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【 CASE REPORT 】

Relapsing Polychondritis and Aseptic Meningoencephalitis

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Abstract:
We herein report a 49-year-old Japanese man with relapsing polychondritis (RP) and aseptic meningoencephalitis. Four years ago, the patient was diagnosed with RP. Prednisolone (PSL) was started at 30 mg/day, and the symptoms promptly disappeared. However, cognitive impairment gradually appeared from six months before hospitalization. Methylprednisolone pulse therapy was immediately initiated, followed by administration of PSL at 1 mg/kg/day. Intravenous cyclophosphamide was combined with PSL. After treatment, the patient's cognitive impairment clearly improved. In conclusion, RP rarely causes aseptic meningoencephalitis, highlighting the need for prompt and aggressive immunosuppressive therapy.

Key words: relapsing polychondritis, aseptic meningoencephalitis, glucocorticoids, immunosuppressants, interleukin-6

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Introduction

Relapsing polychondritis (RP) is a rare rheumatic disease that causes recurrent and repetitive inflammation, mainly in the hyaline cartilage throughout the whole body (1). The ear cartilage is mainly damaged in the early stage of the disease (2). Although the cause of RP has yet to be elucidated, an autoimmune mechanism involving collagen is suspected (1, 2). RP-associated central and peripheral neuropathies occur in 3% of patients (2).

We herein report a case of aseptic meningoencephalitis in RP that was successfully treated with a combination of methylprednisolone pulse therapy and immunosuppressants, such as intravenous cyclophosphamide (IVCY), azathioprine and methotrexate.

Case Report

A 49-year-old Japanese man was admitted to our hospital due to a 6-month history of cognitive impairment. Four years before admission, the patient developed bilateral ear swelling and pain, scleritis, seronegative arthritis, and sensorineural hearing loss. The results of laboratory examinations were as follows: white blood cell count 8,210/μL, hemoglobin 15.1 g/dL, mean corpuscular volume (MCV) 87.3 fL, platelet count 307,000/μL and C-reactive protein (CRP) level 0.17 mg/dL. Anti-type II collagen antibody was positive (30.7 EU/mL: reference value <20 EU/mL), while proteinase 3 (PR3)-antineutrophil cytoplasmic antibody (ANCA) or myeloperoxidase (MPO)-ANCA was negative. No remarkable Sweet's disease-like skin rash was observed. Furthermore, a biopsy of the auricular cartilage showed inflammatory cell infiltration and accumulation, destruction, degeneration, and fibrosis in the tissue. The patient was accordingly diagnosed with RP.

Prednisolone (PSL) was started at 30 mg/day, and the symptoms promptly disappeared. Thus, PSL was gradually decreased and maintained at 4 mg/day in remission for 3 years. However, the patient's unusual forgetfulness was pointed out by his coworkers six months before hospitalization. One month before admission, family members realized that the patient could not completely recall even major events from six months ago. Therefore, he was admitted to our hospital for an assessment of cognitive impairment. He had a history of hypertension diagnosed at 40 years old and

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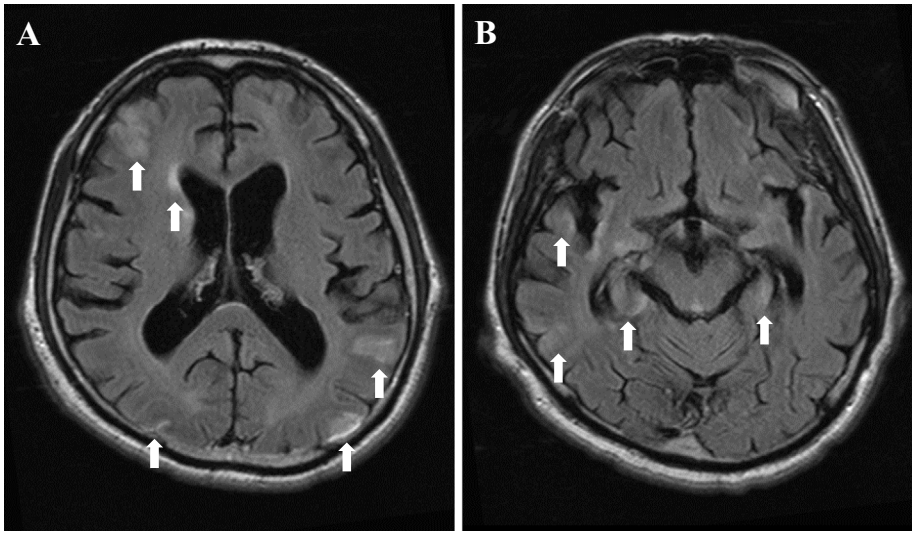

Figure 1. Axial section of T2-weighted gadolinium-enhanced fluid-attenuated inversion-recovery magnetic resonance imaging of the brain showing multiple high-intensity areas with contrast enhancement in the subcortical and perivascular deep white matter (arrows) (A), and the right temporal lobes and bilateral hippocampus (arrows) (B) had noticeable brain atrophy for the patient's age.

had been receiving antihypertensive drugs since then.

On admission, his body weight was 83 kg (body mass index 28.7). He was afebrile (36.9°C), and his blood pressure was 111/69 mmHg. He correctly recited his name and birthday but could not recite the current time or his location. His Mini-Mental State Examination (MMSE) score was 19/30 points. No marked headaches, dizziness, conjunctival hyperemia, swelling or pain in the pinna, hearing loss, arthritis or Sweet's disease-like skin rash were observed. A neurological examination showed no diplopia, dysarthria or stiff neck. Kernig's sign was negative. The deep tendon reflexes were normal, and the pathological reflexes were negative.

The results of laboratory tests were as follows: white blood cell count 6,910/μL, hemoglobin 16.3 g/dL, MCV 89.7 fL, platelet count 239,000/μL, CRP level <0.10 mg/dL, and erythrocyte sedimentation rate 28 mm/h. Anti-type II collagen antibody was positive at 20.8 EU/mL, while anti-N-methyl-D-aspartate (NMDA) receptor antibody, anti-thyroid peroxidase antibody, PR3-ANCA and MPO-ANCA were negative. His thyroid hormone level was within the reference range. A cerebrospinal fluid (CSF) analysis showed colorless fluid but an increased protein level of 54 mg/dL, decreased sugar level of 39 mg/dL, mononuclear cell count of 1/μL, IgG index of 0.61 and increased IL-6 level of 24.2 pg/mL (reference value <4 pg/mL). There were no significant findings in the culture of various viral antibody titers, bacteria, fungi or tuberculosis, and atypical cells were absent on a cytodiagnosis.

T2-weighted gadolinium-enhanced fluid-attenuated inversion-recovery (FLAIR) magnetic resonance imaging (MRI) of the brain showed multiple high-intensity areas with contrast effects in the subcortical and perivascular deep white matter (Fig. 1A), and the right temporal lobes and bilateral hippocampus (Fig. 1B) showed noticeable brain atrophy for the patient's age. Electroencephalography (EEG) revealed a widespread persistent δ wave during drowsiness. On brain perfusion single-photon emission computed tomography (SPECT), a severely impaired blood flow was found in a small area of the left frontal and temporal lobes.

On the 7th day of hospitalization, his disorientation worsened, and he was treated with methylprednisolone pulse therapy (methylprednisolone 1,000 mg/day for 3 days) for aseptic meningoencephalitis in RP, followed by PSL at 80 mg/day (PSL 1 mg/kg/day) for 4 weeks. After the pulse therapy, his cognitive impairment gradually improved. On the 22nd hospital day, the MMSE score improved to 28/30 points. On hospital day 38, IVCY (cyclophosphamide 500 mg/month for 1 day) was initiated in combination with prednisone. Thereafter, the dosage of PSL was gradually decreased every 2 weeks.

The patient was discharged on hospital day 130. Post-discharge, IVCY was performed 6 times, and the dosage of PSL was 20 mg/day at 6 months after the start of treatment. Subsequently, the levels of IL-6 in the CSF were within the reference range (Fig. 2). Furthermore, the multiple high-intensity areas on FLAIR MRI of the brain were ameliorated (Fig. 3A, B), and the δ waves on EEG were decreased. SPECT of brain perfusion also showed an improved blood flow in the left frontal and temporal lobes. The patient was prescribed azathioprine 50 mg/day, but this was discontinued due to hepatic disorder. The patient then received methotrexate 10 mg/week instead, and the dosage of PSL was gradually reduced to 5 mg/day. No relapse occurred within five years after the onset of aseptic meningoencephalitis.

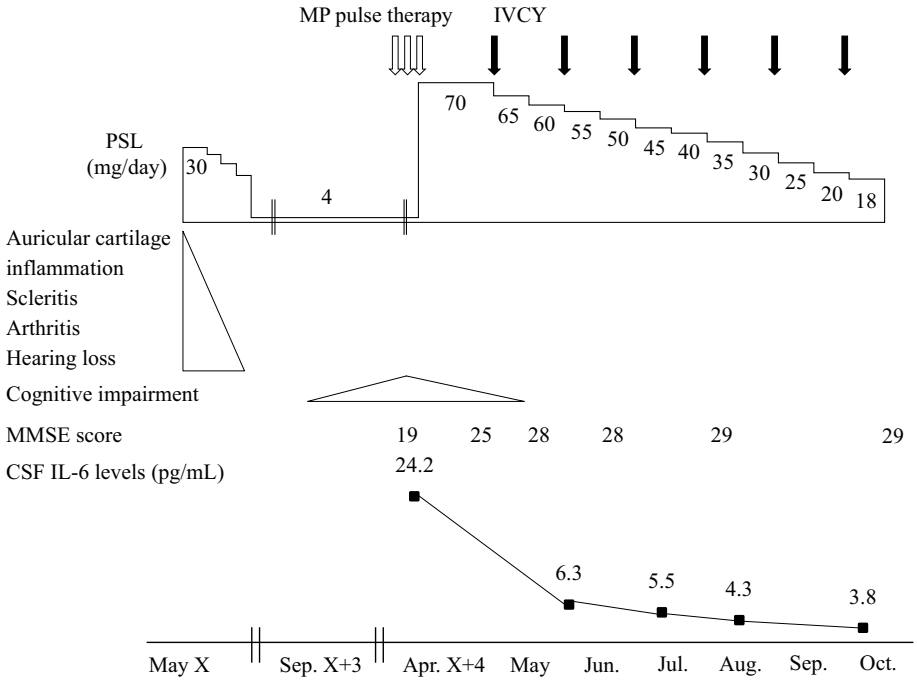

Figure 2. **Clinical symptoms, MMSE score, interleukin-6 levels in the cerebrospinal fluid, and immunosuppressive therapy during hospitalization. PSL: prednisolone, MP: methylprednisolone (white arrows), IVCY: intravenous cyclophosphamide (black arrows), MMSE: Mini-Mental State Examination, CSF: cerebrospinal fluid, IL-6: interleukin-6**

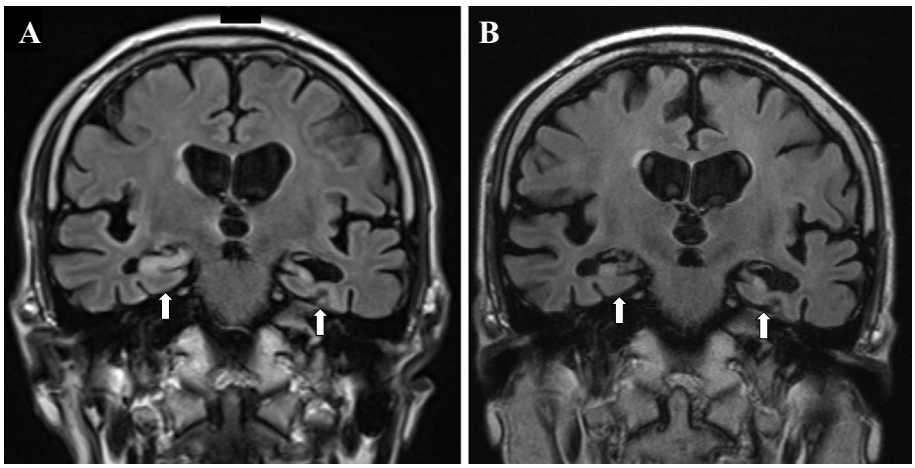

Figure 3. **Coronal section of T2-weighted gadolinium-enhanced fluid-attenuated inversion-recovery magnetic resonance imaging of the brain showing enhancement in the brain surface and the hippocampus before administration of methylprednisolone pulse therapy (arrows) (A). Enhancements were ameliorated after treatment (arrows) (B).**

Discussion

This is a rare case of RP and aseptic meningoencephalitis. In our case, the early diagnosis enabled prompt intervention with the combination of methylprednisolone pulse therapy and IVCY. The combination therapy markedly improved the cognitive impairment and MMSE score as well as the brain MRI, EEG, and SPECT findings in this patient. In addition, we newly found that IL-6 in the CSF was a useful biomarker for evaluating the activity of aseptic meningoencephalitis in RP.

Cases of RP and aseptic meningoencephalitis are rare, with only 37 cases, including the current case, reported (1-30). Table shows the characteristic findings of these cases reported since 2011. The average age was 56.4 (range, 29-75) years old, and the majority were men (27/37, 73.0%). The most common symptom was headache (15/37, 40.5%), followed by impaired consciousness (10/37, 27.0%) and cognitive impairment (8/37, 21.6%). The most common

Table. **Case Reports of Relapsing Polychondritis and Aseptic Meningoencephalitis*.**

Reference	Age/ Sex	Neurological symptoms	Initial therapy	Immunosuppressant and biologics	Outcome	Recurrence
26)	54/M	Emotional disturbance, acoustic and visual hallucination, memory loss	MP pulse therapy	AZA	Recovered	(+)
26)	44/M	Memory loss, irritability, anxiety	One fifth-dose MP pulse therapy	AZA	Recovered	(+)
26)	52/M	Anxiety, insomnia, memory loss, deafness, gait change, urinary incontinence, expressive and receptive aphasia, dullness, acalculia, and papilledema	Half-dose MP pulse therapy	(-)	Recovered	(+)
26)	44/F	Anxiety, insomnia	Half-dose MP pulse therapy	AZA	Recovered	(-)
27)	68/M	Dysarthria	MP pulse therapy	MTX	Recovered	(-)
28)	73/M	Headache, transitory consciousness loss	MP pulse therapy	(-)	Died	(+)
29)	57/M	Headache, seizure	High dose intravenous GCs (dose**)	POCY, MTX, IFX	Recovered	(-)
30)	39/M	Headache, wandering, violence	MP pulse therapy	(-)	Recovered	(-)
2)	58/F	Headache, neck stiffness	Dexamethasone 15 mg/day	IVCY CyA	Recovered	(+)
1)	61/M	Cognitive impairment	MP pulse therapy	MTX	Recovered	(-)
Our case	49/M	Cognitive impairment	MP pulse therapy	IVCY, AZA, MTX	Recovered	(-)

M: male, F: female, PSL: prednisolone, MP pulse therapy; methylprednisolone pulse therapy, mPSL: methylprednisolone, MTX: methotrexate, POCY: oral cyclophosphamide, GCs: glucocorticoids, AZA: azathioprine, IFX: infliximab, IVCY: intravenous cyclophosphamide, CyA: cyclosporine, *: Case reports published since 2011, **: not described

initial treatment was methylprednisolone pulse therapy (18/37, 48.6%), followed by high- or moderate-dosage of glucocorticoids (17/37, 45.9%) and best supportive care (2/37, 5.4%). Importantly, 14/34 cases (41.2%) developed recurrence, and 4/35 cases (11.4%) died, showing high recurrence and mortality rates (data for the several cases were not available). In addition, glucocorticoids alone were used in 21/35 cases (60.0%), and glucocorticoids combined with immunosuppressants were used in 14/35 cases (40.0%). The immunosuppressants used were azathioprine (6 cases), methotrexate (5 cases), oral cyclophosphamide (3 cases), IVCY (2 cases) and cyclosporine and tacrolimus (1 case each). Furthermore, the biologics used were infliximab and adalimumab in one case each. Notably, all eight patients treated with methylprednisolone pulse therapy combined with immunosuppressants recovered. This suggests that the combined use of methylprednisolone pulse therapy and immunosuppressants is effective in improving the prognosis of aseptic meningoencephalitis in RP. Therefore, in the present patient, we initiated methylprednisolone pulse therapy on hospital day 7, followed by immunosuppressants such as IVCY for induction, and azathioprine or methotrexate for maintenance, and no subsequent recurrence was observed under tapered glucocorticoid administration.

Characteristic findings of FLAIR or T2-weighted imaging on brain MRI in patients with RP and aseptic meningoencephalitis include the presence of hyperintensity in the bilateral temporal lobe, including the hippocampus, subcortex, and periventricular white matter (1, 2, 6-8, 10-21, 23, 25-30). The current case showed multiple hyperintensities with contrast enhancement in the subcortical and perivascular deep white matter, right temporal lobes, and bilateral hippocampus on brain MRI. We ruled out bacterial, viral, fungal and tuberculous meningoencephalitis; brain tumors; cerebral infarction; cerebral hemorrhaging; malignant tumors; and paraneoplastic syndromes as soon as possible and made a diagnosis of aseptic meningoencephalitis in RP. Brain MRI also showed marked brain atrophy for the patient's age; however, the cognitive impairment was ameliorated by immunosuppressive therapy, suggesting that the brain atrophy was not associated with cognitive impairment. Similar to the present case, there have been some cases in which brain atrophy was observed by brain MRI among case reports of RP and aseptic meningoencephalitis (14, 20, 21, 28). This suggests that one of the causes of brain atrophy in this case may have been RP and aseptic meningoencephalitis; however, the cognitive impairment of these patients may be able to be ameliorated with proper immunosuppressive treatments. Furthermore, increased CSF IL-6 levels suggested aseptic meningoencephalitis due to an autoimmune mechanism in RP.

The etiology of RP and aseptic meningoencephalitis remains to be fully elucidated. The earliest neuropathologic study of RP-related meningitis was reported by Stewart et al. in 1998. They demonstrated diffuse vasculitis in both medium- and small-sized veins along with nearby white matter necrosis of the autopsied brain (3). However, vasculitis was not found in six cases with a brain biopsy or

autopsy, although infiltration of inflammatory cells centered on lymphocytes was observed (4, 8, 10, 13, 15, 20). While we were unable to perform a brain biopsy in this case, we newly found high levels of IL-6 in the CFS. In addition, decreased levels of IL-6 after treatment correlated with the improvement of cognitive impairment.

This case needed to be differentiated from the recently identified entity of vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome, which has been reported to present with multisystemic inflammation, including RP, arthritis, scleritis, and neurological symptoms (31). However, our patient did not present with a fever, cytopenia, pulmonary infiltrate, pleural effusion, neutrophilic dermatosis, tender plaque, vasculitis or periorbital inflammation. Therefore, VEXAS syndrome was deemed unlikely in our patient.

One limitation of this case report is that whether or not the central lesion was due to RP remains unclear, as RP symptoms were not present when the cognitive impairment appeared. Based on the patient's clinical findings, we excluded anti-NMDA receptor encephalitis, Hashimoto's encephalopathy, neuropsychiatric systemic lupus erythematosus, neuro-Behçet's disease, paraneoplastic encephalitis, drug-induced encephalopathy, mitochondrial encephalomyopathy, infectious encephalitis (especially herpes simplex encephalitis), cerebral hemorrhaging, cerebral infarction and brain tumors. However, we were unable to make a histopathological diagnosis of the central lesion. Although the episode of aseptic meningoencephalitis occurred 4 years after the onset of RP, the following points may support the diagnosis of meningoencephalitis by RP: (1) the MRI findings of our patient were consistent with previous case reports of meningoencephalitis associated with RP, and (2) other possible causes of the central lesion were deemed unlikely.

In conclusion, we encountered a case of RP and aseptic meningoencephalitis with progressive cognitive impairment that was successfully treated with prompt combination therapy using methylprednisolone pulse and immunosuppressants. Measurement of IL-6 in the CSF may be a novel, useful biomarker for this condition.

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

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