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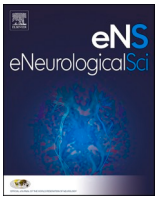

IgG4-related pachyleptomeningitis with inflammatory pseudotumor

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Dear Editor,

1. Introduction

IgG4-related disease (IgG4-RD) is a unique fibroinflammatory disorder with organ system involvement. The neurological manifestations of IgG4-RD are varied, especially leptomeningitis is rare as only six cases have been reported [1–6]. There is no report of pachyleptomeningitis due to IgG4-RD. Here, we report a patient with IgG4-related pachyleptomeningitis with inflammatory pseudotumor.

2. Case presentation

A 50-year-old man, a construction worker with no history of autoimmune or rheumatic disease was admitted to our hospital because of a suspected brain tumor. He reported 3 months of right temporal headaches. Two weeks previously, he experienced intermittent left-sided weakness. His neurological examination was normal. MRI of the brain showed diffuse homogeneous enhancement of the dura and pia mater over the right cerebral hemisphere. There appeared to be an associated tumor-like mass lesion growing into the overlying bone at the right frontoparietal convexity (Fig. 1A and B). MRI of the cervical spine was normal. Contrast-enhanced whole-body CT showed no evidence of malignancy or granulomatous disease. Serum rheumatoid factor concentration was elevated (88 IU/mL, normal range: < 15) and serum anti-cyclic citrullinated peptide (CCP) antibody was negative. Serological testing for other collagen diseases was also negative. Serum IgG4 concentration was 137 mg/dL (normal range, 11–121) and C-reactive protein was 0.42 mg/dL. Angiotensin-converting enzyme, soluble interleukin-2 receptor, and antineutrophil cytoplasmic antibodies were negative. Testing for syphilis, HIV, and tuberculosis was negative. CSF examination showed a cell count of 15/μL (all lymphocytes), protein level of 86.7 mg/dL, glucose level of 63 mg/dL, and IgG index of 1.50. No findings compatible with IgG4-related disease (RD) were noted in any organ system.

To rule out malignancy, a brain biopsy was performed. Histological examination revealed dense and diffuse lymphoplasmacytic infiltration in the pachymeningeal and leptomeningeal tissues; atypical cells were not seen (Fig. 2A and B). The pachymeningeal tissue was marked characterized by fibrous thickening, and lymphoplasmacytic infiltration was continuous with the leptomeningeal tissue in some areas. The details of the meningeal structures are were unclear due to marked meningeal thickening caused by inflammation and fibrosis. Hyalinized fibrosis was present in the interstitial tissue. Obliterative phlebitis, storiform fibrosis, vasculitic involvement, granulomas, and giant cells were not observed. IgG4 immunoreactivity was seen within the dense inflammatory infiltrates (Fig. 2C). IgG4/IgG ratio exceeded 50% in at least three foci. Within the tumor-like mass lesion, infiltration of bone trabecula by plasma cells and foamy cells was observed (Fig. 2D).

The patient was diagnosed with IgG4-related pachyleptomeningitis with inflammatory pseudotumor. Three-day intravenous methylprednisolone (IVMP) was started administered as an acute phase treatment. After twice two courses of IVMP, he was treated with oral prednisolone (0.75 mg/kg/day) and azathioprine (2 mg/kg/day). The dose of oral prednisolone had been reduced was tapered and was maintained at 5 mg/day one year after onset. Follow-up MRI 2 months later showed almost complete disappearance of the pachyleptomeningeal enhancement (Fig. 1C and D).

3. Discussion

The case of IgG4-related pachyleptomeningitis with inflammatory pseudotumor presented here corresponds to a definite diagnosis according to the 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD [7]. On MRI, the pachymeninges were enhancing and hypertrophic; moreover, the enhancement extended into the depths of the sulci.

Neurologically, IgG4-RD may manifest with intracranial or spinal pachymeningitis, hypophysitis, cranial nerve involvement, and peripheral neuropathy. Reported pachymeningitis prevalence rates in IgG4-RD range from 2% to 35% [8]. Leptomeningitis is even rarer, as only six such cases have been reported [1–6]. To our knowledge, pachyleptomeningitis in association with IgG4-RD has not been previously reported.

Among the six previously reported cases of IgG4-related leptomeningitis, three were associated with rheumatoid arthritis [2–4]. These patients had an elevated rheumatoid factor concentration and anti-cyclic citrullinated peptide antibodies. All responded well to corticosteroid administration. Typical brain MRI findings of rheumatoid meningitis include hyperintensities on fluid-attenuated inversion

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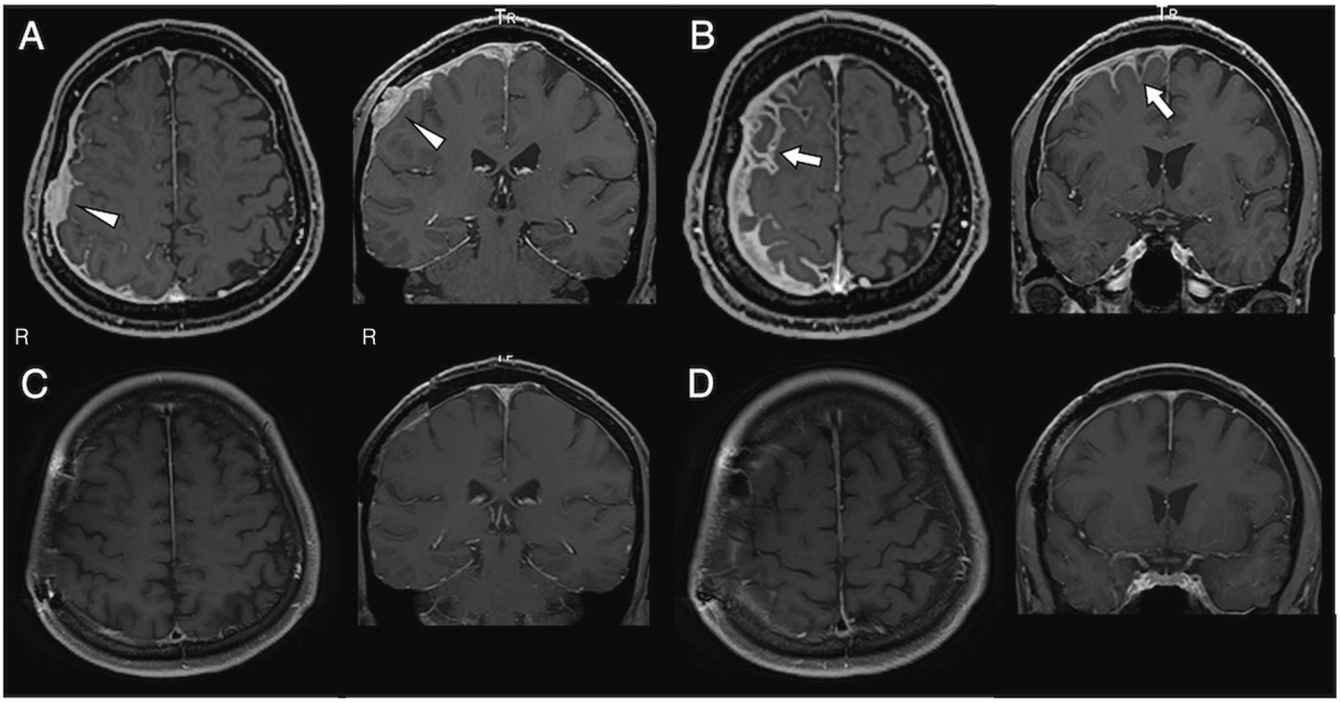

Fig. 1. (A) Post-gadolinium T1-weighted images show pachymeningeal enhancement over the right frontoparietal convexity and a tumor-like lesion contiguous with the dura (arrowheads). (B) Marked leptomeningeal enhancement is shown in the right hemisphere (arrows). Enhancement of the interhemispheric sulci is also observed. (C, D) After 2 months of corticosteroid treatment, the pachyleptomeningeal enhancement significantly improved and the pseudotumor disappeared along with surgical resection.

recovery images and enhancement of the supratentorial meninges. Histopathological features include meningeal lymphoplasmacytic infiltration, vasculitis, and fibrosis; typical rheumatoid nodules are rarely seen. All of these radiological and histopathological features are similar to those of IgG4-related meningitis. Biopsy is necessary if the diagnosis cannot be confirmed using imaging and laboratory testing. We considered that the present Our case was not associated with rheumatoid arthritis or other collagen diseases, and with anti-CCP antibody were being negative. Pathological examination of the meninges showed a prominent infiltrate of IgG4-positive cells with fibrosis, which was not supportive of considered not rheumatoid meningitis.

Histopathologically, obliterative phlebitis and storiform fibrosis are considered highly specific for IgG4-RD and are included in the classification criteria [7]. In our patient, hematoxylin and eosin staining of the meningeal tissue demonstrated diffuse lymphoplasmacytic infiltration and moderate fibrosis; however, obliterative phlebitis and storiform fibrosis were absent. These were not seen in the six previously reported cases of IgG4-related leptomeningitis either. Therefore, obliterative phlebitis and storiform fibrosis may be rare in IgG4-related leptomeningitis.

Our patient is also unique in that an inflammatory pseudotumor was seen on MRI and the pachyleptomeningitis was located only on the side ipsilateral to the pseudotumor. The pseudotumor infiltrated into the adjacent bone, which may have indicated severe local inflammation. We hypothesize that severe inflammation arose from the dural pseudotumor and then spread along the contiguous meninges.

In general, IgG4-RD responds well to corticosteroid administration. Our patient exhibited a striking response in terms of symptoms and radiological findings. Both the pseudotumor and pachyleptomeningitis had almost disappeared on follow-up MRI. It is important to differentiate meningeal involvement of IgG4-RD from pachyleptomeningitis of other causes.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Authors' contributions

KS analyzed the data and drafted the manuscript. TU acquired clinical data and drafted the manuscript. AT, NA, TT, and TS conceptualized and revised the manuscript. HM drafted and revised the manuscript and gave final approval for the published version.

CRediT authorship contribution statement

Koki Suezumi: Writing – original draft, Conceptualization, Data curation. **Taira Uehara:** Conceptualization, Writing – review & editing. **Akihiko Taira:** Data curation, Conceptualization, Writing – review & editing. **Naoki Akamatsu:** Conceptualization, Writing – review & editing. **Tatsuya Tanaka:** Conceptualization, Data curation, Writing – review & editing. **Yuichiro Hayashi:** Writing – review & editing, Conceptualization, Data curation. **Mina Komuta:** Data curation, Conceptualization, Writing – review & editing. **Takayuki Shiomi:** Writing – review & editing, Data curation, Conceptualization. **Hiroyuki Murai:** Conceptualization, Supervision, Writing – review & editing, Data curation.

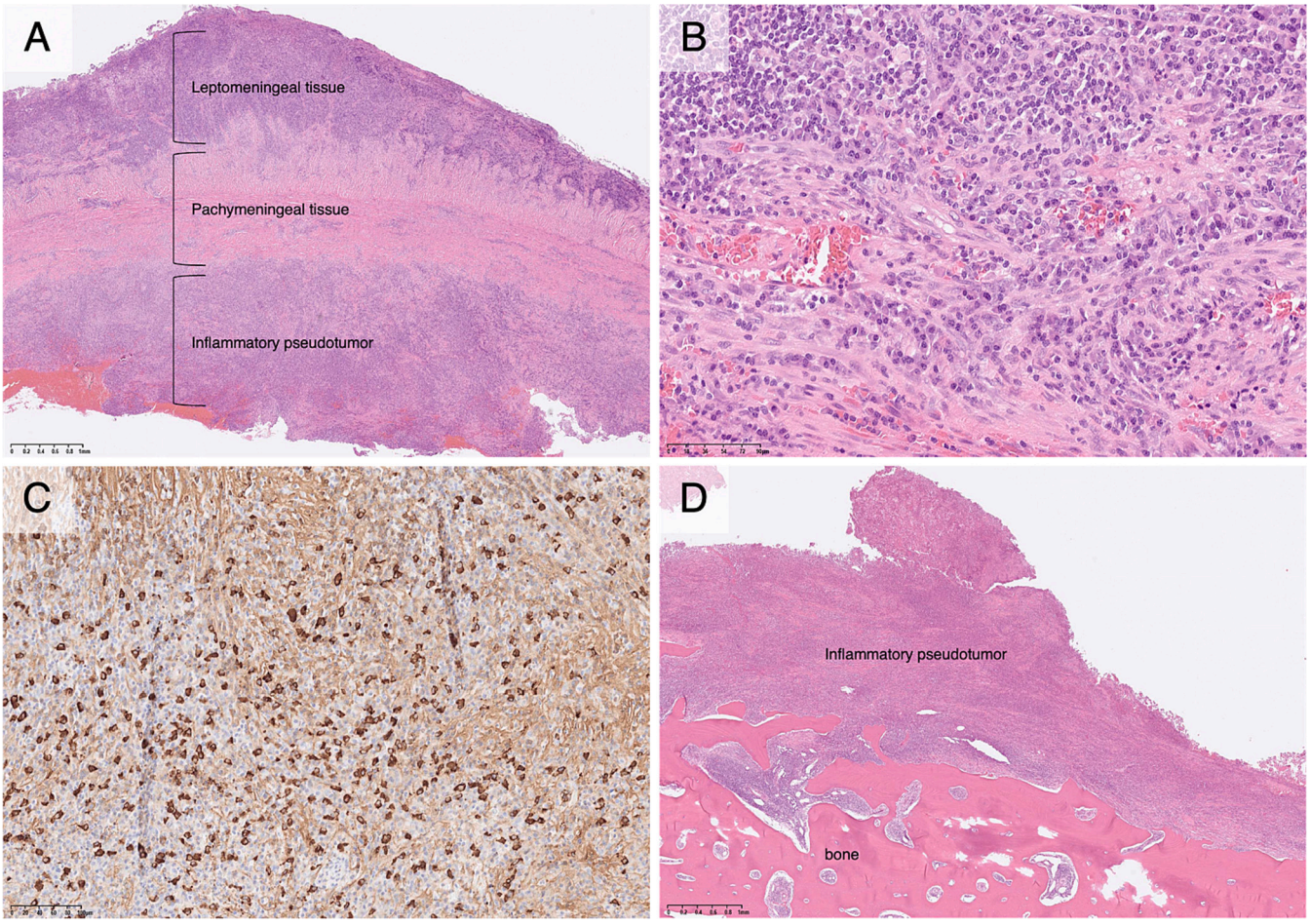

Fig. 2. (A) Hematoxylin and eosin staining of the pachymeningeal and leptomeningeal tissues reveals diffuse lymphoplasmacytic infiltration. Accumulation of small lymphocytes and plasma cells (inflammatory pseudotumor) is seen in continuity with the pachymeningeal tissue. (B) Hyalinized fibrosis and inflammatory cells are present in the leptomeningeal tissue. (C) Immunohistochemical staining for IgG4 shows a high percentage of IgG4+ plasma cells. (D) The tumor-like lesion was highly infiltrated with non-atypical small lymphocytes and plasma cells in the bone trabeculae.

Declaration of Competing Interest

The authors have no competing interests to declare.

Data availability

The datasets generated during the present study are available from the corresponding author upon reasonable request.

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