
Efficacy of rituximab for anti-neutrophil cytoplasmic antibody-associated hypertrophic pachymeningitis: a case series

K. Kobayashi^{1,2}, D. Nakagomi^{1,2}, S. Furuta³, Y. Kobayashi^{1,2}, S. Hanai^{1,2}, M. Yamagata⁵, H. Kawashima⁴, T. Kasuya³, H. Furuya^{3,4}, M. Hiraguri⁴, T. Sugiyama⁵, H. Nakajima³

¹Third Department of Internal Medicine, University of Yamanashi;

²Centre for Clinical Immunology and Rheumatology, University of Yamanashi Hospital;

³Department of Allergy and Clinical Immunology, Chiba University Hospital;

⁴Centre for Allergy and Clinical Immunology, Japanese Red Cross Narita Hospital, Chiba;

⁵Department of Rheumatology, National Hospital Organization Shimoshizu National Hospital, Chiba, Japan.

Kei Kobayashi, MD

Daiki Nakagomi, MD, PhD

Shunsuke Furuta, MD, PhD

Yoshiaki Kobayashi, MD

Shunichiro Hanai, MD

Mieko Yamagata, MD, PhD

Hirotohi Kawashima, MD, PhD

Tadamichi Kasuya, MD

Hiroki Furuya, MD

Masaki Hiraguri, MD

Takao Sugiyama, MD, PhD

Hiroshi Nakajima, MD, PhD

Please address correspondence to:

Daiki Nakagomi,

Department of Third Internal Medicine,

University of Yamanashi,

1110 Shimokato,

4093898 Chuo, Yamanashi, Japan.

E-mail: dnakagomi@hotmail.co.jp

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ABSTRACT

Objective. This study researched the efficacy of rituximab (RTX) in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated hypertrophic pachymeningitis (HP).

Methods. Eight patients were identified by retrospective chart review from local registries at four hospitals in Japan. All patients met the Chapel Hill 2012 Consensus Conference definitions of ANCA-associated vasculitis and had disease complicated with HP. We assessed the dose of glucocorticoids, C-reactive protein (CRP) levels, Birmingham vasculitis activity score (BVAS) and contrast-enhanced magnetic resonance imaging (MRI) findings of HP before and after RTX administration.

Results. Three of eight patients were female. The median age was 68 years. No patients had HP at onset of vasculitis. Two patients had a relapse of HP before RTX administration. RTX was used as the initial treatment for HP in three patients. The daily dose of glucocorticoids, CRP levels and BVAS decreased from baseline to 6 months after RTX treatment in all patients. Evaluation of HP by contrast-enhanced MRI showed improvement in seven of eight cases. All of seven patients achieved sustained remission at 6 months after RTX treatment. No serious adverse events were observed in any patient.

Conclusion. Our case series highlights the efficacy of RTX in patients with difficult-to-treat ANCA-associated HP. Future prospective studies are warranted to establish B-cell depletion therapy by RTX as a treatment option for ANCA-associated HP.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are systemic inflammatory disease in which inflammation primarily

affects small vessels. There are three main forms of AAVs: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA) (1). AAVs can cause lesions in multiple organ systems. In particular, major organ damage can be fatal. Neurological lesions in AAVs often present peripheral sensory neuropathy. In severe cases, movement disorders can also occur. Although lesions affecting the central nervous system including the brain and spinal cord are rare, cerebral haemorrhage or infarction can cause irreversible damage (2).

Hypertrophic pachymeningitis (HP) is a rare disease characterised by chronic inflammation and thickening of the cerebral or spinal dura mater. Thickening and inflammation of the dura mater in HP causes severe headache, dizziness, and various neurologic symptoms if any of the cranial nerves are involved (3). Contrast-enhanced magnetic resonance imaging (MRI) is useful for diagnosis of HP (4). However, owing to the rarity of the disease, diagnosis of HP is often difficult. This may result in a delayed treatment. The aetiology of HP can be idiopathic; infectious, including tuberculosis; drug-induced; or secondary to autoimmune diseases (3). Although rare, HP has recently been reported as a complication of AAVs (4).

Glucocorticoids are recommended as first-line treatment for HP. There are no established second-line treatments for idiopathic HP, but second-line treatment with intravenous cyclophosphamide therapy (IVCY), azathioprine (AZA), and plasma exchange for ANCA-associated HP have been reported (5). Recently, the clinical trials have demonstrated the efficacy of rituximab (RTX) for AAVs (6-8). However, there are still few reports regarding treatment of ANCA-associated HP with RTX (4, 9).

In this study, we report a case series of

eight patients with refractory ANCA-associated HP who were treated with RTX.

Methods

Patients

We conducted a retrospective study of patients who were diagnosed with ANCA-associated HP and were treated with RTX between September 2013 and August 2018. Data were taken from medical records of four Japanese centres. All patients met the Chapel Hill 2012 Consensus Conference definitions of ANCA-associated vasculitis (1). HP was diagnosed by contrast-enhanced MRI and the presence of typical symptoms including headache or cranial nerve disorders. ANCA-associated HP were defined as AAVs patients co-occurred with HP (10).

Assessment

Patient's characteristics included age, sex, diagnosis, ANCA status including myeloperoxidase/proteinase 3 (MPO/PR3)-ANCA, CRP levels, Birmingham vasculitis activity score (BVAS) and organ involvement. In addition, time from AAVs onset to HP onset, time from HP onset to RTX treatment, and the number of relapses including HP or other AAVs lesions before RTX treatment were evaluated. Remission was defined as the absence of any disease activity related to active vasculitis regardless of treatment intensity. Relapse was defined as recurrence of vasculitis requiring treatment change. Refractory HP was defined as resistant to moderate-to-high dose glucocorticoids and any immunosuppressants since AAVs onset. HP symptoms before RTX treatment, treatment history, and areas of dura mater thickening from contrast-enhanced MRI were also surveyed. Symptom improvement, dura mater thickening on contrast-enhanced MRI, ANCA titre, CRP levels, BVAS, dose of glucocorticoids, and immunosuppressant types were evaluated before and 6 months after the RTX treatment. The glucocorticoid dose was converted to the equivalent prednisolone dose.

Statistical analysis

Statistical analysis was performed using

SPSS software, version 22.0J (IBM Japan). Normally distributed continuous data were summarised with means, and non-normally distributed data were summarised with medians. CRP levels, BVAS and dose of glucocorticoids were compared by Wilcoxon test. *p*-values less than 0.05 were considered significant.

Ethics

The ethics committee of University of Yamanashi Hospital approved this study (reference no.: 2071). Informed consent was not obtained from patients because it was not required by local regulations for a retrospective, observational study.

Results

Clinical characteristics of patients at diagnosis of AAVs were shown in Table I. Eight patients who were diagnosed with ANCA-associated HP and treated with RTX were identified. The median age of patients was 68 years. The classification of AAVs at diagnosis was 2 MPA, 4 GPA, and 2 EGPA. At diagnosis of AAVs, PR3-ANCA were positive only in patient no. 6, with seven patients positive for MPO-ANCA. At the time of diagnosis seven out of eight patients presented ear, nose, and throat (ENT) involvement, five out of eight showed lung and peripheral neurological involvement. None of the patients exhibited heart or kidney lesions. HP was not the initial symptom in any patient.

Characteristics at HP onset before RTX are shown in Table II. The time from AAVs onset to HP onset varied widely from 3 to 36 months (median, 8). Two patients experienced HP relapses before RTX treatment. Six patients had severe headache as the HP symptom. Patients also exhibited cranial nerve symptoms, such as hearing loss, dysarthria, dysphagia, and reduced vision. In particular, five patients had eye symptoms. Three patients had dysphagia which were caused by impairment of the glossopharyngeal nerve. Dura mater thickening was observed in various regions. Four patients exhibited elevated ANCA titres at HP onset, with four ANCA-negative patients, although all

patients were ANCA-positive at diagnosis of AAVs. All patients had elevated CRP levels at HP onset (median, 61.5 mg/L). Before RTX treatment, the immunosuppressants were used for vasculitis, especially IVCY and AZA in five patients. Glucocorticoid doses were moderate-to-high before RTX treatment (median, 35 mg/day). Five out of eight patients presented no disease flares before HP onset. HP was a manifestation of the first disease flare. Patient no. 6 and no. 7 had other manifestations at HP onset.

Table III shows changes in symptoms, laboratory values, images, and treatments before RTX administration and after 6 months. Seven patients received RTX 375 mg/m²/week × 4; while one patient (no. 3) received a single dose of 1 g. RTX was administered without immunosuppressants in seven patients. Symptoms related to active HP improved in all patients, although a few symptoms due to irreversible damage remained in some patients. Dura mater thickening evaluated by contrast-enhanced MRI improved in seven patients, while no change was seen in patient no. 2 (Supplementary Fig. S1). Although four patients exhibited elevated ANCA titres before RTX treatment, the titres decreased or turned negative in all patients 6 months after treatment initiation. All patients exhibited normalisation of CRP levels, decrease of BVAS and glucocorticoid doses before RTX treatment (median, 61.5 to 2.0 mg/L, 3.5 to 0, 35 mg/day to 13 mg/day, respectively *p*<0.05) (Suppl. Fig. S2). No serious adverse events such as infections requiring hospitalisation were observed.

Discussion

This is the first case series showing the efficacy of RTX treatment in patients with ANCA-associated HP.

In our case series, MPO-ANCA was positive in seven out of eight patients. In Japan, MPO-positive GPA is frequently seen since Japanese AAVs patients extremely biased to MPO-ANCA positivity (4, 10). Headache was a common symptom, while other symptoms varied depending on the site of dura mater lesions. Not only our cases but also

Table 1. Clinical characteristics, laboratory values and initial treatments of patients at AAVs onset before HP onset.

Age at No AAVs onset	Sex	Classification of AAVs	ENT	ENT	Otitis media	Mastoiditis	Chronic sinusitis	Constitutional symptom	Skin mucosa	Joint	Eye	Heart	Intestine	Peripheral nerve	Kidney	Lung	Muscle	BVAS at AAVs onset	ANCA at AAVs onset (U/mL)	ANCA type	CRP at AAVs onset (mg/L)	mPSL at AAVs onset	Dose of PSL at AAVs onset (mg/day)	Kind of combined IS at AAVs onset	number of AAVs relapses before HP onset
1	68	M	GPA	+	+	-	-	-	-	-	-	-	-	-	-	-	-	1	MPO	266	16.6	-	30	-	0
2	70	M	GPA	+	+	+	+	+	-	-	-	-	-	-	-	-	-	3	MPO	88.5	137	-	30	-	0
3	78	M	GPA	+	+	-	+	-	-	+	-	-	-	-	-	-	+	4	MPO	6.7	409.2	-	20	-	1 Muscle, Otitis media
4	66	F	MPA	-	-	-	-	-	-	+	-	-	-	+	-	-	-	3	MPO	23.7	50.5	-	40	-	0
5	39	F	EGPA	-	-	-	+	+	-	-	-	-	+	+	-	+	-	4	MPO	64.0	27	+	60	IVIG, AZA, IVCY, Tac	3 Intestin, Peripheral nerve, Chronic sinusitis
6	42	F	GPA	+	-	-	+	+	+	+	-	-	-	+	-	+	-	7	PR3	>200	199	-	45	IVCY, AZA	0
7	54	M	EGPA	+	-	-	+	-	-	-	-	-	+	+	-	+	-	4	MPO	84.9	10.3	+	50	AZA, CyA, IVIG	0
8	67	M	MPA	+	+	-	-	+	-	-	-	-	-	+	-	+	+	6	MPO	108.0	72.5	-	30	-	1 Muscle

ANCA: anti-neutrophil cytoplasmic antibody; AAVs: ANCA-associated vasculitis; HP: hypertrophic pachymeningitis; M: male; F: female; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear-nose-and-throat; BVAS: Birmingham Vasculitis Activity Score; MPO: myeloperoxidase; PR3: proteinase3; mPSL: methylprednisolone pulse therapy; PSL: prednisolone; IS: immunosuppressants; IVIG: intravenous immunoglobulin; AZA: azathioprine; IVCY: intravenous cyclophosphamide pulse; Tac: tacrolimus; CyA: cyclosporine; RTX: rituximab.

Table II. Clinical characteristics, laboratory values and treatments for HP of patients at HP onset before RTX treatment.

No	Age at HP onset (month)	Time from AAVs onset to HP onset (month)	Symptoms of HP	Cranial nerve disorder	ENT	ENT media	Otitis media	Mastoiditis	Chronic sinusitis	Constitutional symptom	Skin Mucosa	Joint	Eye	Heart	Intestine	Peripheral nerve	Kidney	Lung	Muscle	EVAS at HP onset	Regions of dura mater thickening	ANCA titer at HP onset (U/mL)	CRP at HP onset (mg/L)	B cell at HP onset RTX treatment (count/ μ L)	Dose of PSL at HP onset RTX treatment (mg/day)	Dose of PSL alter HP onset RTX treatment (mg/day)	Kind of combined IS for HP before RTX treatment	Number of HP relapses before RTX treatment
1	68	3	headache, ophthalmalgia, deafness, ear fullness, hoarseness, dysphagia	V, IX, X	+	+	+	-	-	-	-	-	+	-	-	-	-	-	-	4	middle cranial fossa	184	33.7	no data	20	40	IVCY	1
2	70	7	headache, facial palsy, face imperception, dysarthria	V, VII	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	4	cerebellar tentorium, surroundings of jugular foramen	3.8	45.9	no data	15	mPSL +40	IVCY, AZA, MZB	1
3	80	26	headache, reduced vision	II	+	+	-	+	-	-	-	-	+	-	-	-	-	-	-	4	optic nerve, convexity	<1.0	15.4	no data	30	30	-	0
4	67	14	headache, deafness, dysphagia, dysarthria	VII, VIII, IX	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	middle cranial fossa, cerebellar tentorium	<1.0	80.5	70	16	40	-	0
5	40	3	hoarseness, dysphagia, double vision, taste disturbance	III, IX, X	+	-	-	+	+	-	-	-	+	-	-	-	-	-	-	4	convexity	<1.0	215.6	no data	15	40	-	0
6	43	9	headache, toothache, otalgia, nasal obstruction, face imperception	V	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	6	flat cerebri, convexity	24.2	105.0	185	17	30	-	0
7	55	3	headache, double vision	III, IV, VII	+	-	+	+	+	-	-	-	+	-	-	-	-	-	-	5	middle cranial fossa, convexity	<1.0	77.0	174	40	mPSL +40	IVCY, CyA	0
8	70	36	loss of vision	II	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	1	optic nerve, convexity	6.3	19.4	26	5	50	-	0

HP: hypertrophic pachymeningitis; ANCA: anti-neutrophil cytoplasmic antibody; AAVs: ANCA-associated vasculitis; ENT: ear-nose-and-throat; BVAS: Birmingham Vasculitis Activity Score; mPSL: methylprednisolone pulse therapy; PSL: prednisolone; IVCY: intravenous cyclophosphamide pulse; AZA: azathioprine; MZB: mizoribine; CyA: cyclosporine; RTX: rituximab.

Table. III. Clinical characteristics, laboratory values and treatments at 6 months after RTX treatment.

No	Time from HP onset to RTX treatment (month)	Dose of RTX	Dose of PSL (mg/day)	Kind of combined IS	Improvement of HP symptoms	Remaining HP symptoms	BVAS	Improvement of dura mater thickening	ANCA titre (U/mL)	CRP (mg/L)	B cell (count/ μ L)	Dose of PSL (mg/day)	Kind of combined IS
1	7	375mg/m ² /week x 4	30	-	improved	hoarseness	0	improved	37.3	2.6	1	14	-
2	20	375mg/m ² /week x 4	30	-	improved	sense incongruity	0	no change	<1.0	1.6	no data	12	-
3	0	single dose of 1g	30	-	improved	-	0	improved	<0.5	3.6	no data	10	AZA
4	1	375mg/m ² /week x 4	40	-	improved	deafness	0	improved	<1.0	1.0	0	18	-
5	3	375mg/m ² /week x 4	40	-	improved	-	0	improved	<1.0	2.0	no data	4	-
6	0	375mg/m ² /week x 4	30	-	improved	face imperception	1	improved	7.8	6.0	1	25	IVCY
7	2	375mg/m ² /week x 4	40	CyA	improved	-	1	improved	<1.0	2.0	0	25	CyA
8	0	375mg/m ² /week x 4	50	-	improved	loss of vision	0	improved	<1.0	1.0	1	7	-

HP: hypertrophic pachymeningitis; BVAS: Birmingham Vasculitis Activity Score; ANCA: anti-neutrophil cytoplasmic antibody; PSL: prednisolone; IS: immunosuppressants; AZA: azathioprine; IVCY: intravenous cyclophosphamide pulse; CyA: cyclosporin; RTX: rituximab

previous reports show concomitance of ENT involvement in ANCA-associated HP. Presence of ENT involvement may suggest presence of HP (4, 10). None of the patients exhibited HP at diagnosis of AAVs. ANCA cannot be used as an activity marker of HP, as ANCA were negative in four patients at HP onset (11, 12). On the other hand, CRP levels can be useful for evaluation of HP activity, as CRP levels were higher at HP onset than before HP onset. Therefore, we should consider HP when patients with AAVs have elevated CRP levels, headache, and cranial nerve dysfunction.

The importance of B cells in AAVs is widely known. Moreover lymphocytes, plasmacytes, histiocytes, and epithelioid cells infiltrate dura mater in idiopathic HP and were demonstrated to play a role in HP pathogenesis (3). Other reports show that ectopic lymphoid neogenesis in dura mater could have a role in maintaining immune response (10). Thus, the presence of a lymphocytic and plasmacytic infiltrate leads to a rationale for B cell-targeted therapy in this condition. (5, 6, 13). B cells were depleted in all patients (Table III).

Glucocorticoids are the anchor drug for AAVs, but they can cause various side effects including infections, cardiovascular disease and osteoporosis (14). Those side effects can cause irreversible damage. In some cases vasculitis relapses when the glucocorticoids dose is tapered. Therefore, AAVs are not

usually treated with glucocorticoids alone, and various immunosuppressants are used in combination, including RTX, IVCY, AZA, and methotrexate. Although two patients experienced recurrent HP resistant to initial therapies, RTX therapy was effective in our case series. And it is worth noticing that RTX therapy was successful in five patients resistant to IVCY. Previous case reports also showed successful response to RTX in AAVs-associated HP patients resistant to IVCY. RTX and IVCY were comparable for AAVs in the previous RCTs, but RTX may be more useful than IVCY for HP notably (5-8). In our case series, RTX was effective in not only ANCA positive patients but also negative. Cohort studies have reported similar high response in ANCA-negative AAVs (12).

All patients exhibited elevated CRP levels, which corresponded to the effects of treatment, making CRP levels a possible marker of treatment efficacy. No severe adverse events were observed due to RTX. RTX therapy enabled the reduction of glucocorticoid doses, thus reducing glucocorticoid-related irreversible damage to patients (15).

This study had some limitations. It was a retrospective study with a small sample size that may have been influenced by referral bias.

In conclusion, although HP complicating AAVs are often difficult to treat, RTX is considered safe and effective for such patients.

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