

[CASE REPORT]

Hypertrophic Pachymeningitis with Characteristics of Both IgG4-related Disorders and Granulomatosis with Polyangiitis

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Abstract:

We herein report a 73-year-old man with isolated hypertrophic pachymeningitis (HP) showing serological and pathological characteristics of both IgG4-related disorders and granulomatosis with polyangiitis. The patient presented with chronic onset headaches and ophthalmalgia. Brain magnetic resonance imaging (MRI) revealed a hypertrophic enhanced dura mater. Serum IgG4 and myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) levels were elevated. A dura mater biopsy showed infiltration of numerous IgG4-positive plasma cells and granulomatous inflammation without apparent vasculitic lesions, storiform fibrosis, or obstructive phlebitis. Corticosteroid treatments improved his clinical symptoms and MRI findings. There have been reports of MPO-ANCA-positive IgG4-related HP presenting as granulomatous inflammation in the dura mater.

Key words: IgG4-related disease, hypertrophic pachymeningitis, myeloperoxidase anti-neutrophil cytoplasmic antibody, granulomatosis with polyangiitis, dura mater biopsy, granulomatous inflammation

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Introduction

Hypertrophic pachymeningitis (HP) is an inflammatory disorder characterized by local or diffuse thickening of the intracranial or spinal dura mater (1). Several predisposing conditions have been implicated in HP, including infection, autoimmune disease, tumors, and trauma, although patients with HP of unknown cause (idiopathic HP) are also noted (1). A nationwide survey in Japan revealed that the most frequent cause of HP was anti-neutrophil cytoplasmic antibody (ANCA)-positive (30.2%), followed by IgG4 (8.8%) (1). ANCA-related HP comprises three underlying disorders: granulomatosis with polyangiitis (GPA) (1), microscopic polyangiitis (MPA) (2), and eosinophilic granulomatosis with polyangiitis (EGPA) (3). GPA is the most common cause of ANCA-related HP (4).

IgG4-related diseases are chronic inflammatory disorders with the following pathological characteristics: lymphoplasmacytic infiltration of numerous IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis in various organs (e.g. the salivary glands, thyroid glands, lungs, and pancreas) (5). Elevated serum IgG4 and infiltration of IgG4-positive plasma cells are characteristic features of IgG4-related diseases; however, GPA, EGPA, pulmonary sarcoidosis, and lymphoma have also been reported to present with similar pathological or serological features of IgG4-related diseases (6). Several patients with IgG4-related HP have demonstrated serum positivity for ANCA, and a few patients with HP have shown both clinical features of GPA and IgG4-related disease (7, 8). Furthermore, the presence of granulomatous inflammation, including granuloma formation with multinucleated giant cells, has been reported in patients with IgG4-related HP whose ANCA status was uncertain (9).

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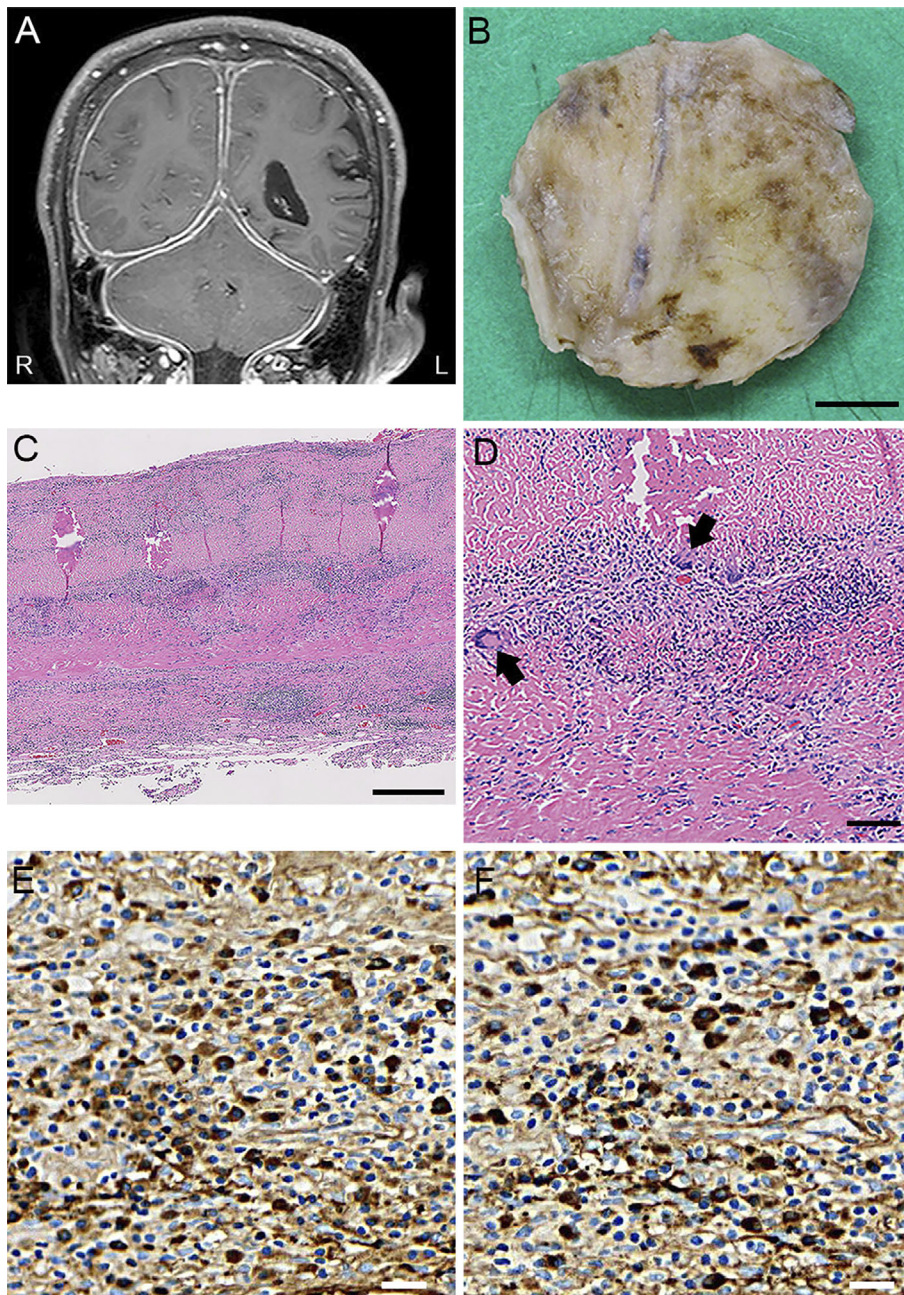


Figure. Imaging and neuropathological findings of the patient. (A) Coronal section of T1-weighted postcontrast image revealed enhancement of the thickened dura mater covering the cerebral hemisphere and cerebellum, predominantly on the right side. (B) Macroscopic observation of the biopsied dura mater showed thickening. This picture was taken from the side of the brain. (C, D) A histopathological examination of the dura mater demonstrated fibrosis, lymphocyte and plasma cell infiltration, and granulomatous inflammation with multinucleated giant cells (black arrows), without apparent vasculitic lesions. Infiltrated plasma cells are immunolabelled for IgG (E) and IgG4 (F). Hematoxylin and Eosin staining (C, D), immunolabeling for IgG (polyclonal rabbit, DAKO, Glostrup, DK-2600, Denmark; 1: 10,000), and IgG4 (mouse monoclonal, ZYMED, South San Francisco, USA; 1: 4,000) (E, F). Scale bar=1 cm (B), 400 μ m (C), 200 μ m (D), and 100 μ m (E, F).

We herein report a patient with HP showing characteristics of both IgG4-related disorders and GPA, such as elevated serum IgG4 levels, infiltration of numerous IgG4-positive plasma cells, granulomatous inflammation without apparent vasculitic lesions in the biopsied dura mater, and serum positivity for myeloperoxidase ANCA (MPO-ANCA).

Case Report

A 73-year-old Japanese man had a medical history of lung cancer 9 years prior to admission. He presented with headaches and ophthalmalgia over a one-year period. He

had also developed blurred vision one month prior to visiting our hospital. A general physical examination revealed no manifestations suggesting GPA, such as sinus pain, nasal discharge, otitis media, or bloody sputum. A neurological examination indicated decreased visual acuity and papilloedema on both sides.

Brain magnetic resonance imaging (MRI) on T1-weighted images with gadolinium administration revealed a hypertrophic enhanced dura mater (Figure A). Computed tomography revealed no abnormalities in the paranasal sinus, lungs, pancreas, or kidneys. Serologic tests revealed elevated levels of serum C-reactive protein (1.12 mg/dL) and IgG4 (156 mg/dL; normal range, <135 mg/dL), with a normal serum creatinine concentration. Serum MPO-ANCA (38.0 IU/mL) and anti-aminoacyl-tRNA synthetase were positive. Other serum autoantibodies suggestive of collagen diseases were negative, including protein 3 (PR3)-ANCA (0.5 IU/mL). There was no apparent evidence of infection with tuberculosis, syphilis, or fungi. A urinalysis showed a pH of 7.0, a specific gravity of 1.015, negative proteinuria, and negative glycosuria. Urinary sediment showed 10 to 19 red blood cells per high-power field. A cerebrospinal fluid examination revealed an elevated opening pressure (21 cm H₂O), no pleocytosis, elevated protein levels (66 mg/dL), and oligoclonal bands. Cytology revealed no malignant cells. A dura mater biopsy from the right convexity showed marked thickening of the dura mater (Figure B, C). A microscopic examination identified fibroinflammatory lesions with lymphoplasmacytic infiltration and foci of granulomatous inflammation, comprising several multinucleated giant cells and histiocytic cell infiltration (Figure C, D), albeit with no apparent vasculitis, storiform fibrosis, or obstructive phlebitis. Immunohistochemical studies revealed an increase in IgG4-positive plasma cells (42 cells per high-power field.) The IgG4-/IgG-positive cell ratio was 70% (Figure E, F).

The patient was treated with intravenous methylprednisolone (IVMP), followed by oral corticosteroid administration. The patient's clinical symptoms and MRI findings subsequently improved. He was treated with 10 mg/day oral corticosteroids as maintenance therapy.

Five months after the first admission, he gradually developed headaches, blurred vision, and right facial numbness. Brain T1-weighted MRI with gadolinium enhancement revealed a hypertrophic enhanced dura mater and swollen right trigeminal nerve. Serum IgG4 levels were normal, while MPO-ANCA test results were negative. Repeated IVMP improved his clinical symptoms and brain MRI abnormalities. His clinical manifestations did not worsen despite tapering of oral corticosteroid.

Discussion

Several cases of IgG4-related HP show serum positivity for ANCA (7, 8). ANCA-positive IgG4-related HP showed fibroinflammatory lesions and numerous IgG4-positive

plasma cells on a pathological examination of the dura mater (7); however, there have been no reports of MPO-ANCA-positive IgG4-related HP presenting as granulomatous inflammation in the dura mater. Other reports have described several patients with IgG4-related HP showing granulomatous inflammation or multinucleated giant cells in the dura mater; however, those patients did not undergo a serum examination for IgG4 and MPO-ANCA (9). Granulomatous inflammation is a pathological characteristic of GPA (4). Although several cases of GPA with HP have demonstrated elevated serum IgG4 levels or IgG4-positive plasma cell infiltration in the biopsied dura mater (7, 8), no patients with GPA showing HP have previously presented with the above-mentioned serological and pathological features suggestive of IgG4-related diseases.

The present patient was excluded from IgG4-related diseases according to the 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-related disease due to the presence of MPO-ANCA and anti-aminoacyl-tRNA synthetase (10). Furthermore, the present case was classified as Wegener's granulomatosis (GPA) by the European Medicines Agency's algorithm (11), albeit with no involvement of organs other than the dura mater. A previous study in Japan reported that MPO-ANCA and PR3-ANCA seropositivity for GPA was 54.6% and 45.5%, respectively (12). A recent report concluded that the presence of ANCA does not influence the pathomechanisms of IgG4-related diseases (13). However, an overlap of ANCA-associated vasculitis and IgG4-related disease has been reported (14). Furthermore, a prior case report suggested that HP caused by GPA and IgG4-related disease might be a spectrum of disorders; however, a pathological examination of the dura mater was not performed in this case (8). The present patient demonstrates that isolated HP can show concomitant pathological and serological features of both IgG4-related disorders and GPA.

In conclusion, we encountered a case of HP with serological and pathological characteristics of both IgG4-related disorders and GPA. Further clinical and neuropathological studies are necessary to elucidate the relationship between IgG4-related HP, MPO-ANCA, and granulomatous inflammation.

Informed consent was obtained from the patient for this case report.

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

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