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【 CASE REPORT 】

Anti-neutrophil Cytoplasmic Antibody-associated Vasculitis Complicated by Periaortitis and Cranial Hypertrophic Pachymeningitis: A Report of an Autopsy Case

Hajime Kaga[1], Atsushi Komatsuda[1], Masaya Saito[1], Mizuho Nara[1], Ayumi Omokawa[1], Masaru Togashi[1], Shin Okuyama[1], Hideki Wakui[1,2] and Naoto Takahashi[1]

Abstract:
Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is a systemic inflammatory disorder categorized as small-vessel vasculitis. We herein report an elderly Japanese man with AAV (granulomatosis with polyangiitis affecting the eyes, nose, lungs, and kidneys) who also showed periaortitis at the diagnosis and developed cranial hypertrophic pachymeningitis (HP) during steroid maintenance therapy. His consciousness disturbance caused by HP improved after steroid pulse therapy, but he died of aspiration pneumonia. Autopsy findings showed giant cells in the thickened pachymeninges and obsolete inflammatory lesions in the aortic adventitia and renal tubulointerstitium. This is the first case of AAV complicated by periaortitis and cranial HP.

Key words: anti-neutrophil cytoplasmic antibody-associated vasculitis, cranial hypertrophic pachymeningitis, granulomatosis with polyangiitis, periaortitis

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Introduction

In the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is categorized as small-vessel vasculitis (1). The three major clinicopathologic variants of AAV are microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) (previously known as Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (1). In Japanese patients with AAV, myeloperoxidase (MPO)-ANCA-positive MPA/renal-limited vasculitis is the most common form of AAV, and approximately half of patients with GPA are positive for MPO-ANCA or proteinase 3 (PR3)-ANCA (2). These clinical features in Japanese patients contrast markedly with those in patients from European countries and the United States (2). Although AAV is characterized by small-vessel inflammation, large-vessel involvement can rarely occur (3-13). For example, in 2004, Chirinos et al. (3) reported a case of fatal aortitis in a patient with MPA and reviewed 13 reported cases of large-vessel involvement in AAV since 1990. Thereafter, similar cases have been reported (4-13).

Cranial and spinal hypertrophic pachymeningitis (HP) is a rare inflammatory disorder characterized by localized or diffuse thickening of the dura mater, causing intracranial hypertension, cranial nerve palsy, and spinal cord dysfunction (14). A nationwide survey of HP in Japan revealed that ANCA-related HP is the most frequent form of this disease (14). Yokoseki et al. (15) recently reported the clinical significance of MPO-ANCA in HP. According to a recent review of published case reports of HP associated with ANCA since 2000, approximately half of patients were Japanese (16).

To our knowledge, there have been three case reports of AAV complicated by large-vessel involvement and dural/epidural inflammation of the spinal cord (5, 6, 10). We

[1]Department of Hematology, Nephrology, and Rheumatology, Akita University Graduate School of Medicine, Japan and [2]Department of Life Science, Akita University Graduate School of Engineering Science, Japan
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Correspondence to Dr. Atsushi Komatsuda, komatsud@med.akita-u.ac.jp

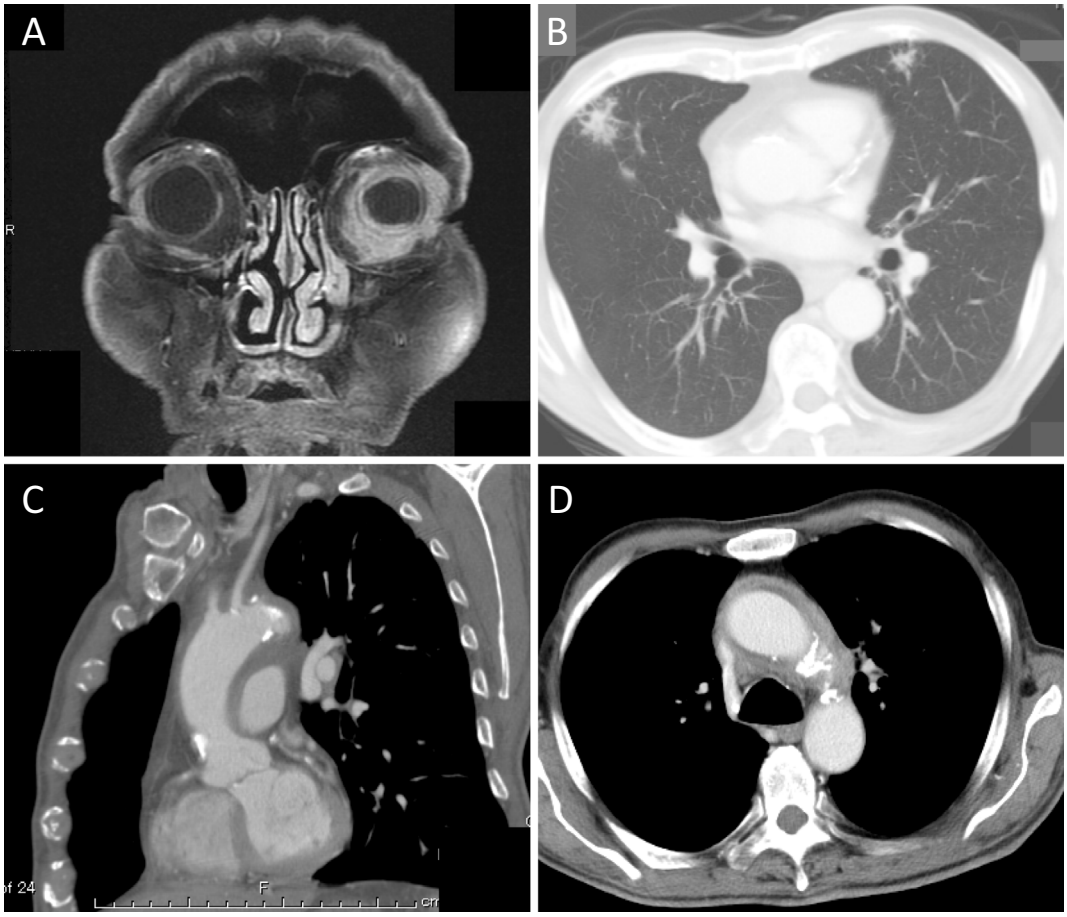

Figure 1. **CT findings at the first admission. CT of the head and chest shows a contrast-enhanced left orbital mass and mucosal thickening of the nasal cavity (A), patchy shadows on the lungs (B), and contrast-enhanced soft tissue shadow around the ascending aorta and aortic arch (C, D).**

herein report the first case of AAV (MPO-ANCA-positive GPA) complicated by large-vessel involvement (periaortitis) and intracranial HP. Our patient died of aspiration pneumonia during steroid therapy. We also describe the autopsy findings.

Case Report

A 69-year-old Japanese man with a 2-year history of refractory uveitis was admitted because of progressive visual disturbance. Contrast-enhanced computed tomography (CT) of the head and chest revealed left orbital tumor and mucosal thickening of the nasal cavity (Fig. 1A), several patchy pulmonary shadows (Fig. 1B), and wall thickening of the ascending aorta and aortic arch (Fig. 1C and D). A dipstick urinalysis showed no proteinuria or hematuria, but elevated levels of β_2-microglobulin (2,244 μg/L) and N-acetyl-β-D-glucosaminidase (12.7 U/L) were observed. Blood urea nitrogen was 11.7 mg/dL, and serum creatinine was 0.86 mg/dL. Serologic tests revealed an elevated level of serum C-reactive protein (CRP) (7.51 mg/dL), a normal level of serum IgG4 (96.4 mg/dL) (normal <135 mg/dL), positivity for MPO-ANCA (38 EU) (normal <20 EU), and negativity for PR3-ANCA (<10 EU) (normal <10 EU) and antinuclear antibodies. A biopsy of the left orbital mass showed necrotizing granuloma surrounded by fibrosis with epithelioid cells, multinucleated giant cells, and leukocyte infiltration (Fig. 2A). A renal biopsy revealed small-sized necrotizing arteritis and tubulointerstitial nephritis with multinucleated giant cell formation (Fig. 2B and C). Based on these findings, he was diagnosed with GPA complicated by periaortitis. After treatment with prednisolone (PSL) (40 mg/day for 4 weeks), his inflammatory symptoms were improved, and the abnormal CT findings in the lungs and aortic arch were resolved (Fig. 3). At that time, serum MPO-ANCA titer was normalized. Two months later, the PSL dose was gradually tapered, and he was discharged. Thereafter, he was treated with 7.5 mg/day of PSL in our outpatient clinic with normalized serum MPO-ANCA titers. However, he became completely blind two years later due to accompanying central retinal artery occlusion.

Six years after the first admission, he gradually developed a consciousness disturbance of two weeks duration. On a physical examination, he had a saddle nose deformity. A urinalysis showed no hematuria or proteinuria. The white blood cell count was 9,000/μL, hemoglobin 10.8 g/dL, and platelet count 210,000/μL. Serum total protein was 6.8 g/dL, albumin 3.2 g/dL, blood urea nitrogen 21.1 mg/dL, creatinine

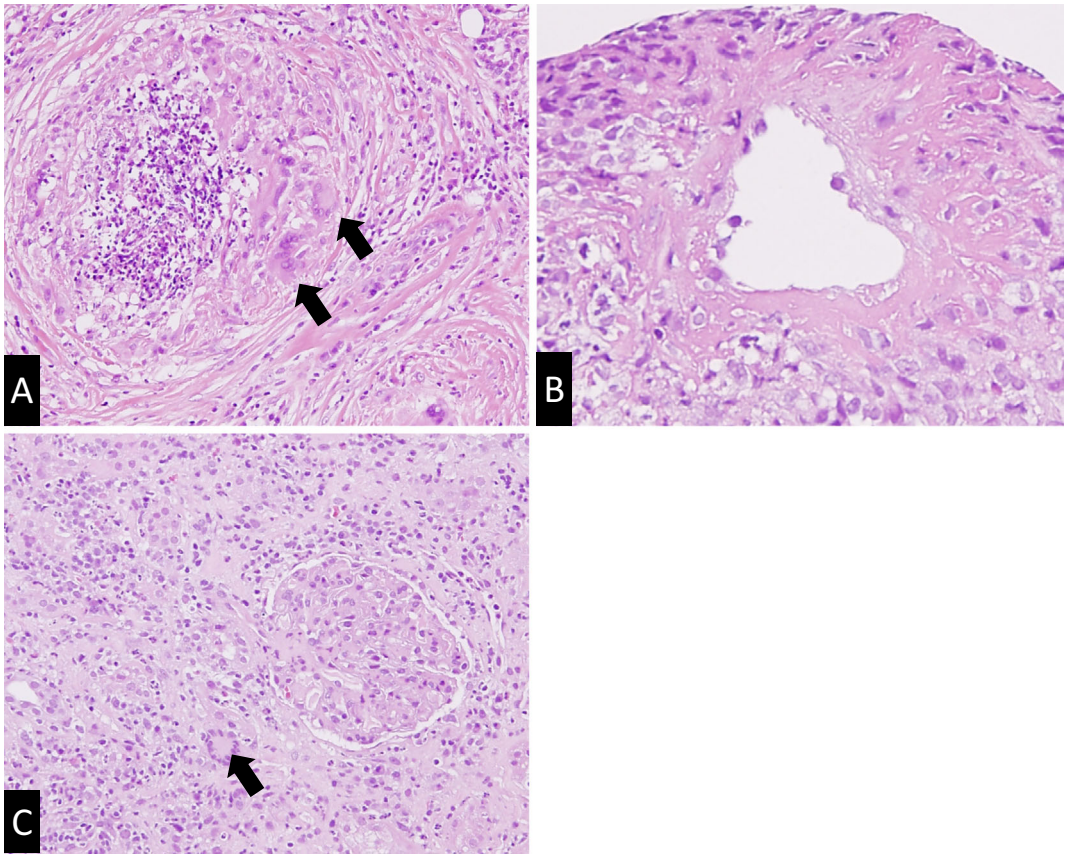

Figure 2. **Pathological findings at the first admission. Biopsy specimens from the left orbital mass show necrotizing granulomas surrounded by fibrosis with epithelioid cells, multinucleated giant cells (arrows), and leukocytic infiltration [A: Hematoxylin and Eosin (H&E) staining, ×100]. Renal biopsy specimens show small-sized necrotizing arteritis and diffuse infiltration of lymphocytes and neutrophils as well as multinucleated giant cells (arrow) in the tubulointerstitium (B: H&E staining, ×200) (C: H&E staining, ×100).**

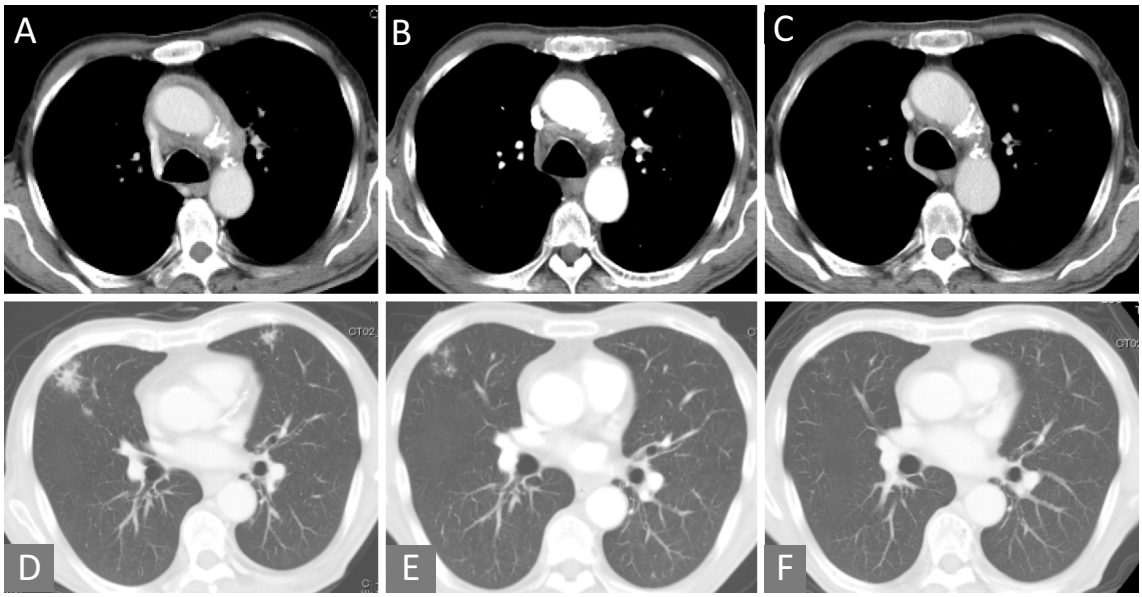

Figure 3. **Improvements of CT findings of large-vessel involvement (A-C) and lung involvement (D-F) after treatment during the first admission. At admission (A, D), two months after treatment (B, E), and four months after treatment (C, F).**

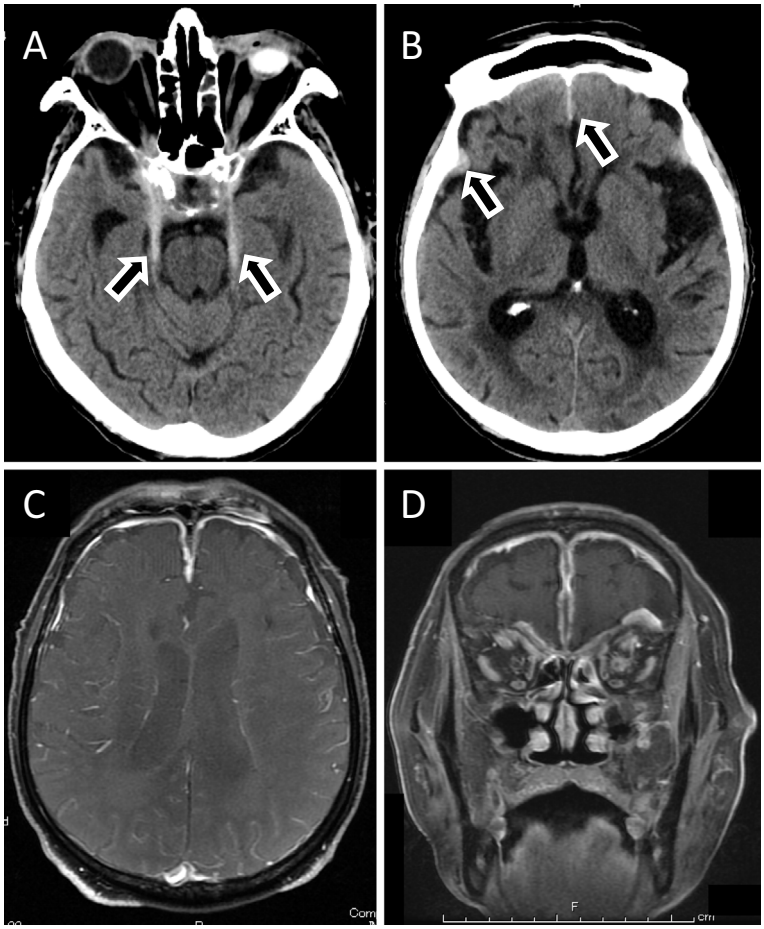

Figure 4. **CT findings at the second admission. Brain CT shows thickened pachymeninges (arrows) (A, B). Gadolinium-enhanced brain MRI shows prominently enhanced pachymeninges (C, D).**

1.03 mg/dL, aspartate transaminase 12 U/L, alanine transaminase 9 U/L, lactate dehydrogenase 152 U/L, sodium 143 mEq/L, potassium 3.5 mEq/L, and chloride 106 mEq/L. Serum CRP was 3.49 mg/dL, IgG 1,434 mg/dL, IgA 338 mg/dL, IgM 62 mg/dL, MPO-ANCA <10 EU, PR3-ANCA <10 EU, β-D glucan ≤3 pg/mL, and endotoxin <2 pg/mL. The QuantiFERON-TB test was negative. An analysis of the cerebrospinal fluid (CSF) showed 30 lymphocytes/μL, protein 218 mg/dL, and glucose 131 mg/dL (serum glucose 152 mg/dL). Cytological and microbiological examinations of the CSF showed negative results. Brain CT showed intracranial thickened pachymeninges (Fig. 4A and B), and brain magnetic resonance imaging (MRI) revealed prominent gadolinium-enhanced pachymeninges (Fig. 4C and D). Based on these findings, he was considered to have developed cranial HP during the course of GPA. He was treated with intravenous methylprednisolone (mPSL) (500 mg/day for 3 days) followed by intravenous PSL (40 mg/day). After mPSL pulse therapy, his consciousness disturbance was improved, and he was able to eat by himself. However, 1 week after starting oral ingestion, he vomited and suffered from aspiration pneumonia. Despite treatment with antibiotics, he died 28 days after the second admission.

An autopsy was done with the consent of his family. The pachymeninges in bilateral frontal regions were markedly thickened and adhered to the cerebral parenchyma (Fig. 5A and B). The microscopic findings were compatible with HP. There was focal lymphocytic infiltration in the cicatricial fibrous tissues (Fig. 5C and D), and multinucleated giant cells were also observed (Fig. 5D). In the subarachnoid and perivascular regions, lymphocytic infiltrates were extensively found. In the aortic arch, cicatricial thickening of the adventitia was observed. Microscopically, dense cicatricial fibrosis was noted in the aortic arch adventitia (Fig. 6), but there were no findings of active necrotizing granulomatous vasculitis. In the bilateral kidneys, irregular scars consisting of tubular atrophy, interstitial fibrosis, and lymphocytic infiltrations were scattered. The lungs were heavy and firm. Patchy consolidations were also scattered. In large areas of the lungs, the dense infiltration of neutrophils was found in the bronchi, bronchioles, and alveoli. Food residue was detected in a bronchiole. The main cause of death was considered to be severe aspiration pneumonia.

Discussion

The present elderly Japanese man was diagnosed with MPO-ANCA-positive GPA affecting the eyes, nose, lungs, and kidneys at presentation based on his clinical symptoms, laboratory data, imaging findings, and histopathologic find-

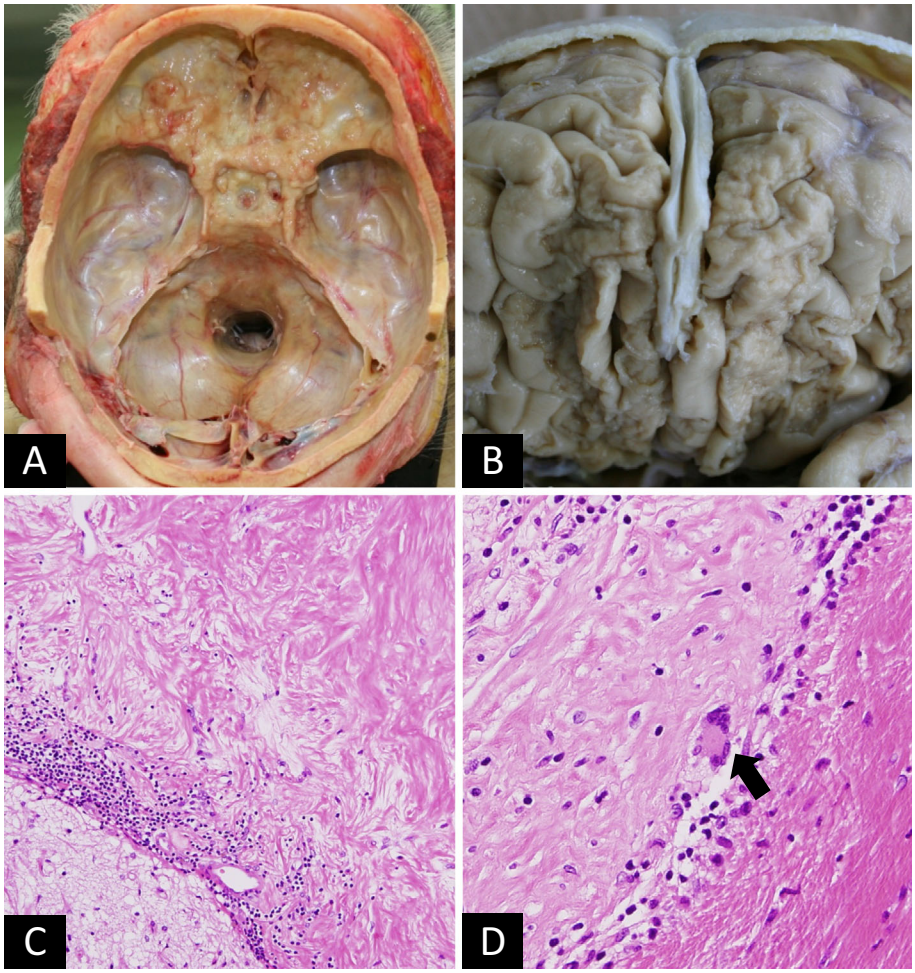

Figure 5. **Pathological findings of HP at autopsy. Macroscopically, the meninges in the bilateral frontal regions are markedly thickened and adhere to the cerebral parenchyma (A, B). Microscopically, the meninges specimens show focal lymphocytic infiltration in cicatricial fibrous tissues [C: Hematoxylin and Eosin (H&E) staining, ×40] and multinucleated giant cells (arrow) (D: H&E staining, ×100).**

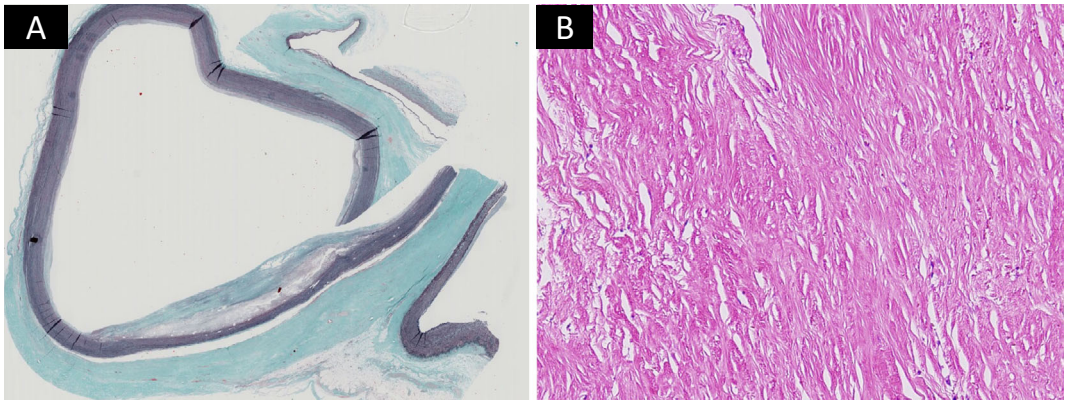

Figure 6. **Pathological findings of the aorta at autopsy. Aortic wall specimens show dense cicatricial fibrosis in the adventitia of the aortic arch (A: Elastica-Masson staining, ×10) (B: Hematoxylin and Eosin staining, ×40).**

ings of necrotizing granulomatous inflammation/necrotizing vasculitis in orbital tumor and renal biopsy specimens. Imaging studies also showed findings of periaortitis. He was successfully treated with initial steroid therapy. However, he developed cranial HP six years later and ultimately died of aspiration pneumonia. Autopsy findings revealed active inflammatory lesions of cranial HP and obsolete inflammatory lesions in the aortic adventitia and renal tubulointerstitium.

To our knowledge, the present case is the first case of AAV complicated by large-vessel involvement (periaortitis) and cranial HP.

Chronic periaortitis may develop in the setting of systemic immune-mediated disorders, such as systemic lupus erythematosus, small-vessel vasculitides such as GPA, and IgG4-related diseases (17). GPA and IgG4-related diseases are also the major causes of HP in Japan (14). In our patient with MPO-ANCA-positive GPA, a high serum level of IgG4 suggesting IgG4-related diseases was not observed. We therefore consider that a similar inflammatory process of GPA involving the small vessels of the aortic wall and the dura mater might have resulted in periaortitis and cranial HP in our patient.

Chirinos et al. (3) compared the clinicopathologic features in well-defined large-vessel vasculitides (Takayasu arteritis and giant cell arteritis) and in reported cases of AAV with large-vessel disease (half of cases had MPO-ANCA or PR3-ANCA positivity). They suggested that large-vessel involvement is a part of the spectrum of AAV rather than overlapping with other large-vessel vasculitides, based on the following features: Manifestations of large-vessel disease in Takayasu arteritis and giant cell arteritis are usually stenotic, while those in cases of AAV with large-vessel involvement are usually non-stenotic, presenting as periventricular soft tissue masses as in our patient, aneurysms, dissection, and/or rupture. The histopathologic findings in AAV with large-vessel involvement have been granulomatous or non-granulomatous vasculitis, or prominent perivasculitis.

Carels et al. (4) reported a case of MPO-ANCA associated periaortitis with histological proof of GPA, and reviewed similar case reports. They suggested that ANCA may be involved in the pathogenesis of periaortitis by inducing vasculitis of the vasa vasorum of the aortic wall, which are indeed small vessels, susceptible to AAV. In our patient, improvement of the contrast-enhanced thickening of the aortic wall after PSL therapy occurred in concert with the decrease in the serum ANCA titer, suggesting that the periaortic lesion was AAV-associated. At the autopsy, the pathological findings of the aorta showed only cicatricial fibrosis in the aortic arch adventitia and no evidence of active necrotizing granulomatous vasculitis. These findings indicate that initial PSL therapy was effective for treatment of AAV-associated periaortitis in our patient.

Although Chirinos et al. (3) found that cases of large-vessel involvement in AAV were reported mostly from Europe and North America, the number of reports on large-vessel involvement in AAV from Japan has recently been increasing (6, 8-11, 13). Ozaki et al. (13) reviewed 24 cases of GPA-associated large-vessel involvement reported in 1990-2015. Among the 19 ANCA-analyzed cases, cytoplasmic-ANCA or PR3-ANCA was positive in 15, and perinuclear-ANCA or MPO-ANCA was positive in 4. All 24 cases had other organ involvement associated with GPA, including the ear, nose, throat, lungs, and kidneys. Only the Japanese case reported by Ozaki et al. (13) had an orbital mass, as observed in our patient.

A recent nationwide survey of HP in Japan revealed that the crude HP prevalence is 0.949/100,000 population and that ANCA-related HP is the most frequent form (14). In 2004, Akahoshi et al. (18) reported the third case of biopsy-proven GPA presenting with MPO-ANCA-positive cranial HP. They reviewed nine similar cases with positive perinuclear-ANCA or MPO-ANCA reported in 1994-2001 and suggested a link between MPO-ANCA-positive GPA and cranial HP. They also suggested the involvement of environmental or genetic factors in the development of this combination of diseases, given that these cases had been reported mainly from Japan. Another review of reported cases of ANCA-associated HP by Saeki et al. (19) in 2004 and a recent review of similar cases reported in 2000-2015 by Li et al. (16) also described demographic characteristics. The review of 31 patients by Li et al. (16) revealed that 19 were from Asian counties (16 from Japan, 2 from China, 1 from Korea), 7 from European countries, 3 from South America, and 2 from North America. According to the literature review by Akahoshi et al. (18), cranial nerve dysfunction, including optic nerve neuropathy and oculomotor disturbance are frequent complications in patients with cranial HP associated with GPA. Our patient was completely blinded at the onset of cranial HP. This might have been caused by our delayed recognition of the development of cranial HP.

Yokoseki et al. (15) recently analyzed the clinical characteristics of 21 patients with ANCA-positive HP (17 MPO-ANCA and 4 PR3-ANCA). Most patients with MPO-ANCA-positive HP showed a central nervous system-limited form and a less severe phenotype than patients with PR3-ANCA-posive HP. Our patient developed cranial HP during low-dose PSL maintenance therapy. At that time, initial systemic inflammations of GPA affecting the eyes, nose, lungs, and kidneys were improved with normalized serum MPO-ANCA titers. Autopsy findings in our patient showed granulomatous inflammation characterized by the appearance of multinucleated giant cells in the markedly thickened dura mater. These pathological findings were compatible with those observed in MPO-ANCA-positive HP (15). We therefore suspect that the cranial HP in our patient was GPA-associated. Brain CT during initial hospitalization did not show thickened pachymeninges, which were observed at the second admission. Because of a good response to initial steroid therapy, we did not administer other immunosuppressive agents, such as cyclophosphamide. This may have been associated with the development of HP during steroid maintenance therapy. According to the results of a recent nationwide survey of HP in Japan, corticosteroids, mostly mPSL pulse therapy followed by oral administration, were administrated as the first choice for HP, resulting in an 87.2% improvement (14). In our patient, mPSL pulse therapy was also effective in treating consciousness disturbance.

In summary, our case indicates that large-vessel involvement and cranial HP can occur in patients with AAV at different times and that cranial HP can develop even in patients

with improved systemic manifestations and normalized serum ANCA titers after initial therapy. To detect this complication at an early stage, careful follow-up observations of neurological symptoms and signs are necessary. Several previous reviews have shown that these complications in AAV, especially in MPO-ANCA-positive GPA, were reported mainly from Japan. This suggests the involvement of environmental or genetic factors in the development of this unique variant of AAV.

The authors state that they have no Conflict of Interest (COI).

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