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Hypertrophic Pachymeningitis and Interstitial Lung Disease in IgG4-Related Disease

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Dear Editor,

IgG4-related disease (IgG4-RD) is an immune-mediated inflammatory condition characterized by elevated serum IgG4 and affected organs being infiltrated by IgG4-positive plasma cells.[1] This disease can affect multiple organs, but rarely involves the central nervous system (CNS).[2] Here we report a case of IgG4-RD presenting as hypertrophic pachymeningitis (HP), which was confirmed in a lung biopsy.

A 57-year-old female presented to our hospital with a throbbing headache that began 1 year previously. The pain persisted in the entire head and was more severe on the right side; the patient also had interstitial lung disease (ILD) (Fig. 1A). Although the patient did not present with joint tenderness, the presence of rheumatoid arthritis was supported by elevated C-reactive protein and an increased erythrocyte sedimentation rate. She had been prescribed methylprednisolone (2 mg/day) and tacrolimus (0.5 mg/day) for rheumatoid arthritis. Brain magnetic resonance imaging (MRI) performed in another hospital 5 months previously did not detect any structural lesions that could explain the headache symptoms (Fig. 1B). The patient had been diagnosed with chronic migraine at that time. Despite taking both acute and preventive migraine medications for 5 months, the headache became more severe and interfered with her daily physical activities and the quality of sleep at nighttime. Brain MRI performed upon admission to our hospital revealed pachymeningeal thickening with enhancement in the right hemisphere (Fig. 1C), which had not been found in the previous MRI. An examination of the CSF revealed slight elevation of the WBC count (12/μL, lymphocyte-dominant), whereas protein (37.2 mg/dL) and glucose (66.0 mg/dL) levels were within the normal ranges. Attributing the headaches to IgG4-RD was considered based on the HP revealed by brain MRI and the ILD comorbidity. We investigated the patient's serum for subclasses of IgG, and found elevated IgG4 (186.4 mg/dL, reference range: 3.9–86.4 mg/dL). A lung biopsy was performed to confirm the diagnosis, because it is safer and easier than a meningeal biopsy. The lung biopsy revealed obliteration of venular vessels and storiform fibrosis with infiltration by lymphoplasma cells (Fig. 1E and F). IgG and IgG4 were found in plasma cells by immunohistochemistry (Fig. 1G and H). Based on the clinical and radiological features observed and the serological and pathological findings, the patient was diagnosed with IgG4-RD.[3] She was treated with a high dose of prednisolone (1,000 mg/day for 5 days), followed by rituximab (375 mg/m^2). Subsequent MRI revealed decreased pachymeningeal enhancement (Fig. 1D).

IgG4-RD can affect various organs, and in this case two organs were involved: the lungs and the brain. The most commonly affected body parts include the pancreas, salivary and lacrimal glands, biliary tract, thyroid, kidney, and lung, while the CNS is rarely involved.[4] Diseases that can affect each of these organs are type 1 autoimmune pancreatitis, Mikulicz disease, IgG-related sclerosing cholangitis, and Riedel's thyroiditis, and their common clinical, laboratory, and histological features have led to them being classified into a single disease, termed IgG4-RD. Recently revised diagnostic criteria for IgG4-RD include 1) clinical or imaging findings

of organ involvement, such as enlargement or dysfunction, 2) elevated serum IgG4, and 3) histologically dense infiltration of lymphocytes/plasma cells and fibrosis.[3] CNS involvement usually presents as HP, with subsequent swelling of the dura mater and neurological symptoms. A previous study of 33 IgG4-related HP patients found that the disease involved various body parts including bones and the salivary gland, lung, kidney, orbit, and retroperitoneal space.[5] Although ten patients (30%) with IgG4-related HP did not show the involvement of other organs, three (9%) patients showed involvement of the lungs, similar to the condition of our patient. The most-common symptom among those 33 patients with IgG4-related HP was headache (67%), followed by cranial nerve palsy (33%), visual disturbance (21%), motor weakness (15%), limb numbness (12%), hearing loss (9%), and seizures (6%). IgG4-RD including IgG4-related HP responds to high-dose steroid ther-

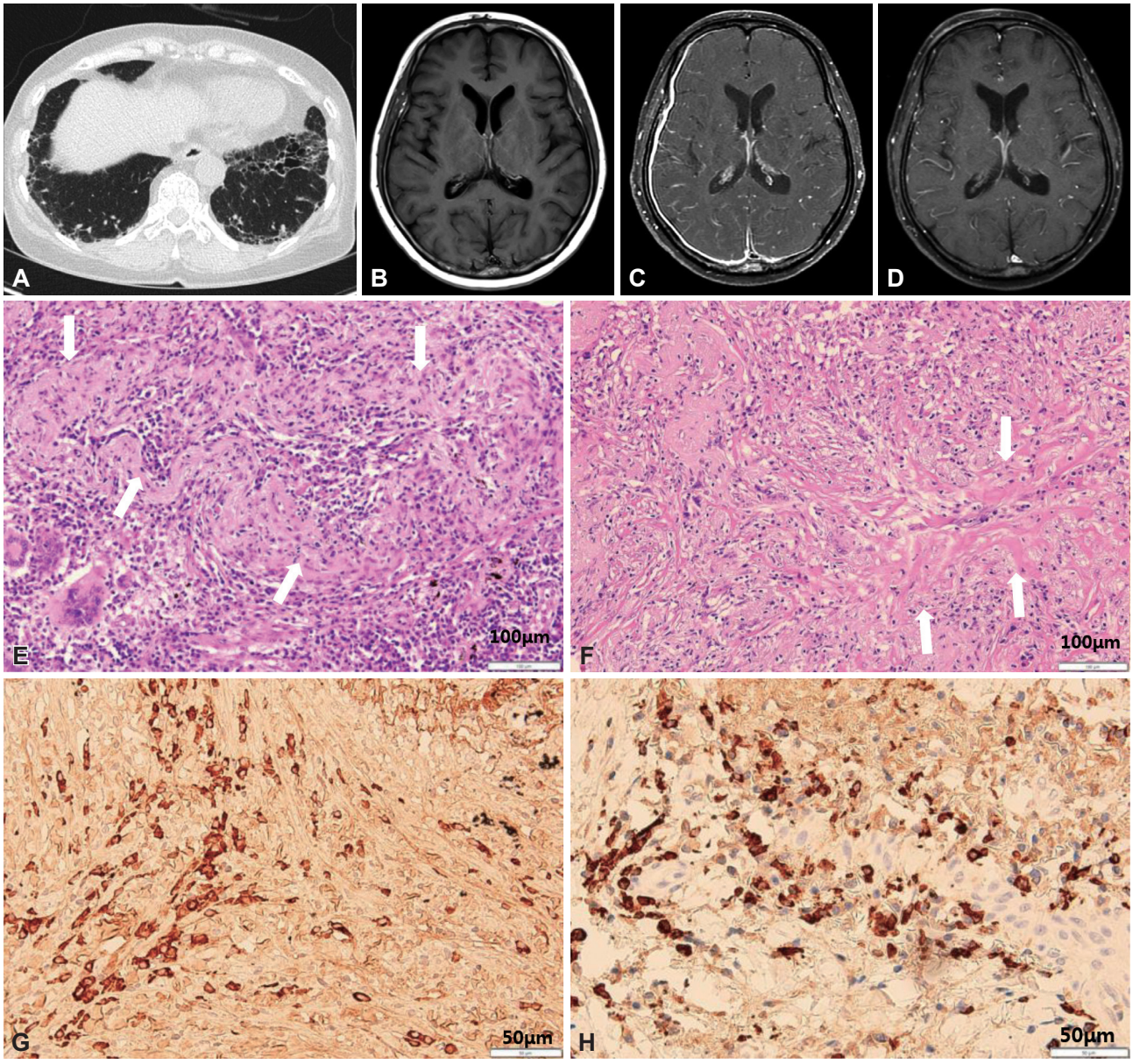

Fig. 1. Findings of chest CT, brain MRI and pathology of the patient with IgG4-related disease. A: Chest computed tomography image shows a bilateral multifocal honeycomb appearance and focal ground-glass opacities. B-D: Brain magnetic resonance imaging. B: Image obtained 5 months prior to the current presentation shows no definite abnormality. C: Axial T1-weighted enhanced image shows focal thickening and dural enhancement. D: Follow-up image after treatment shows that the previously thickened and enhanced lesion has improved. E-H: Pathological features of the surgically resected lung tissue. Obliterating venular vessels (E, arrows) and storiform fibrosis (F, arrows) are observed (hematoxylin and eosin, ×200). Comparison of an IgG-stained field (G; immunohistochemistry, ×400) and an IgG4-stained field (H; immunohistochemistry, ×400). The ratio of IgG4- to IgG-positive plasma cells exceeds 0.4. There are >20 IgG4-stained plasma cells in each high-power field (G).

apies. Immunosuppressants such as rituximab, azathioprine, and cyclosporine can be considered as secondary choices if symptoms recur or do not respond to primary steroid therapy.[6]

The present case suggests that IgG4-RD can cause HP. A recent study of IgG4-RD and idiopathic HP demonstrated that IgG4-RD may be one of the most-common etiologies of HP.[7] Furthermore, IgG4-RD can involve multiple organs, demonstrating that a definitive diagnosis can be made based on a histological examination, which is performed easily and safely in the affected organs.

Ethics Statement

This study was approved by the Institutional Review Board of the Pusan National University Hospital (IRB no. 2112-007-109), with a waiver of the need to obtained informed consents.

Availability of Data and Material

The data sets generated and analyzed during the study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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