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Case Report

Pachymeningitis as a manifestation of ANCA-associated vasculitis: a care report and literature review

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Abstract: Pachymeningitis is a rare cause of headache characterized by dura mater thickening with various origins. We present a 67-year-old male with cranial and spinal pachymeningitis and MPO-ANCA-associated vasculitis, which is considered as the cause of pachymeningitis of this patient. After revision of other 32 reported cases, our study suggested cranial and spinal pachymeningitis could be a manifestation of ANCA-associated vasculitis. Thus, it is important to screen other manifestations of ANCA-associated vasulitis as soon as pachymeningitis was suspected.

Keywords: Pachymeningitis, ANCA, ANCA-associated vasculitis, Wegener's granulomatosis

Pachymeningitis is an inflammatory disorder with dura mater thickening. It is characterized by headache and cranial nerve dysfunction [1]. Currently, we present a case of cranial and spinal pachymeningitis with positive anti-myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), which is considered as the cause of pachymeningitis of this patient.

Case report

A 67-year-old man was admitted to our hospital because of hearing loss for over two years and headache for over two months. Two years prior to admission, the patient experienced left hearing decline without pain or dizziness, and could not be released by routine treatments. Then the patient turned up loss of appetite, hoarseness, coughing after drinking and dysphagia. Six months later, the patient had a sudden complete hearing loss accompanied with dysarthria. A laryngeal polyp was found by our hospital, followed by surgical removal. However, hearing loss wasn't released and the patient continued complaining of hoarseness after surgery. Head magnetic resonance imaging (MRI) was almost normal (**Figure 1A**), and the chronic Green Barre syndrome in the patient was considered as a consequence of slightly elevated protein in cerebrospinal fluid. He received immunoglobulin 15 g/day for 15 days and symptoms got released. Two months prior to admission, the patient developed consistent frontal headache accompanied with dizziness, ataxia, tinnitus, vertigo, right eye pain, abdominal distention, and vision loss in right eye. The headache was not related to the position or time. The patient didn't have fever or unconsciousness, and his urine and bowel movement were normal. Head MRI scan showed slightly thickened dura mater (**Figure 1B**), and cranial pachymeningitis was considered. The patient received non-steroidal anti-inflammatory drugs for several days in a local hospital, however, headache progressed. Ten days prior to admission the patient felt nausea, vomiting and left ear pain. Vomiting but not pain was released after NSAIDs treatment. The patient had a history of diabetes for over ten years, and a history of recurrent otitis media, pharyngitis, rhinitis, and bronchiectasis for several years. He also received appendectomy several years ago. Physical examination indicated decreased laryngeal reflex, decreased bilateral hearing and complete vision loss in right eye.

After admitted to our hospital, head MRI showed the obviously thickened dura mater (**Figure 1C**), indicating a pachymeningitis developed in two months. Nasopharyngeal biopsy showed chron-

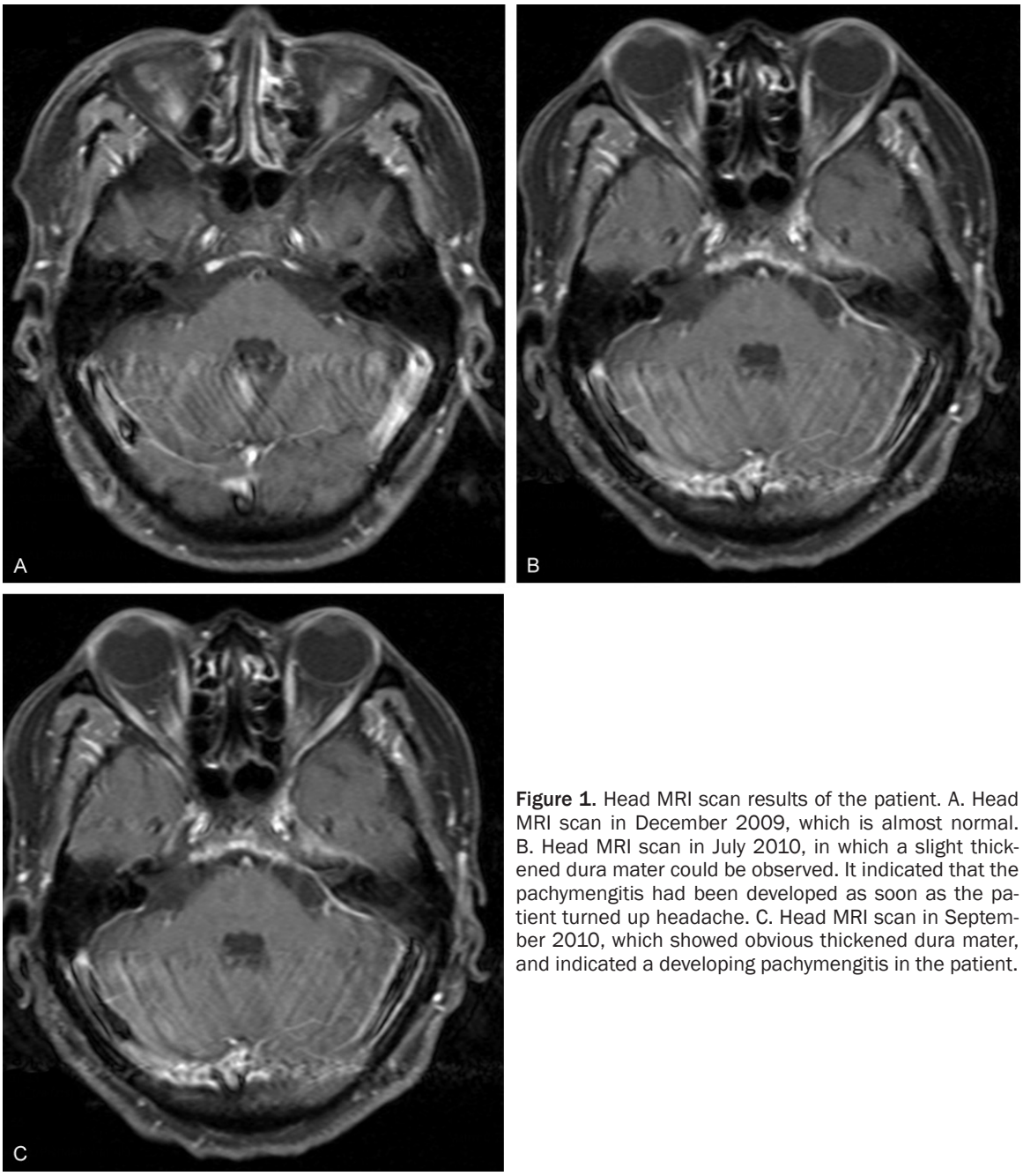

Figure 1. Head MRI scan results of the patient. A. Head MRI scan in December 2009, which is almost normal. B. Head MRI scan in July 2010, in which a slight thickened dura mater could be observed. It indicated that the pachymengitis had been developed as soon as the patient turned up headache. C. Head MRI scan in September 2010, which showed obvious thickened dura mater, and indicated a developing pachymengitis in the patient.

ic inflammation and hyperplasia of lymphatic tissue without granuloma. Bone marrow biopsy indicated low bone marrow proliferation. Thoracic computed tomography (CT) indicated thickened bilateral pleural membranes and revealed mediastinal lymph node. PET-CT scan showed an abnormal increase of Fluorine-18 fluorodeoxyglucose (18F-FDG) absorption in the lateral dura mater of left frontal lobe, the inferior dura mater of left temporal lobe, and the spinal mater of T5-T12 (**Figure 2**). Tumor markers were within the normal range. Lumbar puncture of CSF showed: Nuclear cells: 2-4 × 10^6/L, Protein: 0.84-1.11 g/L, IgG synthesis rate: 139.617 mg/day. Serum examination showed blood urea nitrogen (BUN): 14.16 mmol/L, serum creatinine (SCr): 213.9 μmol/L, ANA: ++ 1:1000, P-ANCA (+), MPO-ANCA (+), PR3-ANCA (-), LF-ANCA (-), BPI-ANCA (-), rheumatoid factor (RF): 47.4 IU/L, CRP: 109.0 mg/L. As a result, the patient was diagnosed as systemic MPO-ANCA-associated, which was con-

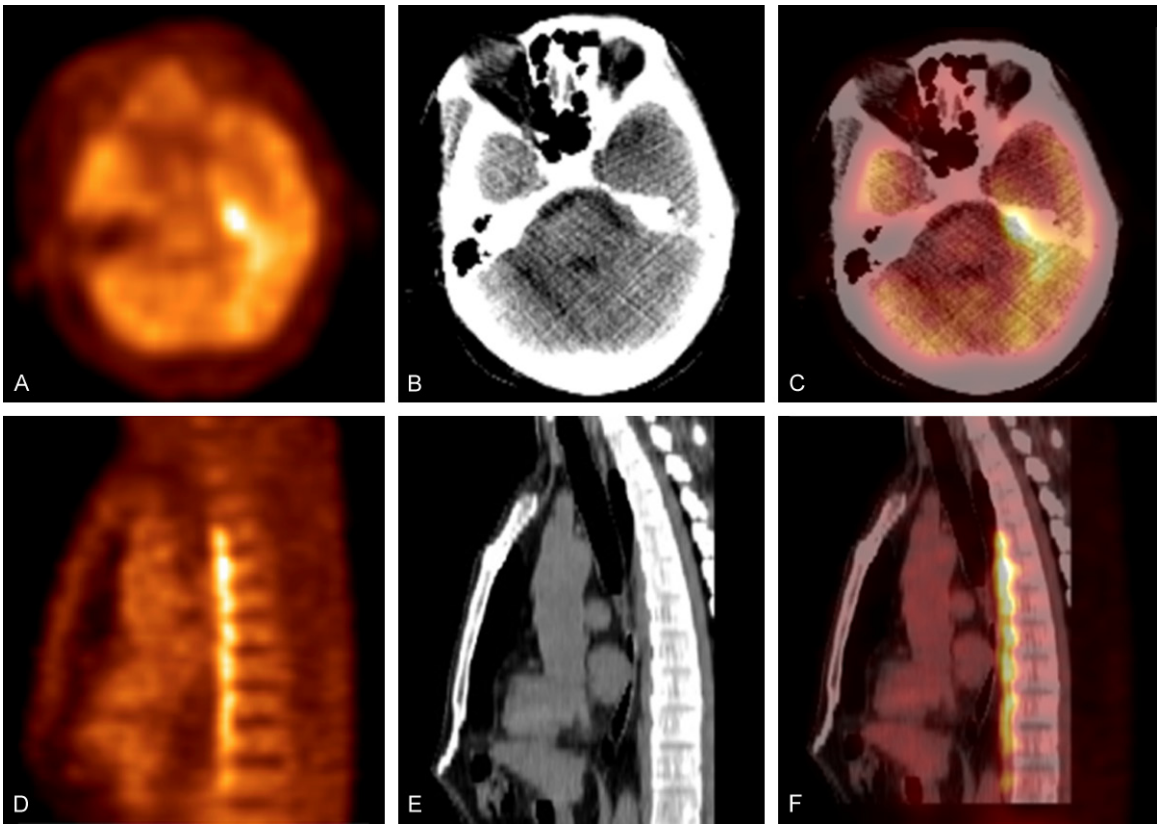

Figure 2. PET-CT images of the head and lumbar spine. A-C. PET-CT images of the head. It showed the absorption of 18F-FDG increased significantly in the lateral dura mater of left frontal lobe and inferior dura mater of left temporal lobe, indicating an active duritis in the associated sites. Other part of the head was normal in PET-CT. D-F. PET-CT images of the lumbar spine. A thickened soft tissue images could be observed anterior to T5-T12 vertebrates with abnormal increased absorption of 18F-FDG. The near fat tissue was clear, and no destruction of the bone or discontinuation of the bone cortex was found.

sidered as the origination of pachymeningitis. Thus methylprednisolone (MP) 500 mg per day and immunoglobulin 20 g per day for 5 days and cyclophosphamide (CTX) 1 g was given to the patient. Headache was released dramatically on the second day of MP therapy initiation. Oral prednisone with gradually decreased dose was consequently given. The patient was discharged two weeks after the steroid treatment initiated and was followed-up regularly in the outpatient department. Nine months after discharge, the p-ANCA and MPO-ANCA turned negative. Four years after discharge, headache did not relapsed, but the renal function was not recovered.

Discussion

Cranial and spinal pachymeningitis is a rare disease characterized by systemic or local inflammatory process of the dura mater and spinal cord, respectively. Our reported patient presented with an intense headache, accompanied by otitis media, rhinitis, renal insufficiency, and MPO-ANCA-positive-status. The headache of the patient was considered to be a consequence of a cranial and spinal pachymeningitis, as suggested by head MRI and PET-CT scan, and was released dramatically when treated by glucocorticoid and immunosuppressive therapy together with MPO-ANCA turning negative. During a four-year follow-up, the patient didn't relapse when the MPO-ANCA kept negative. It indicated MPO-ANCA in this case might be the cause of pachymeningitis.

We reviewed 32 single cases [2-27] of pachymeningitis with ANCA-associated vasculitis, as summarized in **Table 1**. All patients had severe headache at onset as one of the main complaints, and dramatically recovered after treatment with glucocorticoid and CTX. The age of

Table 1. Published case reports of pachymengitis associated with ANCA

Case No	First Author, Year of Publication	Gender	Age	Country	ANCA	Renal involvement	Visual impairment	Hearing impairment	Pulmonary involvement	Meningitis	Pathology	Other complications
01	Horino T, 2010 [2]	M	75	Japan	MPO	-	+	+	-	Cranial	NR	NR
02	Takuma H, 2001 [3]	M	67	Japan	MPO	-	-	+	-	Cranial	NR	Diabetes Insipidus, diabetes mellitus
03	Hayashi Y, 2008 [4]	M	81	Japan	MPO/PR3	+	-	-	-	Cranial	Vasculitis with fibrinoid degeneration in the small arteries of the pancreas and ileocecum, necrotizing glomerulonephritis in kidney	NR
04	Durant C, 2011 [5]	M	53	France	PR3	+	-	-	-	Spinal	Granulomatous vasculitis with necrosis in T12 vertebra	NR
05	Cañas CA, 2011 [6]	F	50	Columbia	PR3	-	+	-	-	Cranial	Polychondritis in ear cartilage, and leukocytoclastic vasculitis in kidney	Relapsing polychondritis
06	Cañas CA, 2011 [6]	F	48	Columbia	PR3	+	+	-	-	Cranial	NR	Relapsing polychondritis
07	Cañas CA, 2011 [6]	F	50	Columbia	PR3	-	+	-	-	Cranial	NR	Relapsing polychondritis
08	Iguchi A, 2013 [7]	F	64	Japan	MPO/PR3	-	+	-	-	Cranial	Ruptured and disrupted elastic layers of the arterial wall with inflammatory cell infiltration in the right orbital mass.	IgG4+
09	Abe T, 2007 [8]	F	34	Japan	MPO	-	-	-	-	Cranial	Inflammatory cell infiltration around the small vessels in the subarachnoid space	Grave's disease
10	Liewluck T, 2008 [9]	M	64	USA	MPO/c-ANCA	-	+	-	+	Cranial	Necrotizing vasculitis in nose	Idiopathic pulmonary fibrosis
12	Greco P, 2007 [10]	M	57	Italy	negative*	-	+	-	+	Cranial	Necrotizing vasculitis in pulmonary nodules	NR
13	Akahoshi M, 2004 [11]	M	60	Japan	MPO	-	-	+	-	Cranial	Granulomatous inflammation in dura mater	NR
14	Jacobi D, 2005 [12]	F	51	France	MPO	-	+	+	-	Cranial	NR	Lymphocytic thyroiditis
15	Salvi F, 2010 [13]	F	69	Italy	MPO	-	+	-	-	Cranial	NR	NR
16	Nagashima T, 2000 [14]	F	53	Japan	MPO	-	+	-	-	Spinal and Cranial	Occasional granuloma , venal phlebitic occlusion, and well-preserved artery in dura mater	NR
17	Bawa S, 2007 [15]	F	36	UK	c-ANCA	+	+	-	-	Cranial	NR	NR
18	Lim EJ, 2011 [16]	F	54	Korea	MPO	-	+	+	-	Cranial	NR	NR
19	Hamilton AJ, 2010 [17]	M	65	UK	MPO	+	-	-	+	Spinal and Cranial	NR	NR
20	Tamura N, 2007 [18]	M	35	Japan	PR3	-	-	+	-	Cranial	Chronic inflammatory changes of Wegener's granulomatosis in nasal mucosa.	NR
21	Kurihara Y, 2011 [19]	M	58	Japan	MPO	-	-	+	+	Cranial	Necrotizing vasculitis in the lung	Type 1 diabetes mellitus

22	Horai Y, 2010 [20]	M	63	Japan	MPO	-	-	-	+	Cranial	NR	NR
24	Just SA, 2011 [21]	F	27	Denmark	PR3	-	-	+	+	Cranial	Vasculitis and granuloma formation in nasal mucosa, necrosis and chronic inflammation with granuloma formation in lung	NR
25	Takazawa T, 2014 [22]	M	74	Japan	PR3	+	+	-	+	Cranial	NR	NR
26	Takazawa T, 2014 [22]	M	72	Japan	PR3	-	+	-	+	Cranial	NR	NR
27	Peng W, 2012 [23]	M	58	China	MPO/PR3	+	+	-	+	Cranial	Granular necrosis and local inflammatory cells infiltration in meningeal biopsies. No granulomatosis was found.	NR
28	Watanabe K, 2013 [24]	F	75	Japan	MPO	+	-	-	-	Cranial	Vasculitis of small-sized arteries in the kidney	NR
29	Mori A, 2013 [25]	M	63	Japan	MPO	+	-	+	-	Cranial	Tubulointerstitial damage of the kidney without any specific glomerular injuries or granulomatous changes	NR
30	Mori A, 2013 [25]	F	70	Japan	MPO	-	-	+	-	Cranial	NR	NR
31	Onyeuku NE, 2014 [26]	M	75	USA	PR3/c-ANCA	-	-	-	-	Cranial	NR	NR
32	Takenaka K, 2014 [27]	F	47	Japan	MPO	-	-	-	+	Spinal	Intraluminal organizing fibrosis in the alveoli of lungs	NR
33	Li S, 2015†	M	67	China	MPO	+	-	+	+	Spinal and Cranial	chronic inflammation and hyperplasia of lymphatic tissue in nasal mucosa	Diabetes mellitus

*PR3-ANCA positive 8 years ago. †Our study. +: present; -: not present; ANCA: antineutrophil cytoplasmic antibody; F: female; M: male; MPO: myeloperoxidase; PR3: anti-proteinase 3; NR: not reported.

the patients varied from 27 to 81 years old, and approximately half of them were male. 16 of them were MPO-ANCA positive only, and ten were c-ANCA positive only. Five patients were both MPO- and PR3-ANCA detectable. Among the MPO-ANCA positive only patients, nine reported ear involvement, with symptoms presented as hearing loss or otitis media, and five reported pulmonary disorders, while among the c-ANCA positive only patients, and two reported ear involvement and three reported pulmonary disorders. Eight MPO-ANCA positive only patients reported pathological results, four of which suggested granulomatous lesions, while eight patients with positive c-ANCA reported pathological results, three of which suggested granulomatous lesions. Based on our literature review, the positive rate of MPO-ANCA seemed slightly higher than that of PR3-ANCA. However, no significant difference could be drawn between different ANCA types. All these cases suggested that cranial pachymeningitis was highly associated with ANCA-associated vasculitis, and the therapeutic strategy and its response of these patients appeared similar with simple ANCA-associated vasculitis. In several case reports with pathological data, granulomatosis could be found in the thickened dura mater and other involved organs [4, 5, 9-11, 14, 18, 19, 21, 23].

Two recently published case series indicated ANCA could be one of the major causes of pachymeningitis [28, 29]. In a nation-wide survey of Japan, 40 out of 159 patients with pachymeningitis were ANCA positive [29]. Among them, the positive rate of MPO-ANCA was more than twice as much as that of PR3-ANCA, which was roughly consistent with our review. Moreover, a study among 12 Chinese patients with pachymeningitis found only one patient to be MPO-ANCA positive [28], and none was c-ANCA positive. These observational studies indicated MPO-ANCA could be more likely to be associated with the presence of pachymeningitis. However, another case collection from Europe recruited 35 CNS-involved granulomatosis with polyangiitis, 84% of which were PR3-ANCA positive. Among the patients studied, 46% had cranial pachymeningitis and 11% had spinal pachymeningitis [30], indicating PR3-ANCA could also be an un-neglectable cause of pachymeningitis although not that common as MPO-ANCA.

According to the above data, some characteristics of ANCA-associated pachymeningitis could be summarized: 1) the majority of patients were middle to senior aged; 2) could develop in patients with previously diagnosed ANCA-associated vasculitis, which could be omitted; 3) MPO-ANCA appeared to be slightly more common than PR3-ANCA in such patients, while PR3-ANCA could also contribute dominantly to this disorder; 4) intense headache was the commonest complaint and responded dramatically to glucocorticoid and immunosuppressive therapy; 5) usually complicated with chronic sinusitis, otitis media, or mastoiditis. Moreover, the co-existence and simultaneous improvement of pachymeningitis and ANCA titer indicated pachymeningitis a composition of ANCA-associated vasculitis.

In summary, our study suggested that both cranial and spinal pachymeningitis could be a manifestation of ANCA-associated vasculitis. It is essential to screen other manifestations of ANCA-associated vasculitis as soon as pachymeningitis was suspected. However, the contribution of ANCA to the pathogenesis of pachymeningitis remained unknown and required further investigation.

Disclosure of conflict of interest

None.

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