

# The Successful Treatment of Myeloperoxidase Antineutrophil Cytoplasmic Antibody-positive Hypertrophic Pachymeningitis in Patients with the Limited Form of Granulomatosis with Polyangiitis Using Methotrexate: Two Case Reports

Shinjiro Kaieda<sup>1</sup>, Naomi Yoshida<sup>1</sup>, Midori Minezaki<sup>1</sup>, Shuri Ushijima<sup>1</sup>, Daisuke Wakasugi<sup>1</sup>, Shiroh Miura<sup>1</sup>, Yusuke Uchiyama<sup>2</sup>, Hiroaki Ida<sup>1</sup> and Tomoaki Hoshino<sup>1</sup>

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## Abstract

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Recent findings have indicated a close relationship between myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-positive hypertrophic pachymeningitis and the limited form of granulomatosis with polyangiitis (GPA). In Japan, MPO-ANCA-positive hypertrophic pachymeningitis predominantly occurs in elderly individuals. We herein describe the cases of two patients with MPO-ANCA-positive hypertrophic pachymeningitis associated with the limited form of GPA who were successfully treated with a combination of corticosteroids and methotrexate. Although methotrexate has been shown to be less effective than cyclophosphamide for inducing the remission of GPA in patients with organ-threatening diseases, its safety and efficacy may make it a useful alternative treatment modality for patients with the limited form of GPA who show meningeal involvement.

**Key words:** granulomatosis with polyangiitis, hypertrophic pachymeningitis, methotrexate (MTX), MPO-ANCA

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## Introduction

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Hypertrophic pachymeningitis is an uncommon disorder that causes localized or diffuse thickness of the dura mater. It is heterogeneous, with a clinical presentation that can include headache, ataxia, and multiple cranial nerve palsy (1). Hypertrophic pachymeningitis has been associated with infectious diseases, malignancies, and autoimmune disorders (1, 2). Granulomatosis with polyangiitis (GPA) has also been associated with hypertrophic pachymeningitis (1). Recent reports on patients with myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-positive hypertrophic pachymeningitis indicate a close relationship with the limited form of GPA (3). In patients with the limited

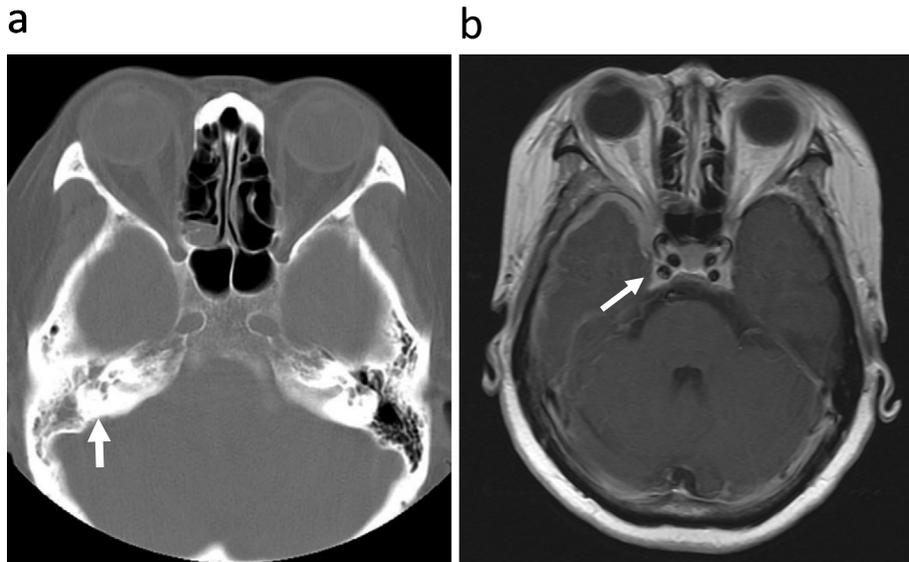
form of GPA, the upper respiratory tract, eye, or lung are primarily affected in the absence of renal disease; the classic histopathologic triad is less frequently observed on biopsy, and the clinical course tends to be relatively benign and protracted (4). Cyclophosphamide and steroids remain the first choice of treatment for extensive GPA, but have potentially severe adverse events (5). As MPO-ANCA-positive hypertrophic pachymeningitis is primarily observed in elderly individuals in Japan, alternative, less toxic, immunosuppressive agents should be considered (3). We herein present two cases of MPO-ANCA-positive-hypertrophic pachymeningitis associated with the limited form of GPA, in which combination therapy with steroids and methotrexate (MTX) contributed to the remission of hypertrophic pachymeningitis. The present study was performed in accordance with the Decla-

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<sup>1</sup>Department of Medicine, Division of Respiriology, Neurology and Rheumatology, Kurume University School of Medicine, Japan and <sup>2</sup>Department of Radiology, Kurume University School of Medicine, Japan

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Correspondence to Dr. Shinjiro Kaieda, shinkaieda@gmail.com



**Figure 1.** (a) A computed tomography image showing right mastoiditis (arrow). (b) A T1-weighted gadolinium-enhanced brain magnetic resonance image showing thickening and the enhancement of the dura mater from the right middle cranial fossa to the base of the frontal lobe, extending to the right cavernous sinus (arrow).

ration of Helsinki and both patients provided their informed consent for the inclusion of their data in this report. Although initially steroid-responsive, clinical manifestations frequently flare up after a reduction in the dose of steroids, MTX contributed to disease remission and it was possible to reduce the dose of steroids without any adverse events in the two present cases.

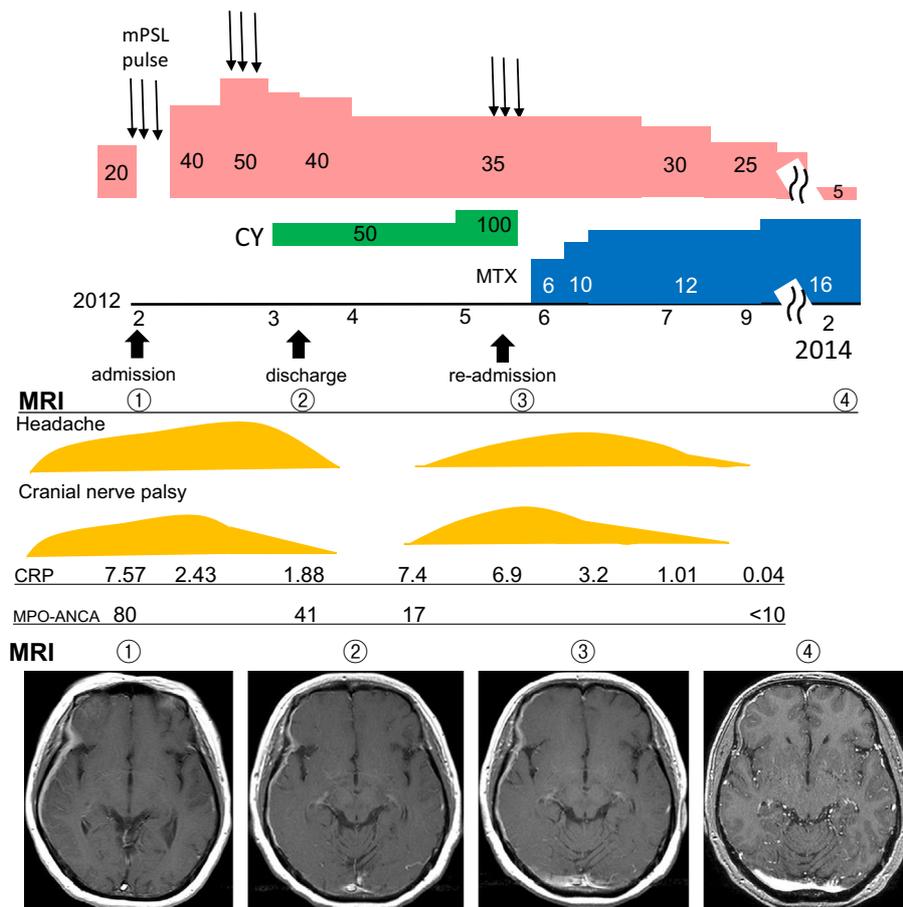
## Case Reports

### Case 1

A 56-year-old woman presented with fever and myalgia in April 2011. Serological tests revealed elevated C-reactive protein (CRP: 3.3 mg/dL; normal <0.3 mg/dL) and MPO-ANCA (1,250 EU; normal <10 EU) levels. Organ damage was not evident, and she had been diagnosed with ANCA-associated vasculitis. Treatment with prednisolone (PSL) (30 mg/day) had been initiated by a previous doctor. Her clinical symptoms and inflammatory response were ameliorated, and the dosage of PSL was gradually tapered. In December 2011, during the tapering of the dosage of PSL to 10 mg/day, right earache and facial nerve palsy occurred. The dosage of PSL was increased to 40 mg daily, resulting in the improvement of the patient's facial nerve palsy; however, the right earache did not improve. She was admitted to our department due to painful right ptosis associated with diplopia that occurred in January 2012. On admission, her height was 156 cm and her body weight was 56 kg. A neurological examination revealed that the horizontal ocular movement of her right eye was severely impaired and that the vertical ocular movement was moderately impaired. She showed decreased visual acuity, a mildly dilated pupil, and the narrow-

ing of the visual field in her right eye. She experienced paresthesia on the right side of her forehead. Deteriorated hearing acuity was observed, and a Rinne test of the patient's right ear was negative. A neurological examination revealed right cranial nerve II, III, IV, V1, and VI palsy. The laboratory data were as follows: white blood cell count, 16,500/mm<sup>3</sup> (89% neutrophils); hemoglobin, 12.6 g/dL; and platelet count, 414,000 cells/mm<sup>3</sup>. Routine blood chemistry and coagulofibrinolytic tests yielded normal results. The erythrocyte sedimentation rate and CRP level were elevated (75.0 mm/h and 6.99 mg/dL, respectively). A urinalysis was negative for urinary protein, and no casts were observed in the urinary sediment. In an immunological test, the patient tested positive for anti-nuclear antibodies, with a titer of 1:40 (a speckled pattern), anti-SS-A antibodies, and rheumatoid factor. The MPO-ANCA titer was elevated (80 EU; normal range <20 EU). The patient's Proteinase3 (PR3)-ANCA and IgG4 levels were within the normal ranges. An examination of her cerebrospinal fluid (CSF) revealed a protein level of 112 mg/dL and a cell count of 23 cells/mm<sup>3</sup> (mononuclear cell dominant). The CSF glucose level was 69 mg/dL. A cytological examination of the CSF showed no malignant cells. Bacterial, mycobacterial, and fungal cultures were negative. Computed tomography demonstrated right mastoiditis (Fig. 1a, arrow). T1-weighted gadolinium-enhanced magnetic resonance imaging (MRI) demonstrated thickening and the enhancement of the dura mater from the right middle cranial fossa to the base of the frontal lobe, extending to the right cavernous sinus (Fig. 1b, arrow). A paranasal mucosal biopsy showed no giant cells, granuloma formation, or fibrinoid degeneration.

A diagnosis of GPA was made according to Watts' algorithm (6). The patient's MPO-ANCA titer was elevated, and



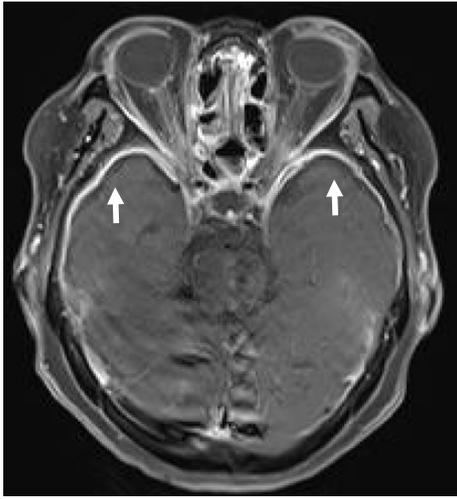
**Figure 2.** The clinical course of Case 1. Follow-up T1-weighted gadolinium-enhanced brain magnetic resonance imaging (①-④). mPSL: methylprednisolone, PSL: prednisolone, CY: cyclophosphamide, MTX: methotrexate, CRP: C-reactive protein (normal range <0.3 mg/dL), MPO-ANCA (normal range <20 EU).

the diagnostic surrogate marker for GPA, chronic mastoiditis, was present for at least 3 months. The patient's lungs and kidneys were unaffected by GPA, suggesting that the disease was limited to the upper airway. Furthermore, hypertrophic pachymeningitis caused cranial nerve II, III, IV, V1, and VI palsy via the induction of cavernous sinus disorder. The hypertrophic pachymeningitis might have been caused by infection, but her cerebrospinal fluid culture was negative. She was diagnosed with MPO-ANCA-positive hypertrophic pachymeningitis associated with the limited form of GPA. The clinical course of Case 1 is shown in Fig. 2. Treatment with methylprednisolone (500 mg, intravenous) was administered for 3 days, followed by PSL (40 mg/day, oral). However, the headache was not ameliorated, and steroid pulse therapy was repeated. Daily oral cyclophosphamide treatment was initiated at 50 mg/day and the dose was subsequently increased to 100 mg/day. Her clinical symptoms, including headache and cranial nerve palsy, improved and follow-up MRI demonstrated the slight improvement of her hypertrophic pachymeningitis (Fig. 2, MRI ②). After discharge from our hospital, during the tapering of the PSL dosage to 35 mg/day, she developed intermittent bloody nasal discharge and headache. A relapse of hypertrophic pachymeningitis was confirmed via MRI (Fig. 2, MRI ③),

and she was re-admitted to our hospital. Steroid pulse therapy was re-administered. MTX (6 mg/week) treatment was initiated, and cyclophosphamide was discontinued. The dose of MTX was increased to 10 mg/week 2 weeks later. Her clinical symptoms gradually subsided and her inflammatory indices started to improve 4 weeks after the administration of MTX. The patient was discharged from hospital in an improved condition and has been monitored on an outpatient basis. The dose of oral MTX was increased to 16 mg/week during the subsequent outpatient course. The patient's hypertrophic pachymeningitis was ameliorated (Fig. 2, MRI ④), and her CRP and MPO-ANCA levels returned to the normal ranges. The patient has remained well for 24 months, it was possible to reduce the dose of PSL to 5 mg/day. No adverse effects, including liver damage, cytopenia, or infection, were observed in association with the administration of MTX.

### Case 2

A 67-year-old woman presented with decreased bilateral visual acuity and hypacusia in March 2012. The visual acuity of her right eye was limited to the perception of light. MRI revealed optic neuritis, otitis media, and chronic sinusitis. Her MPO-ANCA titer was elevated (33 EU; normal



**Figure 3.** Gadolinium-enhanced T1-weighted magnetic resonance imaging of Case 2. The enhanced thickening of dura mater due to hypertrophic pachymeningitis is observed (arrows).

range: <20 EU), and she was suspected of having GPA. Oral PSL (15 mg/day) had been administered by her previous doctor. Although the weakening of the sight in her left eye and hypacusia recovered, the patient developed headache, and the decreased left visual acuity worsened when her dose of PSL was tapered to 5 mg/day. Her CRP level was elevated to 6.42 mg/dL. The dose of PSL was increased to 30 mg/day before admission. She was admitted to our department for treatment in April 2014.

On admission, her height was 148 cm and her body weight was 48.9 kg. The patient presented with severe headaches. Her vital signs were normal. Laboratory evaluations revealed leukocytosis (white blood cell count, 17,300/mm<sup>3</sup> with 92% neutrophils). Routine blood chemistry tests yielded normal results. Her CRP level was elevated (1.66 mg/dL). A urinalysis was negative for urinary protein, and no casts were observed in the urinary sediment. Routine kidney function tests yielded normal results. An immunological test revealed that the patient was negative for anti-nuclear antibodies. Her MPO-ANCA level was slightly elevated (1.8 U/mL; normal range <1.5 U/mL) on admission. The PR3-ANCA level was within the normal range. Hypertrophic pachymeningitis was demonstrated on T1-weighted gadolinium-enhanced MRI (Fig. 3, arrows). Other organs, including her lungs and kidneys, were not affected. Based on Watts's algorithm, she was diagnosed with the limited form of GPA because the diagnostic surrogate markers for chronic sinusitis, otitis media and retro-orbital inflammation were present (6). The clinical course of Case 2 is summarized in Fig. 4.

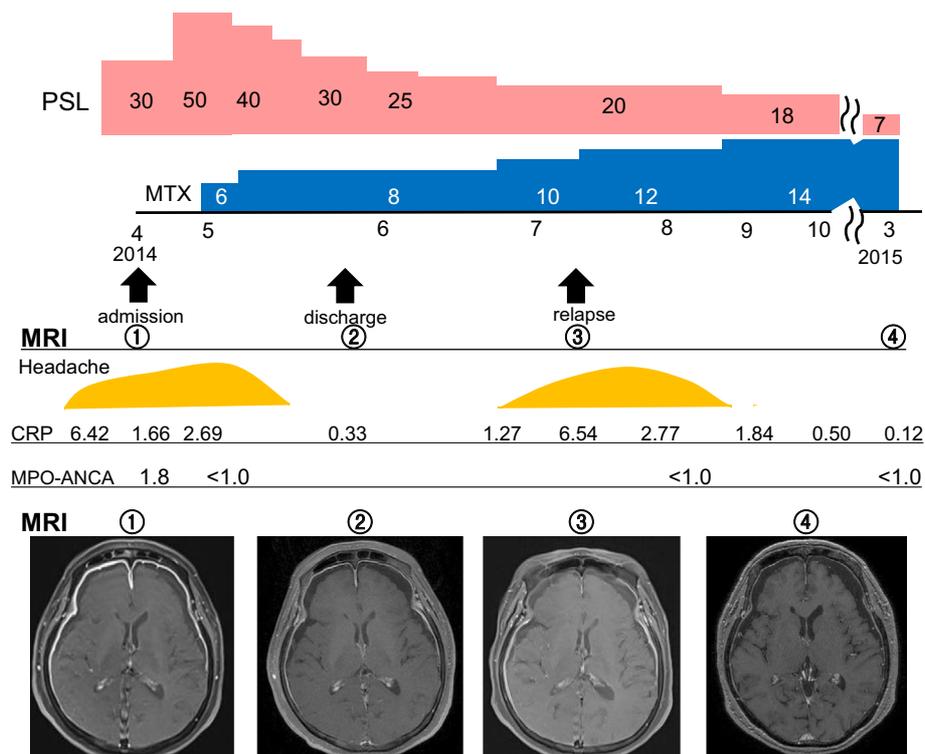
After admission, her PSL dose was increased from 30 mg to 50 mg; however, the effect on the hypertrophic pachymeningitis was transient. Treatment with MTX was initiated at 6 mg/week and then immediately increased to 8 mg/week. Her clinical symptoms started to show gradual improvement at 3 weeks after the initiation of MTX treatment. The thick-

ness of the dura mater was reduced, as shown in Fig. 4 (MRI ②). The patient was discharged from hospital in an improved condition. In the subsequent outpatient course, when the dose of PSL was reduced to 20 mg/day, her CRP level became slightly elevated (1.27 mg/dL) and the MTX dose was therefore increased to 10 mg/week. Although this transiently improved the patient's clinical symptoms, her headaches relapsed and her CRP level increased to 6.5 mg/dL. The exacerbation of hypertrophic pachymeningitis was confirmed via follow-up MRI (Fig. 4, MRI ③). The MTX dose was increased to 12 mg/week, and her clinical course gradually improved. The MTX dose was increased to a maximum of 14 mg/week, and the PSL dose was reduced to 7 mg/day. The patient's hypertrophic pachymeningitis was ameliorated (Fig. 4, MRI ④). No adverse symptoms due to MTX were observed.

## Discussion

Hypertrophic pachymeningitis is an extremely rare disease, characterized by the thickening of the dura mater, mostly around the brain or rarely, the spinal cord. It is caused by fibrosing inflammatory processes and presents as multiple cranial neuropathies and/or transverse myelopathy (1, 3). Hypertrophic pachymeningitis has been reported to occur in association with several underlying disorders, including autoimmune diseases, infections and malignancies (1). Recent reports on patients with MPO-ANCA-positive hypertrophic pachymeningitis indicated a relationship between hypertrophic pachymeningitis and the limited form of GPA (3, 7). Although PR3-ANCA has been shown to be highly specific and sensitive for diagnosing extensive GPA, its diagnostic sensitivity is lower when the disease is limited to the organs of the upper and lower airway (8). In Japan, approximately half of the patients with GPA are positive for MPO-ANCA (9). In Japanese patients with ANCA-positive hypertrophic pachymeningitis, it is likely that MPO-ANCA is dominant in regard to PR3-ANCA (3). In a previous study, 82% of MPO-ANCA-positive hypertrophic pachymeningitis patients were diagnosed with GPA according to Watts' algorithm (3). A high frequency of patients with lesions limited to the dura mater and upper airways was reported (3). The two patients of the present study developed MPO-ANCA-positive hypertrophic pachymeningitis, and the diagnosis of the limited form of GPA was made using Watts' algorithm, which is consistent with these previous findings. When patients develop hypertrophic pachymeningitis, GPA (especially the limited form) should be suspected, and tests should be performed to detect MPO and PR3-ANCA.

If left untreated, hypertrophic pachymeningitis frequently progresses, and although it is initially steroid-responsive, clinical manifestations frequently flare up after a reduction in the dose of steroids, necessitating the addition of immunosuppressive agents (1). One study reported that combination therapy with high-dose steroids and cyclophos-



**Figure 4.** The clinical course of Case 2. Follow-up T1-weighted gadolinium-enhanced brain magnetic resonance imaging (①-④). mPSL: methylprednisolone, PSL: prednisolone, CY: cyclophosphamide, MTX: methotrexate, CRP: C-reactive protein (normal range <0.3 mg/dL), MPO-ANCA (normal range <1.5 U/mL).

phamide was more effective than monotherapy with steroids alone for MPO-ANCA-positive hypertrophic pachymeningitis (3). The addition of cyclophosphamide to steroids significantly reduced the annual relapse rate in patients with MPO-ANCA-positive hypertrophic pachymeningitis (3). However, 9 of 36 and 2 of 36 patients treated with cyclophosphamide suffered from infection and malignancy, respectively (3). As MPO-ANCA-positive hypertrophic pachymeningitis predominantly occurs in elderly individuals, an alternative, less toxic, immunosuppressive agent should be considered (3). In the first of our cases, combination therapy with steroids and oral cyclophosphamide was not effective enough to improve the patient's hypertrophic pachymeningitis. Oral cyclophosphamide transiently improved the patient's clinical symptoms, but a relapse of headache and the elevation of the patient's CRP level occurred when the dose of PSL was tapered.

The effects of MTX on meningeal involvement associated with the limited form of GPA have been reported (10). In that study, one patient was treated with a monthly infusion of MTX (10 mg, intrathecal) and two patients were treated with oral MTX (15-20 mg, weekly). The treatment achieved a complete clinical response in all three patients. Accordingly, we attempted to initiate treatment with MTX and to discontinue cyclophosphamide in our first case. As shown in Fig. 2, MTX contributed to the disease remission. In both of the present cases, increasing the dose of MTX to a maximum of 14-16 mg per week helped to achieve the remission

of the disease and exhibited prominent steroid-sparing effects. In our second case, MTX was administered early, in combination with high-dose steroids. Once the disease flared up, increasing the dose of MTX ameliorated the disease course. Higher doses of MTX may also exert stronger therapeutic effects.

A previous clinical trial demonstrated the efficacy of MTX and cyclophosphamide were clinically equivalent with regard to the remission rates in patients with early ANCA-associated vasculitis and without a life threatening manifestations (11). In contrast, MTX was less effective for achieving remission in patients with extensive GPA and was associated with a high rate of relapse in comparison to cyclophosphamide (4). According to guidelines of The British Society for Rheumatology and British Health Professionals in Rheumatology, a combination of intravenous cyclophosphamide or rituximab and high-dose steroids should be used for treating GPA patients with organ-threatening diseases (12). The involvement of the central nervous system in patients with GPA is rare (2-8%), and the dysfunction of one or several cranial nerves is usually involved (4, 10). Table summarizes 10 previous case reports (including the two present cases) on hypertrophic pachymeningitis and cranial nerve palsy associated with GPA (7, 13-18). Intravenous cyclophosphamide and rituximab were administered in 5 cases because the disease was refractory. Rituximab improved hypertrophic pachymeningitis and cranial nerve palsy in all cases. These 5 cases were all PR3-ANCA-positive and the

**Table. Reported Case Reports of Hypertrophic Pachymeningitis and Cranial Nerve Palsy Associated with GPA.**

Reference	Age/Gender	Affected organ	ANCA	Immunosuppressants
7	60/M	U, L	MPO-ANCA	CY
13	60/F	U	MPO-ANCA	CY
14				
case 1	15/F	U,L	PR3-ANCA	IVCY, MTX, RTX
case 2	35/F	U	PR3-ANCA	IVCY, MTX, RTX
15	36/F	U,K	PR3-ANCA	IVCY, RTX
16	22/F	U,L	PR3-ANCA	MTX, IVCY, RTX
17	27/F	U,L	PR3-ANCA	IVCY, AZA,MTX, RTX
18	50/M	U	PR3-ANCA	IVCY
Current cases				
case 1	56/F	U	MPO-ANCA	CY, MTX
case 2	67/F	U	MPO-ANCA	MTX

U: upper airway, L: lower airway, K: kidneys, AZA: azathioprine, CY: cyclophosphamide  
 MTX: methotrexate, IVCY: intravenous cyclophosphamide, RTX: rituximab

lungs or kidneys were involved in 4 cases. Oral immunosuppressive agents, including cyclophosphamide and MTX effectively improved the disease in 4 cases. These cases were all MPO-ANCA-positive, and the disease was limited to the upper airway in 3 out of 4 cases. The use of intravenous cyclophosphamide and rituximab should be considered if the patient is positive for PR3-ANCA and the lower respiratory system or kidneys are involved. MPO-ANCA-positive hypertrophic pachymeningitis is predominantly associated with GPA in elderly individuals in Japan (3). MTX may be an alternative therapy for MPO-ANCA-positive hypertrophic pachymeningitis and cranial nerve palsy associated with GPA that is limited to the upper airway because of its lower toxicity in comparison to cyclophosphamide.

MTX is widely used for treating patients with RA, and rheumatologists are familiar with the management of its side effects. In comparison to Western countries, the doses of MTX that are initially prescribed to RA patients in Japan are low (6-8 mg/week). To reduce toxicity, we initiated MTX treatment with a lower dose and increased the dose after considering the patient's disease activity. During the clinical course of the present two cases, no adverse effects of MTX (including infection, liver dysfunction, and cytopenia) were observed. The results of histopathological analyses show Th1-predominant granulomatous lesions in patients with ANCA-positive hypertrophic pachymeningitis (3). MTX may have a therapeutic effect on hypertrophic pachymeningitis by inhibiting the activation of T cells (19).

In conclusion, we therefore propose that prompt therapy with steroids and a higher dose of MTX might control disease activity and yield a good prognosis in cases of MPO-ANCA-positive hypertrophic pachymeningitis complicated with the limited form of GPA.

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

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