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Hypertrophic Pachymeningitis Development in Eosinophilic Granulomatosis with Polyangiitis at Relapse of Disease: A Case-Based Review

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Hypertrophic pachymeningitis (HP) presents with thickening of the dura mater in the cerebrum and spine, and its symptoms vary depending on the affected location. The association of HP with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis has been recognized, and most cases are complicated by granulomatosis with polyangiitis. We report the case of a 47-year-old man who presented with HP upon relapse of eosinophilic granulomatosis with polyangiitis (EGPA), with literature review. He presented with disturbance of consciousness, and magnetic resonance imaging (MRI) revealed thickening of the dura mater around the left parietal lobe. Although myeloperoxidase (MPO)-ANCA was positive on EGPA diagnosis, the elevation of MPO-ANCA was not documented at the onset of HP. Brain perfusion scintigraphy showed an increase in blood flow in the left parietal lobe and temporal lobe, and electroencephalogram (EEG) revealed slow waves in the left parietal lobe. He was treated with a high dose of corticosteroid and rituximab, and the slow waves on EEG and brain perfusion were normalized. Although the most frequent symptom of HP is headache, disturbance of consciousness can be the manifestation of HP, and inflammation of HP could affect the cerebral parenchyma, which can be documented as abnormal EEG and perfusion scintigraphy. Literature review revealed that most of the HP in EGPA developed when EGPA relapsed, and was observed in patients with MPO-ANCA positivity. HP develops without evidence of other clinical features of EGPA; therefore, adequate imaging, including contrast-enhanced MRI, is necessary. Rituximab may be effective for treating HP complicated with EGPA.

Keywords: cerebral parenchyma; eosinophilic granulomatosis with polyangiitis; hypertrophic pachymeningitis; MPO-ANCA; Relapse
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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic vasculitis that affects small-to medium-sized vessels and is categorized into three types: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). EGPA, which is the least common AAV, presents with necrotizing granulomatous inflammation and vasculitis with eosinophils and is usually preceded by asthma (Furuta et al. 2019). Two mechanisms are considered for the pathogenesis of EGPA: eosinophilic inflammation through the IL-5 pathway and vasculitis due to neutrophils activated by myeloperoxidase (MPO)-ANCA. However, the details of the association between MPO-ANCA and eosinophilic inflammation remain to be clarified (Furuta et al. 2019).

The most common organ affected by EGPA is the nervous system. Peripheral neuropathy accounts for 51% of disorders in EGPA, whereas central nervous system (CNS) involvement and cranial nerve disorder account for no more than 5% and 3% cases, respectively (Comarmond et al. 2013). Ischemic stroke and hemorrhagic stroke are the major CNS disorders associated with EGPA (Comarmond

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et al. 2013; André et al. 2017).

Hypertrophic pachymeningitis (HP) is a rare disease that results in focal or diffuse thickening of the cerebrum and spinal dura mater. HP presents with various symptoms such as headache, ophthalmological symptoms, and cranial nerve disorder depending on the location of thickening (Yonekawa et al. 2014). HP is classified as idiopathic or secondary. Secondary HP is induced by infections, neoplasms, and autoimmune diseases, such as rheumatoid arthritis, sarcoidosis, and IgG4-related disease (Yokoseki et al. 2014). Recently, the association between HP and AAVs has been recognized, and several studies have reported HP complicated with GPA. However, the complications of EGPA and HP are not well documented. Although the underlying mechanisms of AAV-related HP remain to be elucidated, it is suggested that inflammatory mediators in the middle ear spread to the dura mater through venous return in GPA-related HP (Yokoseki et al. 2014; Sakairi et al. 2019). Herein, we report a rare case of EGPA complicated with HP presenting with consciousness disorder and provide literature review regarding the association between EGPA and HP.

Case Presentation

A 47-year-old Japanese man was admitted to our rheumatology department with transient disturbance of consciousness. Two years before the latest admission, he experienced a fever of 39°C and sore throat. One week later, he experienced numbness and pain in his hands and feet, and it became difficult to walk. Impaired vision in his right eye developed and he was admitted to our hospital (first admission). Laboratory findings were as follows: eosinophils, 7050/μL; MPO-ANCA, 181 U/mL (normal < 3.5); and C-reactive protein (CRP), 14 mg/dL (Table 1). Although he had not been diagnosed with asthma before, pulmonary function tests revealed obstructive disorder, and the level of fractional exhaled nitric oxide was elevated, indicating the presence of subclinical asthma. A nerve conduction study showed a reduction in amplitude and normal conduction velocities, indicating that his sensory abnormality in the extremities was attributed to mononeuritis multiplex. Magnetic resonance imaging (MRI) revealed sinusitis in the frontal and sphenoid sinuses. These findings met the classification criteria of the American College of Rheumatology, and he was diagnosed with EGPA.

The patient was treated with 1,000 mg of intravenous methylprednisolone, followed by 60 mg/day of prednisolone and intravenous cyclophosphamide pulse (IVCY) (500 mg/body). As a result, the inflammatory markers and MPO-ANCA titers were normalized, and an improvement in muscle strength was observed. He was discharged from the hospital 21 months prior to the latest admission. IVCY was performed six times, and was followed by 75 mg/day of azathioprine. Prednisolone was gradually tapered to 9 mg/day at less than 1 mg per month. However, he experienced headache and felt pain in the back of eyes one month prior to the second admission. The CRP levels were elevated to 8.27 mg/dL six days before admission, and antibiotics were not effective. A fever of 37.4°C and difficulty in speaking were documented in the evening, and he repeated the same words and lost his ability to communicate with his family. Moreover, gait disturbance due to mild muscle weakness in right leg was observed, and the patient visited the emergency department and was admitted.

Physical examination results were as follows: blood pressure, 171/118 mmHg; pulse, 125 beats/min; body temperature, 38°C; and 98% oxygen saturation on room air. The neurological examination revealed mild difficulty in word recall, and slight right hemiparesis with hyperreflexia. Laboratory findings revealed normal eosinophil and MPO-ANCA levels (Table 1). Protein levels were slightly elevated in the cerebrospinal fluid (CSF) (Table 1), and IgG index was 1.33. Gadolinium-enhanced MRI showed a thickened dura mater around the left convexity, falx cerebri, and parietal lobe, and perfusion scintigraphy showed an increase in the bloodstream in the left parietal lobe and temporal lobe (Fig. 1A, B). Electroencephalography (EEG) revealed a slow wave in the left parietal lobe (Fig. 1C). Based on these findings, he was diagnosed with HP due to a relapse of EGPA. His symptoms of difficulty in word recalling improved within a few days after treatment with high-dose prednisolone (70 mg/day) and rituximab. Gadolinium-enhanced MRI showed improvement of the thickened dura mater (Fig. 2A). In perfusion scintigraphy, the difference in the bloodstream between the right and left brains disappeared (Fig. 2B). The slow wave in the left parietal lobe disappeared one month after initiation of treatment (Fig. 2C).

Written informed consent for the publication of this case report was obtained from the patient. This study was approved by the ethics committee of the Tohoku University Graduate School of Medicine.

Discussion

The association of AAV has been recognized in HP, and most cases are complicated by GPA. CNS manifestations occur in 2-13% of patients with GPA (Fragoulis et al. 2018), and De Luna et al. (2015) reported that 20 out of 35 patients with GPA involving the CNS were diagnosed with HP. However, little is known about the association between EGPA and HP. To analyze recently increasing data regarding the association between HP and EGPA, we searched the PubMed and Scopus databases from March 2000 until September 2021 using the following keywords: “hypertrophic pachymeningitis,” “pachymeningitis,” “eosinophilic granulomatosis with polyangiitis,” “Churg-strauss syndrome” and “central nervous system.” We also searched the Japanese literature database, Ichushi-Web, using the following keywords, “hypertrophic pachymeningitis” and “eosinophilic granulomatosis with polyangiitis.”

The English literature describing EGPA complicated with HP is scarce, with eleven patients in four retrospective

Table 1. Laboratory findings at the onset of eosinophilic granulomatosis with polyangiitis (EGPA) and hypertrophic pachymeningitis (HP), respectively.

Onset Date	EGPA July/X-2	HP June/X
White blood cells (/μL)	16,800	8,800
Hemoglobin (g/dL)	13.1	13.3
Platelets (/μL)	358,000	298,000
Neutrophil (%)	46.8	86.1
Lymphocytes (%)	8.3	8.8
Monocytes (%)	2.6	4.8
Eosinophil (%)	41.9	0
Basophil (%)	0.4	0.3
Total protein (g/dL)	6.3	6
Albumin (g/dL)	2.6	3.5
Total bilirubin (mg/dL)	0.7	1.3
Aspartate aminotransferase (U/L)	23	19
Alanine aminotransferase (U/L)	24	19
Lactate dehydrogenase (U/L)	238	181
Alkaline phosphatase (U/L)	Unknown	70
y-Glutamyl transpeptidase (U/L)	119	71
Blood urea nitrogen (mg/dL)	11	11
Creatinine (mg/dL)	0.68	0.84
Creatine phosphokinase (U/L)	89	43
Glucose (mg/dL)	131	173
Sodium (mmol/L)	139	138
Potassium (mmol/L)	3.6	3.4
Chloride (mmol/L)	101	103
C-reactive protein (mg/dL)	14	12.55
Serum immunoglobulin G4 (mg/dL)	157	52
MPO-ANCA (U/mL)	181	1
Urinalysis		
Protein	(±)	(−)
Glucose	(4+)	(−)
Occult blood	(−)	(−)
Cerebrospinal Fluid		
Cell Count (/mL)	0	0
Protein (mg/dL)	40	88
Glucose (mg/dL)	69	82
Adenosine deaminase (U/L)	Unknown	< 2.0
Soluble interleukin-2 receptor (U/mL)	Unknown	134

X-2, two years before the year X; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody.

studies and four case reports. We excluded 2 articles because of inadequate information (André et al. 2017; Liu et al. 2021). In addition, we found 10 articles in the Japanese literature, and have summarized the 18 patients in Table 2 (Lio et al. 2001; Maki et al. 2001; Kanesaka et al. 2005; Ito 2012; Furuya et al. 2015; Iizuka et al. 2015; Shibata et al. 2018; Toda et al. 2018; Aoyama et al. 2019; Matsuura et al. 2019; Nakano et al. 2019; Sakairi et al. 2019; Kobayashi et al. 2020; Kurihara et al. 2020; Shiraishi et al. 2021; Izuka et al. 2022).

Among the 16 patients available, nine were men and seven were women. The age at the onset of HP ranged from 40 to 78 years (mean 58 years; median 56 years). Four of 17 patients (24%) presented with thickening of the

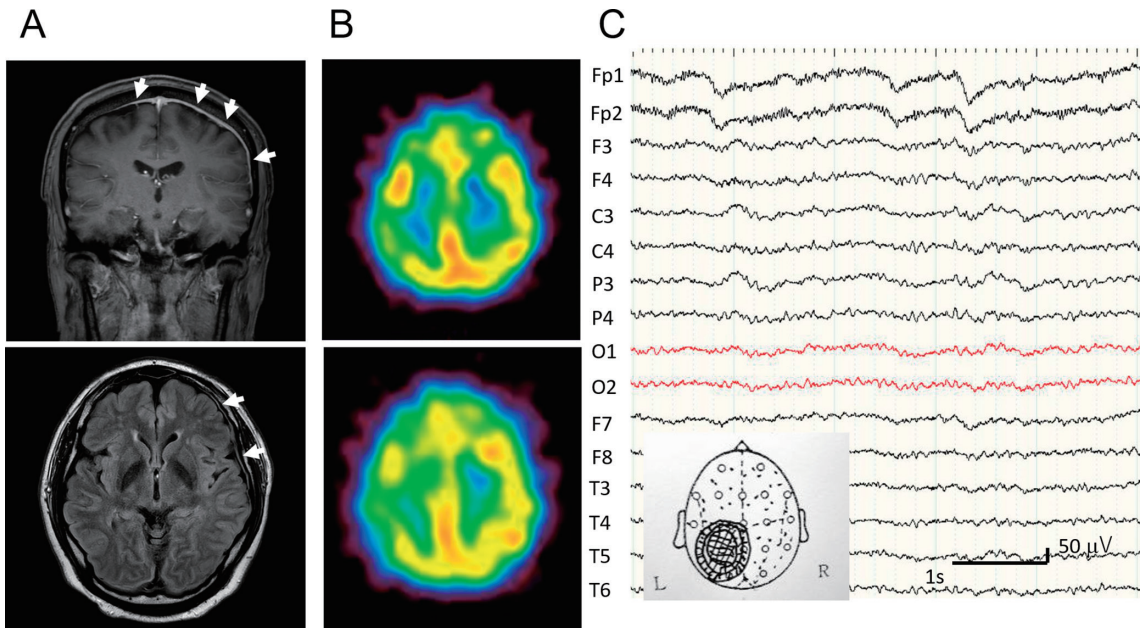

Fig. 1. Clinical images at the onset of hypertrophic pachymeningitis.
A. Magnetic resonance imaging (MRI) findings with gadolinium-enhanced T1 (upper) and FLAIR (lower). White arrows indicate the thickened dura mater. B. Brain perfusion scintigraphy. C. Electroencephalogram. The internal illustration shows the location of the slow waves.

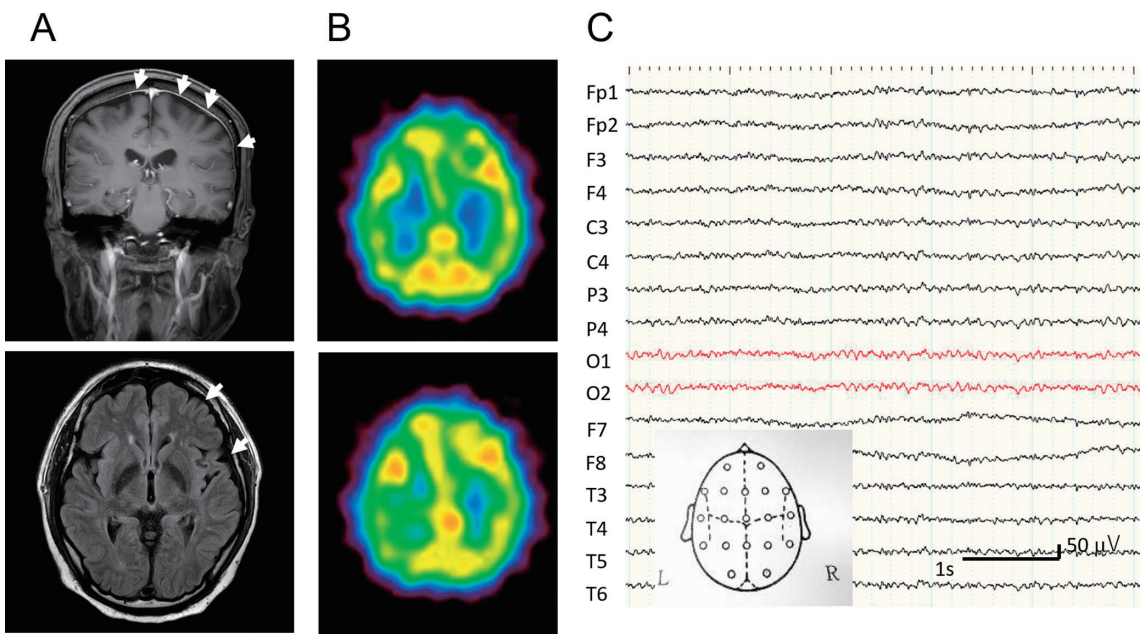

Fig. 2. Clinical images one month after the onset of hypertrophic pachymeningitis.
A. Magnetic resonance imaging (MRI) findings with gadolinium-enhanced T1 (upper) and FLAIR (lower). White arrows indicate improvement of the thickened dura mater. B. Brain perfusion scintigraphy. C. Electroencephalogram. The internal illustration shows the disappearance of the slow waves.

spinal dura mater. Shimojima et al. (2017) reported that among seven patients with GPA complicated with HP, none presented with spinal cord lesions. The French Vasculitis Study Group reported that 4 (20%) of 20 patients with GPA complicated with HP presented with spinal cord lesions (De Luna et al. 2015). Although reporting bias must be considered, these findings suggest that thickening of the spinal dura mater may occur more frequently in EGPA than in GPA.

Information about clinical manifestations was available in 17 patients, and the most common symptom was headache (11 patients, 65%). Importantly, 16 of 17 patients (94%) whose initial symptoms were available were diagnosed with HP when EGPA relapsed. This is in contrast to

Table 2. Clinical characteristics of EGPA complicated with HP.

Case	Age (years)	Sex	ANCA	Initial eosinophil count (/μL)	Location of HP	Elevation of ANCA at HP onset	Symptoms at HP onset	Timing of HP	Initial treatment	Treatment for HP	Reference
1	47	M	MPO	7050	Intracranial	-	Consciousness disturbance	Relapse	IVMP, IVCY, AZA	PSL, RTX	Present case
2	40	F	MPO	N/A	Intracranial	-	Hoarseness, dysphagia, double vision, dysgeusia	Relapse	mPSL, PSL, IVIG, AZA, IVCY, Tac	PSL, RTX	Kobayashi et al. 2020
3	42	M	-	N/A	Intracranial	-	Headache	Relapse	N/A	PSL, IVCY	Nakano et al. 2019
4	47	F	N/A	9450	Intracranial	-	Headache, facial pain and paralysis, hearing loss	Relapse	PSL	PSL, CPA, AZA	Lio et al. 2001
5	48	M	MPO	N/A	N/A	N/A	Cranial neuropathy	N/A	N/A	Corticosteroid, mizoribine	Sakairi et al. 2019
6	55	M	MPO	N/A	Intracranial	-	Headache, double vision	Relapse	mPSL, PSL, AZA, CyA, IVIG	PSL, mPSL, RTX, IVCY, CyA	Kobayashi et al. 2020
7	73	F	MPO	9600	Intracranial	-	Fever, headache, blurred vision of left eye	Relapse	IVMP, IVIG, IVCY, AZA	IVMP, PSL, mepolizumab	Izuka et al. 2022
8	78	M	-	1360	Intracranial	-	Headache, diplopia	Onset	PSL	-	Shiraishi et al. 2021
9	40	F	MPO	N/A	Intracranial	-	Headache, fever, dysgeusia, abducens nerve disorder	Relapse	IVMP, IVIG, BMZ, AZA, IVCY, TAC	BMZ, RTX	Furuya et al. 2015
10	47	F	N/A	N/A	Cervical spine	N/A	Paralysis, neck pain, bladder and rectal disturbance	Relapse	N/A	Laminectomy, cervical discectomy, IVMP, immunosuppressants	Ito 2012
11	57	M	MPO	N/A	Intracranial and spinal	N/A	Headache, paralysis, paresthesia, bladder and rectal disturbance	Relapse	N/A	CPA, RTX, IVMP, PSL, mepolizumab	Kurihara et al. 2020
12	65	F	N/A	N/A	Intracranial	N/A	Headache, nausea, fever, cranial nerve paralysis	Relapse	Corticosteroid	IVMP, corticosteroid	Kanesaka et al. 2005
13	70	F	MPO	8588	Intracranial	N/A	Headache, orbital apex syndrome	Relapse	PSL, steroid pulse	IVMP	Toda et al. 2018
14	74	M	N/A	N/A	Spinal	N/A	Chest and back pain, difficult to work, hypesthesia below Th6	Relapse	Corticosteroid, IVIG	Laminectomy, IVMP, CPA	Aoyama et al. 2019
15	75	M	N/A	N/A	Intracranial	N/A	Headache, reduced vision	Relapse	Corticosteroid, IVCY, IVIG, AZA	Corticosteroid, IVCY	Iizuka et al. 2015
16	76	M	MPO	14900	Spinal	N/A	Chest and back pain, hypesthesia, paraparesis	Relapse	Corticosteroid, IVIG	Corpectomy, IVMP, IVCY	Matsuura et al. 2019
17	N/A	N/A	MPO	N/A	Intracranial	-	N/A	Relapse	N/A	N/A	Maki et al. 2001
18	N/A	N/A	MPO	18000	Intracranial	N/A	Headache, reduced vision, ocular motility disorder, facial palsy	Relapse	PSL	IVMP, IVIG	Shibata et al. 2018

AZA, azathioprine; BMZ, Betamethasone; CPA, cyclophosphamide; CyA, cyclosporine; IVCY, intravenous cyclophosphamide; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MPO, myeloperoxidase; mPSL, methylprednisolone; N/A, not available; PSL, prednisolone; RTX, rituximab; TAC, tacrolimus.

the report of GPA, which revealed that 60% of patients with GPA complicated with HP were diagnosed with HP upon the onset of GPA (Holle and Gross 2011).

Although the positivity of MPO-ANCA in EGPA has been reported to be approximately half (Saku et al. 2018), 11 of 13 patients (85%) coexisting with EGPA and HP were positive for MPO-ANCA. Therefore, the relative risk of MPO-ANCA positivity for complicating HP was 6.2 in EGPA. ANCA-positive patients with EGPA are more likely to present with symptoms of vasculitis, such as neuropathy and glomerulonephritis. Moreover, an association between ANCA positivity and relapse is indicated in EGPA (Marvisi et al. 2019). In our analysis, 16 of 17 patients were diagnosed with HP at EGPA relapse, and 85% showed ANCA positivity. Taken together, relapse in EGPA with MPO-ANCA positivity results in a higher risk for HP. The ratio of MPO-ANCA to PR3-ANCA in ANCA-associated HP was 0.81 to 4.25 (Yokoseki et al. 2014; Yonekawa et al. 2014; Choi et al. 2017; Shimojima et al. 2017; Sakairi et al. 2019; Xiao et al. 2020), and MPO-ANCA positivity was relatively predominant. One of the reasons for this is that most of these reports were from Asian countries. Regarding laboratory findings at the onset of HP, the levels of MPO-ANCA upon the onset of HP were within the normal range in all patients whose information was available. Therefore, the change in the titers of MPO-ANCA seemed not to be a useful marker for evaluating disease relapse, especially in EGPA with HP.

Our patient developed thickening of the dura mater around the left convexity, falx cerebri, and parietal lobe. Following the cranial fossa, convexity is the second most common lesion with thickening of the HP (Yokoseki et al. 2014). Consciousness disturbance, which accounts for 13.2% of the symptoms of HP (Yonekawa et al. 2014), was observed in our patient. EEG showed a slow wave in the left parietal lobe, and perfusion scintigraphy showed an increase in blood flow in the left parietal lobe and temporal lobe. These findings indicated that the cerebral parenchyma adjacent to the thickened dura mater was affected. Recently, Shiraishi et al. (2021) reported the dura mater biopsy of HP complicated with EGPA although the eosinophil count of their patient was mild and did not exceed 1,500/μL (Shiraishi et al. 2021, Table 2). It showed inflammatory cell infiltration, but there did not exist eosinophil

infiltration, granuloma, nor vasculitis. On the other hand, MPO-ANCA-positive GPA patient showed granulomatous inflammation and $CD20^+$ B cell clusters with $CD21^+$ $CD35^+$ follicular dendritic cells in the thickened dura mater (Yokoseki et al. 2014). Yokoseki et al. (2014) suggested that ectopic lymphoid neogenesis in granulomatous lesions of the dura mater is important for immune responses in these situations. However, MRI revealed no abnormalities, except for ischemic changes. Moreover, although it was considered that the inflammation spread from the dura mater to the cerebral parenchyma, CSF showed only a slight elevation in protein levels. Ito et al. (2010) reported a patient with catatonia induced by idiopathic HP, and MRI did not reveal abnormalities in the parenchyma. In contrast, EEG showed continuous delta waves mixed with theta waves. These changes disappeared after corticosteroid treatment (Ito et al. 2010). Slow waves such as delta and theta waves occur when postictal state as well as brain function decreases, although the association between slow waves and blood flow is poorly understood. Together with our case, inflammation of HP affects cerebral parenchyma, increasing blood flow, and suppressing activity of the cerebral cortex, as shown by EEG.

Detailed treatment information was available for 13 patients with HP and EGPA. As the initial therapy, corticosteroid monotherapy was administered to five patients, and five patients were treated with IVCY; intravenous immunoglobulin and other immunosuppressants were used in other cases. After the onset of HP, two patients were treated with corticosteroid monotherapy. Four patients were treated with IVCY and five patients received rituximab treatment. Three patients who presented with thickening of the spinal dura mater underwent surgery. Two patients were treated with mepolizumab. Mepolizumab, an anti-interleukin-5 monoclonal antibody, significantly maintained remission in relapsed EGPA patients (Wechsler et al. 2017). However, few studies have reported the efficacy of mepolizumab for treating EGPA complicated with HP. Considering the absence of eosinophilic inflammation in HP complicated with EGPA, other intervention would be appropriate. Rituximab, an anti-CD20 chimeric monoclonal antibody, is effective in case of refractory EGPA (Thiel et al. 2017; Mutoh et al. 2021) and ANCA-associated HP (Kobayashi et al. 2020).

In conclusion, although HP is usually complicated in GPA, its occurrence in EGPA is also possible. Importantly, most of the HP in EGPA is observed upon relapse of the disease and is observed in patients with MPO-ANCA positivity. Sometimes, inflammation of HP affects the cerebral parenchyma, causing changes in blood flow and brain waves. HP can develop without evidence of other clinical features of EGPA; therefore, adequate imaging, including contrast-enhanced MRI, is necessary. Rituximab may be an effective treatment for HP associated with EGPA.

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Author Contributions

K.M. reviewed the literature and wrote the manuscript; S.N. assessed neurological findings and wrote the manuscript; H.S., H.F., T.I., and H.H. were involved in the clinical management; T.S. provided patient management, wrote the manuscript, and supervised the entire process.

Conflict of Interest

The authors declare no conflict of interest.

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