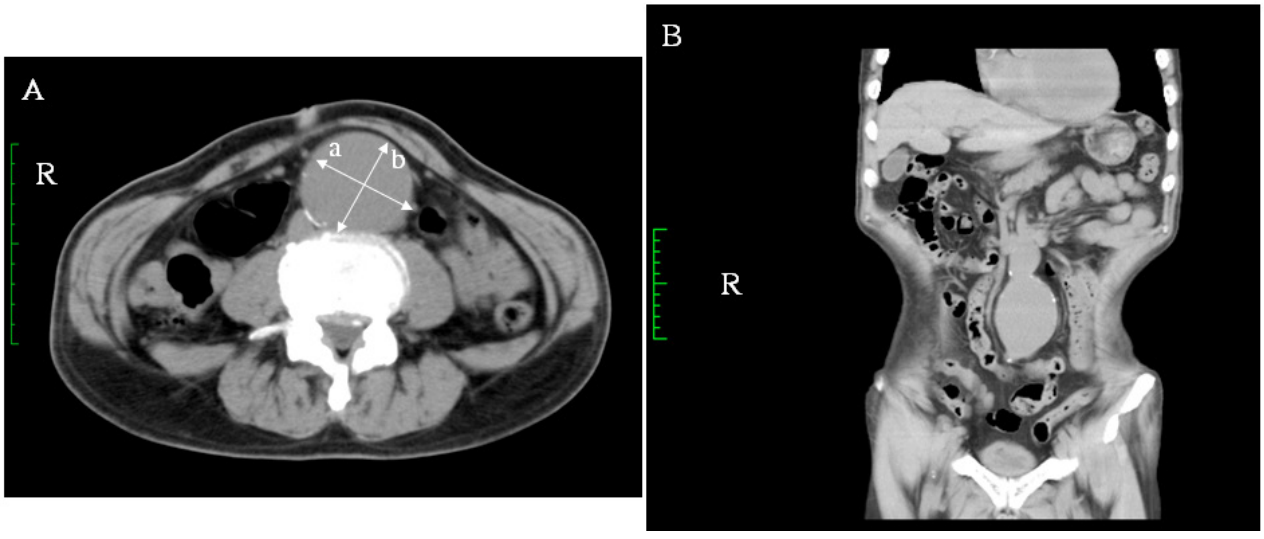

Figure 2. Axial (A) and coronal (B) plain CT images at the abdominal level in Case 2.

Sizes of the abdominal aorta at admission to our hospital were 53 mm × 50 mm (A: a×b), respectively. The abdominal aorta at admission was aneurysmic.

he complained of intermittent abdominal discomfort. Therefore, he underwent replacement therapy with a bifurcated prosthetic graft but not endovascular stent graft therapy for the AAA due to chronic kidney disease. He had no major complications from the operation. He currently does not have been relapsing MPO-AAV. As he is presently treated with a nifedipine CR 20 mg tablet, a losartan 25mg tablet, and an atenolol 25mg tablet per day, his blood pressure is usually in the range of 110–120 / 60–70 mmHg.

2.3 Case 3

An 86-year-old Japanese woman had previously been treated for hypertension and hyperuricemia in a general hospital. Her serum creatinine levels were 0.59 mg/dL (normal range: 0.65–1.07 mg/mL) 2 years previously and 5.51 mg/dL one day before admission to our hospital. Blood pressure was usually in the range of 110–140 / 60–80 mmHg with treatment by a telmisartan 40 mg tablet per day only. She was hospitalized in our hospital due to elevated serum creatinine with microhematuria. She had never smoked.

Laboratory evaluation revealed that MPO-ANCA, serum creatinine, and serum C-reactive protein levels were elevated to 44,600 U/mL (normal range: <3.5 U/mL), 6.06 mg/dL (normal range: 0.65–1.07 mg/mL), and 13.18 mg/dL (normal range: <0.30 mg/mL), respectively. The eGFR was decreased to 6 mL/min/1.73m^2; C3 and C4 levels were 131 mg/mL (normal range: 80–140 mg/mL) and 31.7 mg/mL (normal range: 11.0–34.0 mg/mL), respectively. Results of various antinuclear antibody tests, including anti-double stranded DNA antibody, were negative, except for MPO-ANCA. Urinary red blood cells were 100↑/high power field. Her urine protein-to-creatinine ratio was 4.78 g/g · creatinine. Physical examination on admission revealed purpura on both lower extremities. She was diagnosed as having MPO-AAV with renal insufficiency. Coronal and axial CT images at admission had revealed the presence of an AAA (Figure 3A, B), which was enlarged (33 mm × 29 mm). There was no indication for surgery for the AAA, which had not grown.

Therefore, we started hemodialysis therapy 3 times per week and treatment with 500 mg intravenous methyl-prednisolone pulse therapy on 3 consecutive days. After completion of methyl-prednisolone pulse therapy, 40 mg prednisolone per day was administered. With treatment by prednisolone, almost all laboratory findings had improved: MPO-ANCA, creatinine level, and C-reactive protein were reduced to 252 U/mL, 4.81 mg/dL, and 0.08 mg/dL, respectively. Urinary red blood cells were 1–3/high power field. Therefore, she was maintained on hemodialysis therapy three times a week. Prednisolone must be carefully tapered to avoid recurrent activity of MPO-AAV. She currently does not have been relapsing MPO-AAV. As she is presently treated with a nifedipine CR 10 mg tablet and telmisartan 40 mg per day, her blood

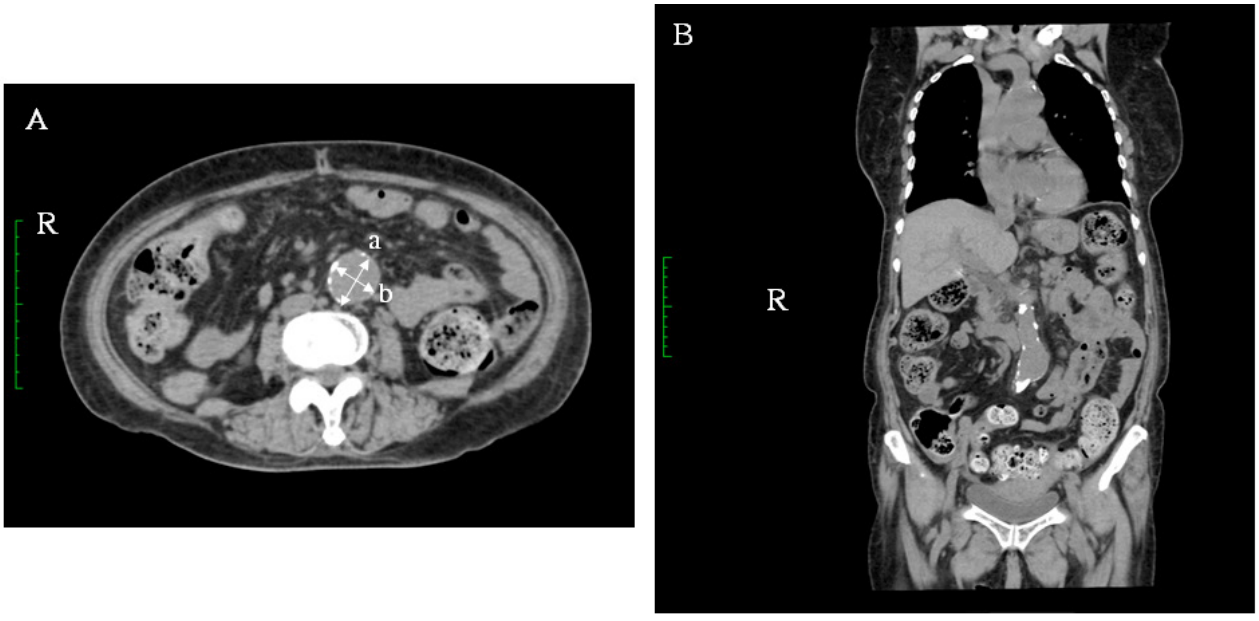

Figure 3. Coronal (A) and axial (B) plain CT images at the abdominal level in Case 3.

Sizes of the abdominal aorta at admission to our hospital were 33 mm × 29 mm (A: a×b), respectively. At admission, the abdominal aorta was slightly enlarged.

pressure is usually in the range of 100–110 / 50–60 mmHg. To date, the AAA had not grown. We must follow up the AAA closely based both symptoms and CT scans.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Discussion

MPA with MPO-ANCA positivity is a systemic necrotizing vasculitis; it is generally characterized as affecting small and medium-sized blood vessels. As MPO-AAV has been used to characterize small vessel vasculitis, aortic aneurysm has been generally unrecognized as complication of AAV. However, we experienced three cases with aortic aneurysm as a complication of MPO-AAV. Case 1 involved the onset of Stanford type B descending aortic dissection during treatment for MPO-AAV. Case 2 and Case 3 had AAAs at the time of our diagnosis of MPO-AAV. How long they had the AAAs prior to diagnosis of MPO-AAV is uncertain. There have been a few reports of large vessel involvement in AAV [10, 11], and these reports state that AAV might result in large vessel inflammation.

The Japan Intractable Diseases Information Center had reported 8,511 cases of MPA in Japan at the end of 2016 [12]. We estimated that the prevalence of MPA in Japan was 68.1 cases per million using the population of Japan reported as 124,955,000 at the end of 2016 by the Statistic Bureau, Ministry of Internal Affairs and Communications [13]. Fukuda et al. reported that the prevalence of AAA was 4.1% in patients with hypertension aged >60 years in Japan [14]. Previous ultrasound screening studies showed that among males aged 65 and 80 years, the prevalence of AAA was from 4% to 8% [15-18]. Although it is difficult to assess the prevalence and incidence of thoracic aortic aneurysm (TAA) because TAA is a clinically silent disease, the annual incidence of TAA was estimated to be 5.6 and 10.4 cases per 100,000 patient-years in two studies [19, 20]. It is difficult to prove that AAV might involve large vessels. We found no pathological evidence of this in our patients. We must consider whether the pathema in MPO-AAV was complicated by aortic aneurysm by chance or if the aortic aneurysm was related to clinical pathology. AAV is an extremely rare disease, and aortic aneurysm is also comparatively rare. We suggest that the probability of both MPO-AAV and aortic aneurysm occurring simultaneously through separate pathologies is very remote. It is more reasonable to consider that the pathology of MPO-AAV is related to the development of aortic aneurysm. Chirinos et al. [10] reported a case of aortic dissection of the descending aorta due to MPA; they mentioned that ANCA might play a role in ANCA associated large vessel disease. In short, MPO-AAV might involve large vessels such as the aorta.

The aorta is an elastic artery, and as such is quite distensible. The aorta consists of a mixture of smooth muscle, nerves, intimal cells, endothelial cells, fibroblast-like cells, and a complex extracellular matrix. The vascular wall consists of several layers known as the tunica externa, tunica media, and tunica intima. The thickness of the aorta requires an extensive network of tiny blood vessels called vasa vasorum, which feed the tunica externa and tunica media outer layers of the aorta [21]. Both tunica externae and tunica media of the vasa vasorum in the aortic wall are nutrient vessels for the aorta. The structure of the vasa vasorum varies with size, function, and location of the vessels. The vasa vasorum includes small-sized blood vessels. We could not demonstrate the pathological findings because our patient in case 2 underwent endovascular stent graft therapy for the AAA. In an animal model, Angouras et al. [22] reported that impaired vasa vasorum flow of the aorta leads to abnormal morphology of the elastin and the collagen fibers of the media, resulting in increased aortic stiffness, which causes aortic dissection.

In our patients, large vessel vasculitides might have resulted in the vasculitides in the vasa vasorum. Therefore, MPO-AAV might involve large vessels such as the aorta in rare cases. That MPO-AAV might involve large vessels is an important consideration. Therefore, patients with MPO-AAV should be examined by CT scan to check for the presence of aortic aneurysm to treat the patient as safely as possible. Furthermore, we need to avoid the recurrence of MPO-AAV and strictly control blood pressure to prevent aortic enlargement.

4 Conclusion

Aortic aneurysm is a clinically silent disease which can develop life-threatening. MPO-AAV also might become life-threatening. Therefore, we consider that patients with MPO-AAV should be examined by CT scans to check for presence of aortic aneurysm.

Conflict of interest: The authors have no conflicts of interest to declare.

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