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CASE REPORT

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MPO-ANCA-positive Wegener's granulomatosis presenting with hypertrophic cranial pachymeningitis: case report and review of the literature

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Abstract We describe a case of hypertrophic cranial pachymeningitis (HCP) associated with Wegener's granulomatosis (WG) in a 60-year-old man presenting with chronic headache and multiple cranial nerve neuropathies. A test for antibodies to the neutrophil cytoplasmic protein myeloperoxidase (MPO-ANCA) was positive in this case. We review the literature on perinuclear (p)-ANCA-related HCP, including our case. This case indicates the link between MPO-ANCA-positive WG and HCP.

Key words Hypertrophic cranial pachymeningitis (HCP) · MPO-ANCAWegener's granulomatosis (WG)

Introduction

Wegener's granulomatosis (WG) is a systemic necrotizing, granulomatous vasculitis of unknown origin that mainly affects the upper and lower respiratory tracts and the kidneys.[1,2] Any organ system can be involved, however, and neurologic involvement is not rare, reported in 22%–54% of cases during the course of the disease, with variable clinical manifestations.[2–5] A test for anti-neutrophil cytoplasmic antibody (ANCA) is useful in the diagnosis of several types of primary vasculitis. The cytoplasmic (c)-ANCA pattern or proteinase 3 (PR3)-ANCA is associated almost exclusively with WG, whereas myeloperoxidase (MPO)-ANCA positivity is relatively rare in WG.

Recently, there is an increasing number of reported cases of p-ANCA-positive hypertrophic cranial pachymeningitis (HCP). A relative of MPO-ANCA-positive HCP with a variant of WG, also called the limited form of WG, is currently under consideration. Herein we report a patient with MPO-ANCA-positive HCP associated with biopsy-proven WG.

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Case report

A 60-year-old man was admitted to a community hospital in July 2001 because of an 8-month history of severe right-sided headache causing nausea and vomiting. One year earlier, he had noticed right-side hearing difficulty and earache. He was first referred to the Department of Otorhinolaryngology of our hospital in November 2000, where right facial nerve palsy and right-side otitis media were diagnosed. His clinical symptoms gradually diminished following intravenous and topical steroid therapy, but a drug-induced eruption probably due to steroids appeared during the therapy. Since then, he was found to have frequent progressive headaches on the right side and diplopia, and he experienced weight loss of 10 kg in 8 months before the referral to us.

On admission, the patient was afebrile and normotensive with a normal pulse rate. On physical examination, his hearing was impaired on the right side, but meningeal signs were absent. Neurologic examination revealed right cranial nerve VI and VIII palsy and bilateral papilledema. Laboratory studies showed microhematuria without renal dysfunction. The erythrocyte sedimentation rate (ESR) was 89 mm/h, white blood cell (WBC) count 5840/mm^3, hematocrit 25.3%, platelet count 376000/mm^3, and C-reactive protein (CRP) 12.8 mg/dl. Tests for antinuclear antibody, rheumatoid factor, and syphilis were negative; and the serum level of angiotensin-converting enzyme was within normal limits. A tuberculin skin reaction was also negative. An enzyme-linked immunosorbent assay was positive for MPO-ANCA at a titer of 23 EU (normal $<$ 10 EU) but negative for PR3-ANCA. Lumbar puncture demonstrated an initial pressure of 275 mm H_2O, with 70/mm^3 WBCs (predominantly lymphocytes); cerebrospinal fluid (CSF) protein was elevated at 393 mg/dl; the glucose level (44 mg/dl)

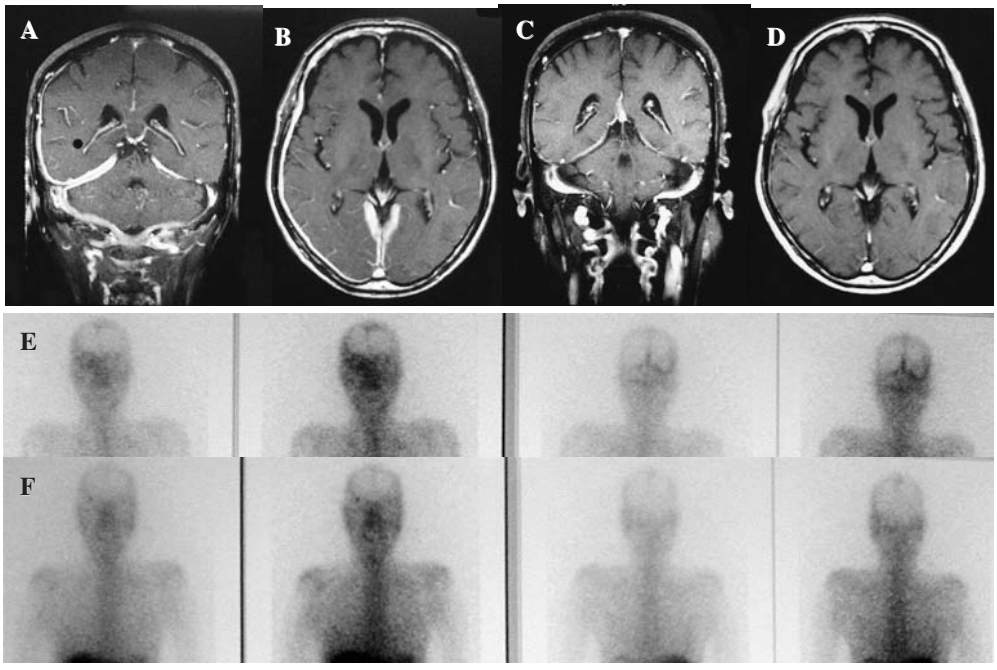

Fig. 1. Pretreatment coronal (**A**) and axial (**B**) T1-weighted gadolinium-enhanced magnetic resonance imaging (MRI) scans of the brain demonstrating a thick, brightly enhanced tentorium and right cerebellar dura mater. Posttreatment coronal (**C**) and axial (**D**) MRI scans demonstrating reduced enhancement from the cerebellar tentorium to the posterior cranial fossa. Pretreatment (**E**) and posttreatment (**F**) gallium scintigrams. The pretreatment scintigram demonstrates positive uptake extending from the right temporal region to the posterior cranial fossa, whereas the posttreatment scintigram demonstrates markedly decreased uptake

was normal. No microorganisms were found on the smear or in the culture, and tumor cells were absent on smear and cytologic examinations.

Roentgenography and computed tomography (CT) of the chest showed pleural thickening, infiltration, and reticular shadows in bilateral upper lobes. A gadolinium-enhanced magnetic imaging (MRI) study of the brain revealed thickening of the tentorium and right cerebellar dura mater (Fig. 1A,B). Gallium scintigraphy showed positive uptake extending from the right temporal region to the posterior cranial fossa (Fig. 1E). At the time of admission, CSF findings and chest radiographic studies indicated a probability of tuberculous meningitis.

Despite the empiric antituberculosis therapy, his symptoms and signs did not change. Microscopic examination of biopsy specimens from the dura mater of the right temporal area showed granulomatous inflammation with focal accumulation of histiocytes and multinucleated giant cells. Focal vasculitis-like lesions were also observed (Fig. 2). Various stains for mycobacteria, fungi, and other microoganisms were all negative. These findings were compatible with those of Wegener's granulomatosis. Repeated urinalysis revealed persistent microhematuria and occasional sediment abnormalities. Renal biopsy specimens did not show any crescentic, segmental sclerosis or tuft adhesion on microscopic analysis or any immunoglobulin deposit on immunofluorescence analysis.

The patient was allergic to prednisolone and methylprednisolone, so a combination of dexamethasone (5 mg/day), cyclophosphamide (50 mg/day), and sulfamethoxazole/trimethoprim (800 mg/160 mg per day) was started. The headache subsided gradually, and inflammatory reactions were markedly diminished with the disappearance of MPO-ANCA (Fig. 3) 1 month after the treatment. At the same time, the follow-up MRI scan demonstrated reduced enhancement from the cerebellar tentorium to the posterior cranial fossa (Fig. 1C,D,F).

Discussion

A 60-year-old man presented with otitis media and facial nerve palsy, followed by headache and multiple cranial nerve palsies. HCP was diagnosed by enhanced MRI scans, and WG was diagnosed based on the histological findings of the dura mater in addition to the abnormal chest radiograph.[1]

Hypertrophic cranial pachymeningitis is a rare disease that manifests as variable neurological symptoms, such as headache, cranial nerve palsies, and ataxia. It is caused by chronic inflammation and thickening of the dura matter[6] and was first described by Charcot and Joffroy in 1869.

Although HCP cases have been increasingly reported with the use of CT and contrast-enhanced MRI, their pathogenesis remains obscure. Early reports of HCP were described in relation with syphilis or tuberculosis, and some of them were associated with infection, collagen-vascular diseases, sarcoidosis, malignancy, and drugs, although most of the reported cases were idiopathic. In general, headache and cranial nerve palsies were the most commonly observed clinical manifestations, and MRI with gadolinium enhancement appeared to be the most sensitive imaging method.[6]

In recent reports on larger cohorts of patients with WG, a relatively higher frequency of neurological manifestations have been indicated. Peripheral neuropathy was the most common form of neurological involvement, whereas central nervous system (CNS) involvement of WG was rare

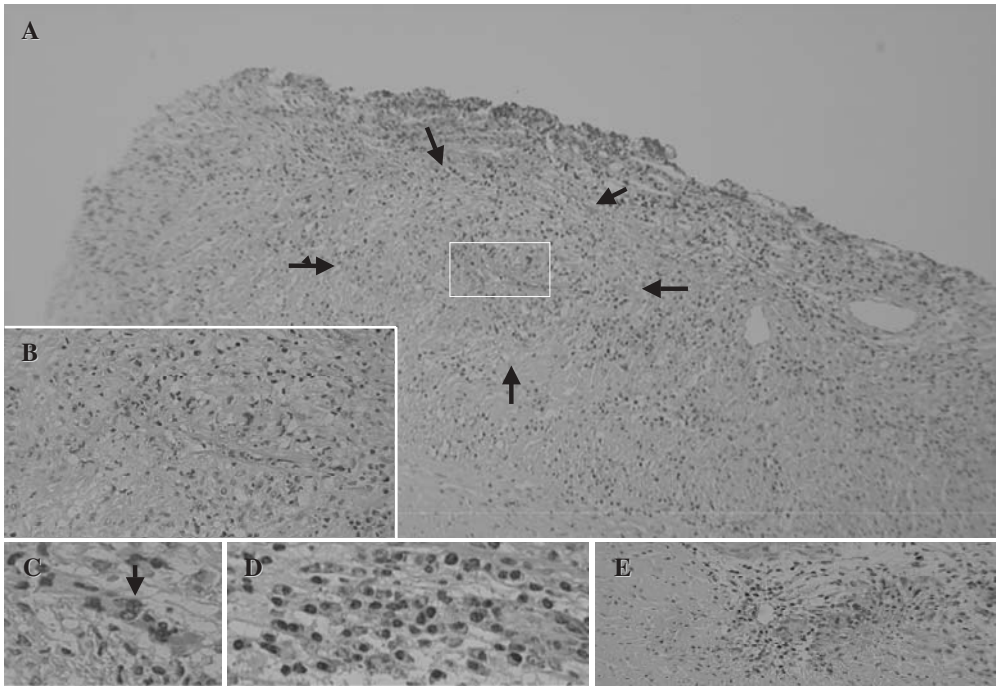

Fig. 2. Histopathological findings in a biopsy specimen of the dura mater. **A, B** Note the granulomatous inflammation with focal aggression of histiocytes and occasional multinucleated giant cells (*arrows, box*). **C, D** High-power view of an area showing multinucleated giant cells (**C**, *arrow*) and marked infiltration of lymphocytes and plasma cells (**D**). **E** Vasculitis-like lesions are seen focally. **A–D** H&E. **E** MT stain. **A** × 100. **B–E** × 400

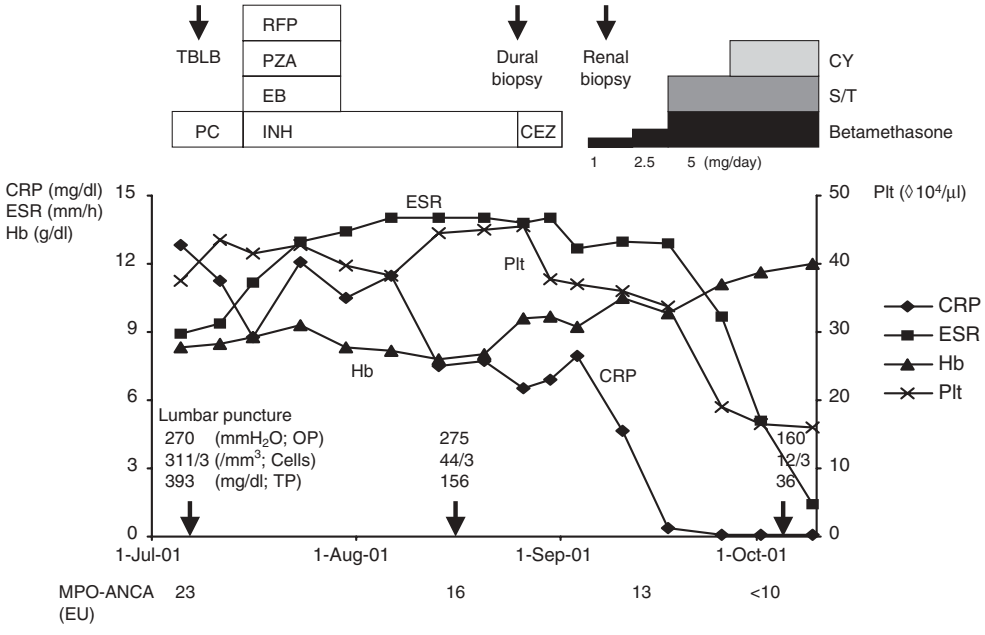

Fig. 3. Clinical course of the patient. *CEZ*, cefazolin sodium (2 g/day); *CRP*, C-reactive protein; *CY*, cyclophosphamide (50 mg/day); *EB*, ethambutol hydrochloride (750 mg/day); *ESR*, erythrocyte sedimentation rate; *Hb*, hemoglobin; *INH*, isoniazid (300 mg/day); *MPO-ANCA*, myeloperoxidase anti-neutrophil cytoplasmic autoantibody; *OP*, opening pressure; *PC*, sulbactam sodium/ampicillin sodium (6 g/day); *Plt*, platelets; *PZA*, pyrazinamide (1200 mg/day); *RFP*, rifampicin (450 mg/day); *S/T*, sulfamethoxazole/ trimethoprim (800/160 mg per day); *TBLB*, transbronchial lung biopsy; *TP*, total protein

(4%–8%).[2,4,5] Three pathological mechanisms of nervous system involvement have been recognized: (1) contiguous spread of granuloma from paranasal sinuses into the brain and cranial nerves; (2) formation of intracranial granulomas directly (e.g., meningeal granulomatosis); and (3) vasculitis (e.g., cerebral vasculitis or vascular myelopathy).[3] In addition to neurologic manifestations, it has been reported that ear involvement such as otitis media is not unusual and could appear as an initial clinical symptom in patients with WG.[7]

Although c-ANCA has been shown to be highly specific and sensitive for diagnosing generalized WG, the sensitivity is lowered when the disease is localized, with-out renal involvement. Inversely, p-ANCA or MPO-ANCA is found in up to 10% of WG patients and is associated with less organ involvement.[8] Moreover, ANCA has been studied and found in both vasculitic and nonvasculitic neuropathy of patients with peripheral neuropathy.[9] A relationship of ANCA with CNS disorders has not been evaluated.

Table 1. Characteristics of reported cases with p-ANCA positive HCP

Study	Age/ sex	Clinical features	CRP ESR	Pathology	p-ANCA	CSF (OP, cells, protein)	Treatment	Outcome	Note
Ishikura et al.,[10] 1994	63/F	Headache, fever	17.5 160	N.A.	+(IIF)	220 mmH_2O 14/3/mm^3 119 mg/dl	PSL, AZP	Improved	IC(+)
Sasaki et al.,[11] 1995	77/F	CN II, transverse myelopathy	Negative Normal	N.A.	+(IIF)	N.A. 10/mm^3 45 mg/dl	S-pulse, PSL	No change	ANA(+) ssDNA(+)
Sindo et al.,[12] 1997	64/M	Headache, CN II–IV, VI, Horner's syndrome	Positive Increased	Fibrotic thickening, cellular infiltrates	+(IIF)	275 mmH_2O 31/mm^3 28 mg/dl	S-pulse, PSL	Improved	RF(+)
Takahashi et al.,[13] 1998	47/F	Headache, fever, episcleritis	4.2 107	N.A.	518EU (MPO, <10))	200 mmH_2O 48/mm^3 49 mg/dl	S-pulse, PSL	Improved	PTU Tx for Graves' disease
MGH,[14] 1999	75/F	Headache, CN VII, VIII, weakness	N.A. 113	Granuloma, epithelioid/giant cell	128 U/ml (MPO, <2.8)	125 mmH_2O 82/mm^3 57 mg/dl	S-pulse, PSL, CY	Improved	Dx: WG
Sugiyama et al.,[15] 1999	70/M	Headache, CN III, V–VIII	3.1 120	Caseous necrosis, epithelioid/giant cell	26EU (MPO)	80 mmH_2O 3/mm^3 32 mg/dl	PSL, CY	Improved	RF(+)
Nagashima et al.,[16] 2000	53/F	Paraplegia, CN I, II, VI–VIII	Positive N.A.	Fibrosis, granuloma, epithelioid/giant cell	25 U (MPO, <10)	N.A. N.A. 130 mg/dl	PSL, AZP	Improved	Dx: WG
Kono et al.,[17] 2000	56/F	Headache, fever, myalgia	17.1 124	Necrotizing vasculitis, fibrinoid necrosis (skin), CGN (kidney)	321EU (MPO, <10)	220 mmH_2O 4/mm^3 6 mg/dl	S-pulse, PSL	Improved	Dx: MPA
Takuma et al.,[18] 2001	67/M	Headache, diplopia, CN IV–VI, Diabetes insipidus	Negative N.A.	N.A.	80EU (MPO, <10)	N.A. 38/mm^3 82 mg/dl	S-pulse, PSL, CY	Improved	ANA(+)
Present case	60/M	Headache, papilledema, CN VI–VIII	12.7 89	Granulomatous inflammation, vasculitis/giant cell	23EU (MPO, <10)	270 mmH_2O 222/3/mm^3 393 mg/dl	Betamethasone, CY, ST	Improved	Dx: WG

CN, cranial neuropathy; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CGN, crescentic glomerulonephritis; CSF, cerebrospinal fluid; OP, opening pressure; IIF, indirect immunofluorescence; N.A., not available; PSL, prednisolone; AZP, azathioprine; S-pulse, steroid pulse therapy; CY, cyclophosphamide, ST, sulfamethoxazole/trimethoprim; IC, immune complex; ANA, antinuclear antibody; ssDNA, anti-ssDNA antibody; RF, rheumatoid factor; PTU, propylthiouracil; Tx, treatment; Dx, pathological diagnosis; MPA, microscopic polyangiitis

Recent reports on patients with p-ANCA-positive HCP indicate a relation of HCP with limited WG- or ANCA-associated vasculitis. In patients with ANCA-positive HCP or chronic meningitis, it is likely that the p-ANCA pattern is dominant in regard to the c-ANCA pattern.

To date, 10 cases of patients with p-ANCA positive HCP, including our case, have been reported in the literature;[10–18] the features of these reported cases are summarized in Table 1. Four cases were associated with propylthiouracil therapy,[13] WG,[14,16] and microscopic polyangiitis,[17] respectively; the remaining cases also had various immunological abnormalities. The median age of the patients was 63 years (range 47–75 years), with a female/male ratio of 3:2. The ESR and the CRP level were elevated in most cases. In the CSF, the initial pressure was elevated, and there was lymphocytic pleocytosis and an increased protein level.

Involvement of cranial nerves I–XIII has been reported,[19] but cranial nerves II, VI, VII, and VIII are most frequently affected, which is consistent with the WG cases reported previously.[4] Corticosteroid therapy is initially effective in most HCP cases, but combination therapy including an immunosuppressant such as cyclophosphamide is recommended in HCP · associated with WG.[14,16,20] To our knowledge, our case is the third reported case of biopsy-proven WG presenting with p-ANCA-positive HCP. Furthermore, the fact that the cases of this disease mainly have been reported from Japan reminds us of the involvement of environmental or genetic factors in the development of this disease.

Conclusions

Myeloperoxidase-ANCA is associated with small-vessel vasculitides and may be linked to a lesser disease extent or limited forms of WG, especially CNS complications and HCP. Therefore, it is useful to add serologic testing for ANCA to the workup of patients presenting with HCP, although a role for MPO-ANCA in the pathogenesis of HCP is unclear at present. This case illustrates the association between the limited form of WG and HCP and emphasizes that MPO-ANCA-positive HCP is a distinct disease entity.

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