Inflammatory Pseudotumor of the Brain Parenchyma with IgG4 Hypergammaglobulinemia

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Abstract

A 58-year-old woman with a 1-month history of right hand clumsiness and speaking difficulty was admitted to our hospital. A neurological examination revealed sensory aphasia and right hemiparesis. Her laboratory tests showed elevated serum levels of IgG and IgG4, pancytopenia, and liver dysfunction. The results of the imaging studies of her abdomen were compatible with sclerosing cholangitis. Brain MRI showed extensive signal abnormalities in the left hemisphere on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, extending from left internal capsule to the cerebral peduncle with an irregularly enhancing lesion in the left parietal lobe. A brain biopsy revealed lymphocyte and plasma cell infiltration and reactive gliosis. Most of the plasma cells were IgG positive; however, IgG4-positive plasma cells were sparsely observed. After the initiation of betamethasone treatment, her symptoms and the brain MRI abnormalities showed significant improvement. The brain biopsy results did not meet the current criteria of IgG4-related disease. This is the first reported case of a tumefactive lesion of the brain parenchyma with serum IgG4 elevation, which was responsive to steroid treatment. The accumulation of a greater number of reports on the pathological investigation of cases of possible IgG4-related disease may help to elucidate the exact role of IgG4 in IgG4-related disorders.

Key words: IgG4, inflammatory pseudotumor, brain biopsy


Introduction

IgG4-related disease is a fibroinflammatory condition that is characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate that is rich in IgG4-positive plasma cells, and often, but not always, elevated serum IgG4 concentration (1). The involvement of various organs in IgG4-related disease, including the pancreas, salivary glands, and lacrimal glands has been reported (2, 3), and comprehensive diagnostic criteria were proposed in 2011 (4). Organ-specific criteria have also been established for autoimmune pancreatitis and Mikulicz’s disease, because the symptoms of the disease vary depending on the organs that are affected (5, 6). In the central nervous system (CNS), hypophysitis and pachymeningitis are already recognized as IgG4-related diseases (7, 8). However, the organ-specific diagnostic criteria for these CNS entities have not been established.

In recent years, a relationship between IgG4-related disease and inflammatory pseudotumors (IPTs) has been suggested. IPTs are a heterogeneous group of diseases with inflammatory cell infiltration and variable fibrotic responses. A subgroup of IgG4-related IPTs has been reported in the pancreas, lung, liver, and breast (9). These IPTs are associated with elevated serum IgG4 concentrations coupled with IgG4-positive plasma cell infiltration within the lesions. IgG4-related IPTs of the central nervous system are extremely rare, and have only been reported in the dura, ven-
tricle, orbit, pituitary gland, and around a cranial nerve (10-14). IgG4-related IPTs in the brain parenchyma have not previously been reported. We herein present the first report of a tumefactive lesion in the left parietotemporal parenchyma of the brain in a patient with an elevated serum IgG4 concentration.

Case Report

A 58-year-old woman with a 1-month history of right hand clumsiness and speaking difficulty was admitted to a local hospital due to a change in her consciousness. She was drowsy and mute. Her eyes showed conjugated deviation to the right, and she had right hemiparesis. A blood gas analysis showed respiratory failure, which led to intubation and maintenance on a mechanical ventilator. Valproic acid and levetiracetam were administered. She was transferred to our hospital. Following the transfer, she was extubated after her consciousness showed improvement.

Upon admission, she was mildly debilitated, her temperature was 37.2℃, and her blood pressure was 104/46 mmHg. She was conscious and her speech was fluent with phonemic and verbal paraphasia. A neurological examination revealed right hemiparesis and her deep tendon reflexes were slightly increased on the right side. She showed a bilateral extensor planter response. There were no abnormalities in her eyes, skin, or lymph nodes. Her laboratory tests revealed mild pancytopenia, liver dysfunction, and elevated serum levels of IgG (2,260 mg/dL) and IgG4 (261 mg/dL, normal range: 4.8-105). Her serum was negative for monoclonal proteins and urinary Bence-Jones proteins. The soluble interleukin-2 receptor (sIL-2R) concentration was 750 U/mL (normal range: 145-519). There were no abnormal findings in the tests for angiotensin converting enzyme (ACE), myeloperoxidase and proteinase 3 anti-neutrophil cytoplasmic antibodies (MPO- and PR3-ANCA), anti-DNA antibodies, and anti-Sm antibodies. Bone marrow aspiration revealed normocellular marrow without abnormalities. Abdominal ultrasonography showed intrahepatic bile duct dilatation, which was prominent in the enlarged left lobe of the liver as well as mild splenomegaly with ascites. Abdominal CT and magnetic resonance cholangiopancreatography revealed diffuse irregularity and mild wall thickness of the intrahepatic bile ducts without bile duct obstructions (Fig. 1). These findings were compatible with sclerosing cholangitis. A liver biopsy was considered, but was not performed due to thrombocytopenia (5.8×10^4/μL). Chest X ray and CT images showed no significant abnormalities.

A cerebrospinal fluid (CSF) examination revealed an increased protein concentration (73 mg/dL) without pleocytosis. No infectious agents were identified by microscopy or culture. A brain MRI scan, which was obtained after the administration of gadolinium, showed an irregularly enhancing lesion in the left parietal lobe. Extensive signal abnormalities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images were seen in the left hemisphere, where they extended from the left internal capsule to the cerebral peduncle. A mass effect was present on the surrounding sulci with a midline shift (Fig. 2). Fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed intense uptake in the left parietal lesion (Fig. 3). A brain biopsy was performed. The examination of the specimen showed lymphocyte and plasma cell infiltration as well as reactive gliosis. Although most of the plasma cells were IgG positive, the IgG4 positive plasma cells were sparsely observed (Fig. 4). No gene rearrangements were detected in the T cell receptors or immunoglobulins. Anaplastic lymphoma kinase (ALK) staining was also negative. Her symptoms and brain MRI abnormalities showed significant improvement after the intravenous administration of betamethasone was initiated to relieve brain edema. As the administration of betamethasone was continued, her liver dysfunction also improved. The dose of the anti-epileptic medications were gradually decreased, but her generalized seizures recurred, starting with jerks in her right hand. An electroencephalogram revealed sharp waves in the left parieto-occipital regions. Her seizures were controlled with increased doses of anti-epileptic medications. Her steroid treatment was tapered to 15 mg/day.

Figure 1. The abdominal CT (a) and magnetic resonance cholangiopancreatography (MRCP) (b) findings. Before treatment, the images reveal diffuse irregularity and mild wall thickness of the intrahepatic bile ducts without bile duct obstructions. The arrows indicate stenosis and dilatation of the intrahepatic bile ducts.
of oral prednisolone without the exacerbation of her symptoms. She was transferred to a rehabilitation hospital. Her clinical course is shown in Fig. 5.

Discussion

We herein present the case of a patient with an elevated serum IgG4 concentration and sclerosing cholangitis, who had an inflammatory mass lesion in the brain parenchyma, that showed marked regression after the initiation of betamethasone treatment. A brain biopsy specimen revealed massive plasma cell infiltration, which was sparsely stained with IgG4 antibody.

This is the first report to show an inflammatory mass lesion in the brain parenchyma in a patient with an elevated serum IgG4 concentration. The differential diagnoses of a tumefactive lesion of the brain include vasculitis, granulomatous diseases, leukencephalopathy, and lymphoma. Although her sIL-2R level was mildly elevated, no gene rearrangements were identified and the ALK staining of the biopsied tissue was negative, FDG-PET revealed no abnormal uptake other than that in the mass lesion in brain, and bone marrow aspiration showed no signs of hematological diseases. Furthermore, there were no histopathological findings of lymphoma in the biopsied tissue of the brain. Thus, it would be impossible to diagnose this patient with lymphoma. The absence of pathological changes of vasculitis or granulomatous diseases in the biopsied specimen, MPO- and PR3-ANCA, and ACE, and specific abnormalities in the eyes or skin, were not suggestive of ANCA-associated vasculitis or sarcoidosis. The subacute onset of the patient’s symptoms and her remarkable responsiveness to the administration of steroids were not compatible with progressive multifocal leukencephalopathy, tuberculosis, or other infectious diseases. In fact, the tumefactive lesion in the patient’s brain parenchyma, her simultaneous liver dysfunction

Figure 2. The brain MRI findings. Brain MRI before treatment (a-e) and 3 months after the initiation of steroid treatment (f-j). Axial FLAIR images (a-c, f-h), diffusion-weighted images (d, i), gadolinium-enhanced T1W images (e, j). Extensive areas of high intensity are observed in the FLAIR and DW images in the white matter surrounding the left hemisphere, extending from the left internal capsule to the cerebral peduncle with partial Gd enhancement (a-e). Marked improvement is observed after steroid administration (f-j). The arrow indicates the site of brain biopsy.

Figure 3. The fluorodeoxyglucose-positron emission tomography (FDG-PET) findings. Before treatment, FDG-PET revealed intense uptake in the left parietal lesion.
(which was compatible with sclerotic cholangitis), and her IgG4 hypergammaglobulinemia, all responded well to steroid treatment. The clinical course and the results of the various above-mentioned tests led us to consider that this was a case of IgG4-related disease.

There are several reports describing IgG4-related intracranial mass lesions in the dura, ventricle, orbit, and around a cranial nerve (10-12), and a few reports in which parenchymal lesions associated with IgG4-related disease have been suggested. Kim et al. reported the parenchymal involvement of IgG4-related pachymeningitis without a histological examination of the involvement (14). Joshi et al. showed leukoencephalopathy, which was not responsive to steroid treatment, in a patient with autoimmune pancreatitis (8), however, they did not perform a brain biopsy. Ishihara et al. showed a case of mass lesions in the brain parenchyma and spinal cord that responded well to steroid treatment (15). In these cases, IgG4-related disease was suspected. However, the biopsy specimens either did not show a sufficient number of IgG4-positive plasma cells to meet the diagnostic criteria or the serum IgG4 levels were not elevated. In our case, the patient’s serum IgG4 elevation and the presence of sclerosing cholangitis as a medical comorbidity, in addition to the remarkable response to steroid treatment, all supported the diagnosis of the brain lesion as an IgG4-related disease. According to the diagnostic criteria of IgG4-related disease, which were proposed in 2011 (4), this case was compatible with a diagnosis of “possible IgG4-related disease”.

Several previous reports have shown cases in which IgG4-
related diseases of the brain were suspected but have not provided pathological evidence of the disease (15, 16). There are a few possible reasons for the sparse staining of the inflammatory mass lesion with IgG4 antibody in the present case.

First, it is possible that IgG4 infiltration is a secondary reaction, which was induced by primary inflammation. Whether or not IgG4 is an anti-inflammatory agent is controversial. The disulfide bonds between the heavy chains of the IgG4 molecule are unstable. This instability of the chains causes an intra-chain reaction in the heavy chain of the IgG4 molecules and interaction between IgG4 molecules, leading to the formation of an ineffective immune-complex (1). These characteristics suggest that IgG4 could be anti-inflammatory, rather than pro-inflammatory. Alternatively, an unknown cytokine (rather than IgG4), might be responsible for the inflammation. If this is the case, then IgG4 might not be detectable in the very active site of the lesions; rather, it would be detected on the periphery of the site as a result of a secondary reaction.

Second, there is a possibility that the biopsy specimen did not come from a site with active pathological changes due to IgG4. Although the biopsy targeted the area that showed high FDG and methionine uptake in PET-CT and gadolinium enhancement on MRI, the possibility still remains that the site of the biopsy was not appropriate.

Third, it is possible that there was an occult etiology other than IgG4-related disease in the space occupying lesion in our case, such as malignant lymphoma. There are previous reports of IgG4-related diseases in which an occult lymphoma was later revealed (17). Even though no genetic abnormalities were observed, this case should be followed up carefully due to the possibility of lymphoma.

Fourth, it is possible that brain parenchymal lesions of IgG4-related disease do not contain many IgG4-positive plasma cells. There might be a specific pathological characteristic of brain parenchymal lesions in patients with IgG4-related disease which is distinct from the pathological changes that occur in other organs with IgG4-related disease. If so, the current pathological criteria should be modified to account for the specific pathological findings that are identified in brain lesions.

We presented the case of a patient with a tumefactive lesion in the brain parenchyma with an elevated serum IgG4 concentration and, sclerosing cholangitis, which was considered to be a case of IgG4-related disease. The patient’s brain lesion, IgG4 hypergammaglobulinemia, and liver dysfunction responded well to steroid therapy. The results strongly suggest that the brain mass was an IgG4-related disease. However, IgG4-positive plasma cells were sparsely observed in the biopsied specimen, possibly due to the above-mentioned reasons. In the future, further pathological examinations in such cases would help to improve the understanding of the characteristics of possible IgG4-related diseases that do not meet the current criteria of the disease.

This is the first report describing a tumefactive lesion of the brain parenchyma in a patient with an elevated serum IgG4 concentration who successfully responded to steroid
The results of the brain biopsy did not meet the current criteria for IgG4-related disease. The accumulation of a greater number of case reports of possible IgG4-related disease, in which pathological examinations are performed might help to elucidate the pathogenesis of IgG4-related disease, as well as the exact role of IgG4 in IgG4-related disorders.

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

References