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CASE REPORT

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CD8$^+$ T lymphocytes infiltrate predominantly in the inflammatory foci of MPO-ANCA-positive thoracic hypertrophic pachymeningitis in a patient with HLA-A24

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Abstract Hypertrophic pachymeningitis (HP) is extremely rare and an inflammatory process that thickens the dura mater. A 59-year-old Japanese woman developed backache, became paraplegic, and magnetic resonance imaging revealed diffuse thickening of the thoracic dura mater encompassing the spinal cord. Although a test for myeloperoxidase antineutrophil cytoplasmic autoantibody (MPO-ANCA) was shown to be positive, vasculitis was not found and CD8$^+$ T lymphocytes that predominated in the inflammatory foci. Both interleukin (IL)-2 and IL-6 were markedly elevated in not only sera but also cerebrospinal fluids, very much higher in the latter. Human leukocyte antigen (HLA) typing revealed A24 positivity, suggesting this molecule was interacting with CD8$^+$ T lymphocytes. It was suggested that immunological disharmony and autoimmunity would play a pivotal role in the development of HP under genetic background of HLA-A24, and HP would be one feature of multiple organ involvement in ANCA-associated diseases.

Key words CD8$^+$ T cells · Human leucocyte antigen (HLA) A24 · HLA-B51 · Hypertrophic pachymeningitis (HP) · Myeloperoxidase antineutrophil cytoplasmic autoantibody (MPO-ANCA)

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Introduction

Hypertrophic pachymeningitis (HP) is an extremely uncommon fibrosing process that causes a localized or diffuse thickening of the dura mater, but little has known about pathogenesis.[1] In the present case of myeloperoxidase antineutrophil cytoplasmic autoantibody (MPO-ANCA) positive HP with dural thickening of the thoracic lesion, CD8$^+$ T lymphocytes infiltrated predominantly in inflammatory foci with markedly high titer of interleukin (IL)-2 and IL-6 in cerebrospinal fluids (CSF). Human leukocyte antigen (HLA)-A24, which was positive in this case, has been proposed recently as the molecule interacting with CD8$^+$ T lymphocytes in various diseases and pathological phenomena.[2–6]

We report a rare case of HP, discuss a possible autoimmune mechanism that could be postulated in the etiology, and refer to the high frequency of HP in the Japanese population from the genetic point of view.

Case report

The patient gave written consent to take part in this study.

A 59-year-old Japanese woman became febrile with a disturbed gait after flu-like symptoms, and was admitted to our center in May 2005. She had been complaining of a progressive thoracic backache for a few months.

On admission, she was clear but almost paraplegic. She showed the absence of previous renal or pulmonary symptoms resulting from vasculitic involvement, such as proteinuria, hematuria, interstitial pneumonia, or alveolar hemorrhage. She also had no meningeal signs, papilledema, visual field defects, cranial nerve palsies, pyramidal signs, ataxia, or involuntary movements. Neurologic examination showed slightly exaggerated patellar tendon reflex and bilateral ankle clonus with sensory disturbance of the legs. Body temperature was 38.7ºC.

Urinalysis was normal. Hematological examination revealed a white blood cell count of 12,100/μl (96.0% segmented neutrophils, 1.6% lymphocytes, 1.8% monocytes, 0.5% eosinophils, 0.1% basophils), a hemoglobin level of 12.4 g/dl, and a platelet count of 41.1×10^4/μl. Erythrocyte sedimentation rate (ESR) was 71 mm/h, and the serum C-reactive protein (CRP) concentration was 20.4 mg/dl. Liver enzyme levels and renal function tests were within normal limits. Tests for antinuclear and anti-double stranded DNA antibodies, rheumatoid factor, and syphilis were negative. A tuberculin skin test was also negative. The serum level of angiotensin-converting enzyme was within normal limits. An enzyme-linked immunosorbent assay was positive for MPO-ANCA at a titer of 90 EU (normal <10 EU) but negative for proteinase 3-ANCA. Serum electrophoresis was normal, and blood cultures for mycobacteria and *Treponema palliidum* hemagglutination tests were negative. Repeated cultures for possible pathogens were negative. Lumbar puncture demonstrated an initial pressure of 24 cm-H_2O, pleocytosis with a predominance of mononuclear cells (68/3), and on examination of the CSF; protein was elevated at 2500 mg/dl; glucose level (38 mg/dl) was normal, and positive for both Nonne–Apelt and Pandy test. No microorganisms were found on smear or in culture, and tumor cells were absent on smear and cytologic examination.

Radiographs of the cervical and thoracic spine showed no abnormalities. Magnetic resonance imaging (MRI) revealed diffuse thickening of the dura mater compressing the thoracic cord at the Th1 to Th8 vertebral levels (Fig. 1A). The thickened dura was isotense in T1-weighted images and hypotense in T2-weighted images. T1-weighted post-contrast MRI demonstrated diffuse dural enhancement. Thickened dura mater encompassed the spinal cord resulting in a bizarre shape (Fig. 1B).

Neurological exacerbation progressively appeared, so urgent laminectomy was performed. At operation, the dura was markedly bumpy and thickened. Microscopic examination of the material showed dural thickening with dense, hyalinized collagen tissue and demonstrated diffuse foci of inflammation with infiltration of small lymphocytes and plasmatoid cells. Fibroblasts were plump and swollen, and collagen bundles were dense with mild vascular proliferation. There were no epithelioid granulomas or giant cells, and no evidence of vasculitis (Fig. 2A). Periodic acid Schiff, Ziehl-Neelsen, and Warthin-Starry stains all were negative for microorganisms such as fungi, acid-fast bacilli, or spirochetes. Using monoclonal antibody of both CD4 and CD8, immunohistochemical staining of the same material showed that the inflammatory infiltrate was composed of $CD8^+$ T lymphocytes predominantly (Fig. 2B) with very scarce $CD4^+$ ones.

The patient was diagnosed as having MPO-ANCA positive HP, and was treated with three courses of high-dose steroid pulse (each course consisted of intravenous methylprednisolone, 1 g per day for 3 days) every week and succeeding oral prednisolone, 0.8 mg/kg (40 mg) daily, followed by tapering. Immediately after the initiation of treatment, clinical symptoms due to HP subsided, but gait disturbance and numbness still remained, requiring efforts for rehabilitation to advance comprehensive quality of life. With further treatment, the serum levels of CRP, ESR, and MPO-ANCA all returned to normal. To control the disease activity, in addition to the above treatments, intravenous cyclophosphamide pulse and cyclosporine were combined. The patient has had no evidence of a recurrence after over 25 months of follow-up.

Cytokine levels between exacerbation and remission in both sera and CSF are shown in Table 1. Interleukin-2 and IL-6 were markedly elevated in not only sera but also CSF during exacerbation, while, levels of tumor necrosis factor (TNF)-α remained within normal limits regardless of disease activity in the disease course. The result of HLA typing

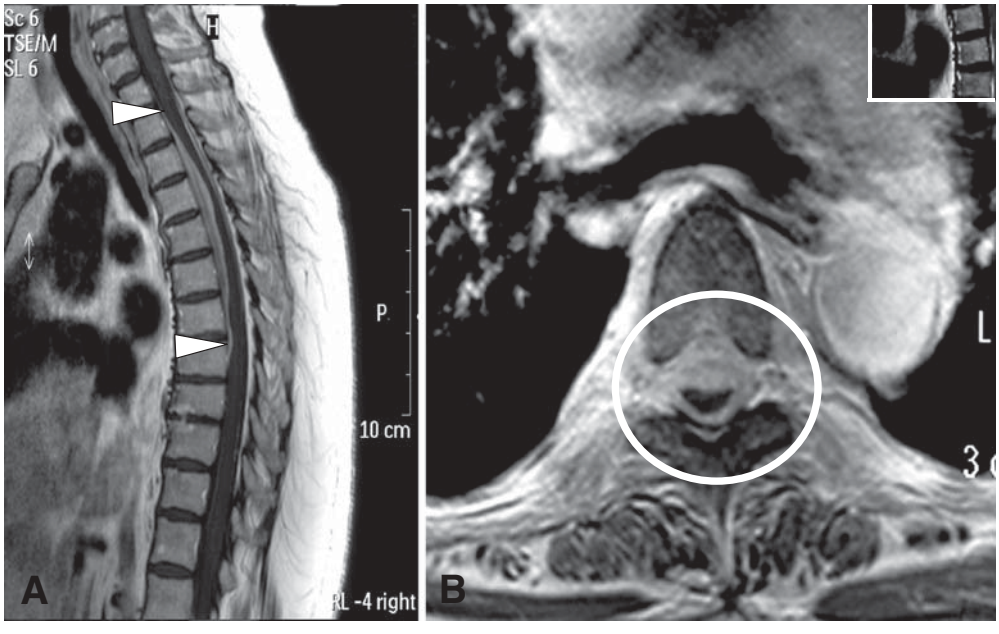

Fig. 1. **A** Magnetic resonance image (MRI) of the spinal cord in thoracic lesions. Gadolinium-enhanced contrast MRI showed a longitudinally extending mass lesion anteriorly compressing the spinal cord at the Th1 to Th8 vertebral levels (*arrowheads*). **B** The vertical view of the lesion showed that the thickened dura mater clearly encompassed the spinal cord, resulting in a bizarre shape of the thoracic spinal cord (*circle*)

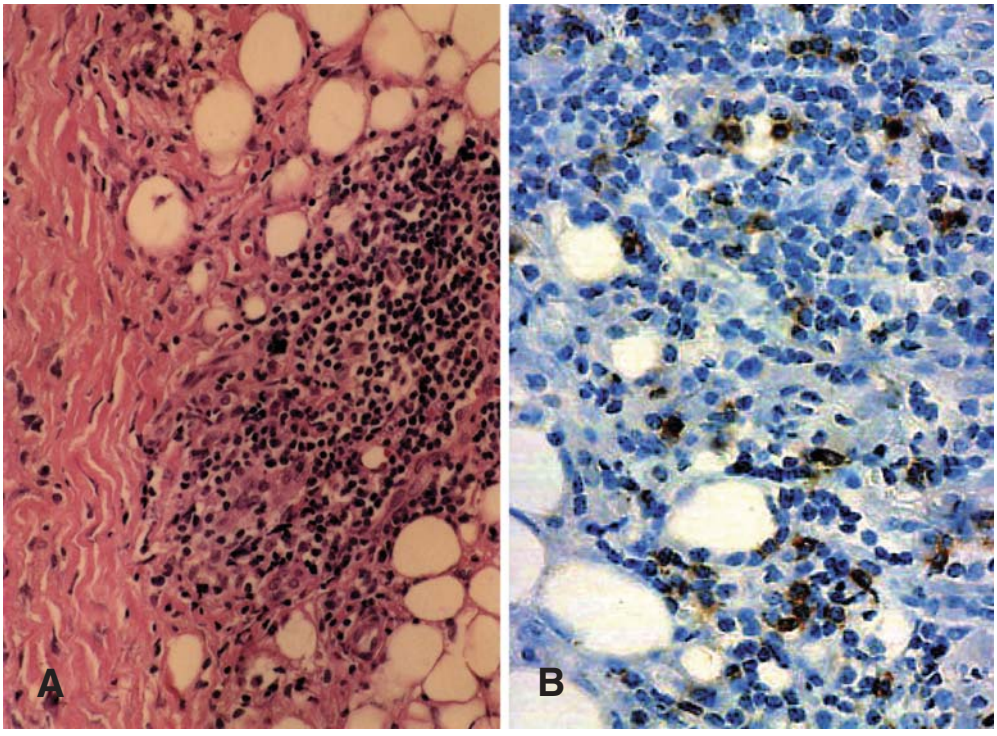

Fig. 2. **A** Histologic specimen from the thickened dura mater, showing hyalinized collagen tissue and demonstrated diffuse foci of inflammation with infiltration of small lymphocytes and plasmatoid cells. Fibroblasts were plump and swollen, and collagen bundles were dense with mild vascular proliferation. There were no epithelioid granulomas or giant cells, and no evidence of vasculitis (H&E staining, ×120). **B** Lymphocytes composed of inflammatory foci were positive against anti-CD8 monoclonal antibody, but not against anti-CD4 immunohistochemically. (×180)

Table 1. Levels of cytokines in both sera and CSFs

Cytokine	Exacerbation		Remission	
	Serum	CSF[b]	Serum	CSF
sIL-2R[a] (U/ml) (Normal: 220–530)	682	2770	156	<85
IL-6[c] (pg/ml) (Normal: <4)	212	1220	6.3	1.4
TNFα[d] (pg/ml) (Normal: <5)	<5	<5	<5	<5

[a] Soluble interleukin-2 receptor
[b] Cerebrospinal fluid
[c] Interleukin-6
[d] Tumor necrosis factor α

was positive for HLA-A24, -A26, -B51, -B60, -DR11, and -DR12 by the polymerase chain reaction-reverse sequence specific oligonucleotide method.

Discussion

The patient had spastic paraplegia, and thickened dura mater of the thoracic spinal cord was demonstrated on serial MRI, revealing HP (Fig. 1A,B). Hypertrophic pachymeningitis is a fibrosing inflammatory process that thickens the dura mater. In the case reported here, diagnosis of HP was made on the basis of MRI data together with biological inflammation, a compatible clinical presentation including aches and nerve palsies, and finally histopathological findings of the removed material (Fig. 2A). No possible cause of HP was detected apart from MPO-ANCA. Further, the association of HP, biological inflammation, positive MPO-ANCA, markedly elevated cytokine levels of IL-2 and IL-6 (Table 1), and subsequent remission with immunosuppressive therapies must be suggestive of an autoimmune mechanism in etiology.

Although the number of HP case reports has gradually increased with the use of computed tomography (CT) and contrast-enhanced MRI,[7,8] their pathogenesis still remains obscure. Of importance was serological MPO-ANCA positivity. ANCA comprises cytoplasmic (c) and perinuclear (p) types. While c-ANCA is highly specific for Wegener's granulomatosis (WG), p-ANCA could be detected in patients with a variety of diseases, including microscopic polyangiitis (MPA), Churg–Strauss syndrome, primary pauci-immune necrotizing and crescentic glomerulonephritis, and a limited form of WG. The present case showed the absence of vasculitis not only from the clinical view of symptoms, but also in the histological examination of the thoracic lesion. Although it is probable that closer investigation of MPA cases will reveal HP, the possibility of WG should be an initial consideration in patients with ANCA-positive HP regardless of the pattern of ANCA. Cases of p-ANCA-positive WG with HP were reported to lack the typical clinical triad represented by the upper and lower respiratory tract and renal involvement.[9] In the present case, the clinical presentation was not suggestive of WG, and the removed tissue of HP also revealed no vasculitic findings (Fig. 2A). Judging from differential diagnosis of MPO-ANCA positive diseases, HP may be one of the clinical features of multiple organ involvement in ANCA-associated diseases.[10] Therefore, when a patient with ANCA-associated disease complains of

Table 2. Review of reported cases with p-ANCA positive hypertrophic pachymeningitis

Case	Age/Sex	p-ANCA	CRP (mg/dl)	ESR (mm/hr)	ANA	RF	Note	Treatment	Outcome	Reference no.
1	64/M	+(IIF)	Elevated	N.A.	N.A.	+	Horner's syndrome	PSL	Improved	11
2	53/F	25 EU	N.A.	N.A.	N.A.	N.A.	WG, Tumor	PSL, AZA	Dead	12
3	47/F	518 EU	Elevated	107	–	N.A.	Graves' disease	PSL	Improved	13
4	63/M	+(IIF)	17.5	160	N.A.	N.A.	Immune complex(+)	PSL, AZA	Improved	14
5	64/M	18 U	N.A.	100	–	N.A.	WG	PSL, AZA	Improved	15
6	77/F	+(IIF)	Negative	Normal	+	+	ssDNA, Transverse myelopathy	Pulse-PSL, PSL	No change	16
7	70/M	99 EU	6	N.A.	+	+	Cranial neuropathy	PSL, CYC	Improved	17
8	64/M	+(IIF)	Positive	Increased	N.A.	+	Cranial neuropathy	Pulse-PSL, PSL	Improved	18
9	56/F	321 EU	17.1	N.A.	–	N.A.	MPA	PSL	Improved	19
10	63/F	+	17.5	N.A.	N.A.	N.A.	Silicon exposure	PSL, AZA	Improved	20
11	47/F	518 EU	4.2	107	+	+	RA, Graves' disease, PTU	Pulse-PSL, PSL	Improved	21
12	67/M	80 EU	–	N.A.	+	N.A.	Diabetes insipidus, Tumor	PSL, CYC	Improved	22
13	75/F	+	15.4	N.A.	+	N.A.	SjS	Anti-Tbc	Improved	23
14	75/F	128 U	N.A.	113	–	–	WG	Pulse-PSL, PSL, CYC	Improved	24
15	70/M	26 EU	3.1	120	N.A.	+	Caseous necrosis, epithelioid cells	PSL, CYC	Improved	25
16	53/F	25 U	Positive	Elevated	N.A.	N.A.	WG	PSL, AZA	Improved	26
17	56/F	321 EU	17.1	124	N.A.	N.A.	MPA, necrotizing vasculitis	Pulse-PSL, PSL	Improved	27
18	67/M	80 EU	Negative	N.A.	+	N.A.	Diabetes insipidus	Pulse-PSL, PSL, CyA	Improved	28
19	60/M	23 EU	12.7	89	–	–	WG	β-Methasone, CYC	Improved	29
20	61/M	63 EU	14.4	122	–	63	Silicosis	Pulse-PSL, PSL	Improved	30
21	67/M	38 EU	4.1	92	×60	81	Silicosis	PSL	Improved	30
22	51/F	160(IIF)	47	78	1:2000	N.A.	SjS, Hepatitis B Vaccine	Pulse-PSL, CYC, MTX	Improved	31
23	59/F	90 EU	20.4	71	–	–	$CD8^+$ T cells, HLA-A24, -B51	Pulse-PSL, CYC, CyA	Improved	Present case

p-ANCA, perinuclear antineutrophil cytoplasmic antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; RF, rheumatoid factor; IIF, indirect immunofluorescence; N.A., not available; PSL, prednisolone; WG, Wegener's granulomatosis; AZA, azathioprine; ssDNA, anti-single stranded DNA antibody; Pulse-PSL, steroid pulse therapy; CYC, cyclophosphamide (including endoxan pulse therapy); MPA, microscopic polyangiitis; RA, rheumatoid arthritis; PTU, propylthiouracil; SjS, Sjögren's syndrome; Anti-Tbc, anti-tuberculosis drugs; CyA, cyclosporin; MTX, methotorexate; CD, cluster of differentiation; HLA, human histocompatibility leukocyte antigens

neurological abnormalities, it is important to consider the possibility of HP and carry out appropriate investigations. Further studies of ANCA-positive HP should be essential in order to understand better the pathogenesis between ANCA-associated disease and HP.

To our knowledge, only 23 cases of patients with p-ANCA positive HP, including our patient, have been reported in the literature (Table 2).[11–31] Certainly in some cases, an inflammatory reaction with various immunological abnormalities has been shown. Corticosteroid therapy was effective and clinical features resembled those of ANCA-associated vasculitis. No published study has illustrated the relation between $CD8^+$ T lymphocytes and HP. Only in CSF, relative increases in $CD4^+$, $CD8^+$ and activated T lymphocytes in aseptic meningitis[32] and enhanced function of $CD8^+$ T lymphocytes in histoplasma meningitis[33] were reported, suggesting an active immunological inflammatory process. We believe our case is the first report of histologically proven $CD8^+$ T lymphocytes' association with HP being MPO-ANCA-positive. Judging from the predominance of $CD8^+$ T lymphocytes in the inflammatory foci (Fig. 2B) besides high cytokine levels of IL-2 and IL-6 during the active phase in both serum and CSF, especially markedly elevated in the latter (Table 1), immunological disharmony might be attributable to the distinct role of $CD8^+$ T lymphocytes, which would be of particular relevance to HP. Interestingly, the fact that over half of p-ANCA-positive HP published are from Japan (Table 2) reminds us of the environmental or genetic factors in the development of HP. While the HLA-A24 allele is the most common in Japanese people (more than 60%), the relation between $CD8^+$ T lymphocytes and HLA-A24 has been recently postulated in the pathogenesis of human diseases.[2–6,34] The case reported here demonstrated HLA-A24 positivity, and $CD8^+$ T lymphocytes infiltrated predominantly the HP inflammatory lesions (Fig. 2B). These data strongly suggest that HP might be restricted genetically, and would provide a novel thought in relation to pathogenesis in HP. Because $CD8^+$ T lymphocyte activity was blocked by anti-HLA-A24 and anti-CD8 antibodies in hepatitis C virus infection,[35] it is suggested that $CD8^+$ T lymphocytes could interact with HLA-A24 molecules presented de novo in inflammatory foci of HP. It might be possible that HP associated with ANCA would represent a novel disease entity and could be a form of vasculitis. Additionally, HLA-B51 is frequently detected in Japanese patients with Behcet's disease, which is also known as silk-road disease. In the light of the majority of case reports of HP being Japanese (Table 2), considered together with the present case of HLA-B51 positivity, genetic and geographic environmental factors could be involved in the occurrence of HP. Further studies will address these questions.

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