Hypertrophic Pachymeningitis and Tracheobronchial Stenosis in IgG4-related Disease: Case Presentation and Literature Review

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Abstract

Immunoglobulin G4 (IgG4)-related disease is a distinctive mass-forming disorder with frequent systemic involvement, most commonly in the pancreas, salivary glands and lacrimal glands. A few cases of dural involvement and one case of central airway stenosis have also been described. We report here a rare case of IgG4-related disease with intracranial hypertrophic pachymeningitis and irregular tracheobronchial stenosis. We review four previously reported cases of IgG4-related pachymeningitis. We currently lack international standards for the diagnosis of extrapancreatic IgG4-related disease. Based on the findings of the present case and those reported previously, we discuss the distinctive features of IgG4-related pachymeningitis.

Key words: IgG4-related disease, hypertrophic pachymeningitis, tracheobronchial stenosis, IgG4 positive plasma cells, central nervous system


Introduction

Immunoglobulin G4 (IgG4)-related disease is a recently defined disease entity that is characterized by a high serum IgG4 concentration and various complications, including Mikulicz’s disease, autoimmune pancreatitis (AIP), Riedel’s thyroiditis, sclerosing cholangitis, retroperitoneal fibrosis, tubulointerstitial nephritis (1, 2) and lung lesions, such as hilar lymphadenopathy, pseudotumour (3) and interstitial pneumonia (4). These complications suggest that IgG4-related disease encompasses a spectrum of systematic diseases. IgG4-related lesions exhibit similar histopathological findings, including abundant infiltration of IgG4+ plasma cells and high-grade sclerosis (5). However, hypophysitis is the only central nervous system (CNS) involvement reported to date (6), and few reported cases of IgG4-related disease have exhibited central airway stenosis.

Herein, we describe a patient with intracranial IgG4-related pachymeningitis and irregular tracheobronchial stenosis and compare the pathological findings before and after steroid therapy. The differential diagnosis of hypertrophic pachymeningitis and central airway stenosis, and the diagnostic criteria for IgG4-related pachymeningitis, are discussed within the context of a literature review.

Case Report

A 70-year-old man was admitted to our hospital in mid-August 2006 after the sudden appearance of hoarseness. The patient had a history of bilateral submaxillary gland swelling starting approximately 3 years earlier, which showed a tendency for further gradual enlargement. Parotid gland enlargement was also noted 1 year previously. He had become aware of dysphagia, weight loss and diminished ability to control left facial movement 3 months prior to his August 2006 admission. He had a past history of diabetes. At the time of admission, the patient was 176 cm tall and weighed 60.8 kg. His temperature was 36.7°C, pulse rate was 72 beats/min and blood pressure was 108/82 mmHg.
Routine physical examination showed bilateral enlargement of the parotid and submaxillary glands in the head and neck region. Neurological examinations revealed the following abnormalities in the cranial nerve (CN): decreased facial sensation in the left CN V2 and V3 regions supplied by CN V, left peripheral facial palsy due to the involvement of CN VII, and rightward-deviating curtain sign, dysphagia and hoarseness due to the involvement of CN IX and X. All other physical examination findings were unremarkable.

The patient’s peripheral blood cell count was normal and a biochemical examination revealed the following: total protein, 9.0 g/dL (normal range, 6.5-8.0 g/dL) [serum protein fractionation: albumin, 33.9%; α1-globulin, 3.7%; α2-globulin, 4.8%; β-γ-globulin, 57.6% (although β-γ-globulin could not be separated, no apparent M protein was detected)]; aspartate aminotransferase, 28 IU/L; alanine aminotransferase, 21 IU/L; alkaline phosphatase, 599 U/L (normal range, 124-367 U/L); amylase, 31 IU/L (normal range, 44-127 IU/L); C-reactive protein, 0.19 mg/dL (normal range, 0.00-0.30 mg/dL); and glycated hemoglobin (HbA1C), 9.1% (normal range, 4.3-5.8%). The patient’s erythrocyte sedimentation rate (ESR) was elevated to 95 mm/h (normal range, 1-7 mm/h) and the serum angiotensin-converting enzyme (ACE) level was 9.1 U/I (normal range, 7.0-25.0 U/I). Antinuclear antibody, autoantibodies to SS-A (Ro) and SS-B (La) and antineutrophil cytoplasmic antibody (ANCA) tests were negative and normal. The patient’s thyroid hormone level was within the normal range. IgG and IgG4 levels were elevated to 8,044 mg/dL and 2,600 mg/dL, respectively. Other serological tests were within the normal range. A lumbar puncture revealed pleocytosis (29.6/mm³: mononuclear, 25.6/mm³; polymorphonuclear, 4/mm³). Cytological examination of the cerebrospinal fluid showed higher than normal plasma cell numbers, but no evidence of atypia.

Brain magnetic resonance imaging (MRI) revealed diffuse hyperplasia of the supra- and infratentorial and cerebellar tentorial dura mater, indicating hypertrophic pachymeningitis (Fig. 1A). Computed tomography (CT) of the head demonstrated bilateral enlargement of the lacrimal, parotid and submaxillary glands (Fig. 1B-D). CT scans of the chest revealed irregularly demarcated nodules and slight ground-glass opacity, distributed predominantly in dorsal regions directly subjacent to the pleura of both lungs (Fig. 2A). Furthermore, soft-tissue covering appeared predominantly on the right side around vertebral bodies T9-11, accompanied by contrast enhancement (Fig. 2B). 18-Fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) showed obvious FDG accumulation coinciding with the above find-
ings. Fig. 3A shows FDG accumulations mainly in the salivary glands, bilateral hilar mediastinal lymph nodes and thoracic perivertebral soft tissues.

A detailed bronchoscopic examination of the pulmonary lesions revealed capillary dilatation in the primary bronchi, which were generally edematous and exhibited multiple elevated central lesions. Fig. 4A shows stenosis of the left primary bronchus, with elevated lesions at its bifurcation into the upper and lower trunks. To establish a diagnosis, biopsy specimens of the parotid gland and a bronchial elevated lesion were subjected to routine hematoxylin & eosin (H&E) and IgG4 antibody staining. Pathological examination revealed chronic inflammation and fibrosis in both lesions, as well as numerous plasma cell infiltrations. Immunohistochemical analysis indicated that the majority of plasma cells were IgG4+.

The patient was diagnosed with IgG4-related disease, and treatment with 50 mg/day of oral prednisolone was initiated. The patient’s general condition, including weight loss and dysphagia, improved immediately after treatment; his hoarseness improved slightly but persisted. A videofluoroscopic examination of swallowing showed a tendency for the amelioration of swallowing function, but the recurrent left laryngeal nerve palsy continued. The patient regained his usual vocal quality after about 12 months.

Approximately 1 month after the initiation of steroid therapy, a review of the results of various imaging examinations showed dramatic improvement in the following findings: the cranial MRI finding of hypertrophic pachymeningitis (Fig. 1E), the cranial CT findings of bilateral enlargement of the lacrimal, parotid and submaxillary glands (Fig. 1F-H), the chest CT findings of pulmonary nodular densities and reticular shadows of both lungs and soft tissues around the lower thoracic vertebral bodies (Fig. 2C, D)) and the 18 FDG-PET/CT findings of FDG accumulations in the bilateral hilar and mediastinal pulmonary lymph nodes (Fig. 3B). The serum IgG4 level had also decreased to 530 mg/dL. At 2 months after the start of treatment, bronchoscopic re-examination demonstrated the disappearance of bronchial elevated lesions (Fig. 4D), and pathological examination of transbronchial biopsy (TBB) specimens showed that the marked IgG4+ plasma cell infiltration had resolved almost completely (Fig. 4E, F).

This case is notable because IgG4-related pachymeningitis and torus lesions of the bronchial mucous membranes are very rare, and because we were able to compare the pathological findings before and after steroid therapy and confirm the disappearance of IgG4+ plasmacytes after treatment.

Discussion

The present case fulfills all of the following diagnostic criteria for IgG4+ Mikulicz’s disease (MD) established by the IgG4+ multiorgan lymphoproliferative syndrome (MOLPS)/MD Research Group in 2008: 1) symmetrical swelling of pairs of lacrimal, parotid, or submandibular glands persisting for more than 3 months; 2) elevated serum IgG4 (>135 mg/dL); and 3) histopathological features, including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells >50%) with typical tissue fibrosis or sclerosis. Thus, the condition in the present case represented the comprehensive concept of an IgG4-related disease (7). At present, the IgG4+ MOLPS disease entity is integrated into the diagnostic category of IgG4-related disease.

Furthermore, hypertrophic pachymeningitis, interstitial pneumonia, paravertebral soft tissue around the thoracic vertebrae, and mediastinal lymphadenopathy identified by imaging examinations such as CT, MRI, and FDG-PET/CT were all markedly ameliorated by glucocorticoid treatment. A pathological examination of the elevated lesions on the bronchial mucosa identified during the bronchoscopic examination revealed intense infiltration by IgG4+ plasma cells. Based on these findings, we considered that the patient might have an IgG4-related disease.

Additionally, the patient reported in this case study had a history of diabetes. Concurrent autoimmune pancreatitis (AIP) should be considered in patients with IgG4-related disease complicated by diabetes. However, the current patient had no jaundice and few abdominal symptoms. Furthermore, the imaging examinations, including abdominal CT, MRI, and magnetic resonance cholangiopancreatography (MRCP), did not reveal any narrowing of the main pancreatic duct or pancreatic enlargement, which are characteristic features of AIP. Based on the absence of these diagnostic criteria, AIP was considered unlikely (8). Furthermore, the serum alkaline phosphatase level was elevated, which required consideration of concurrent IgG4-related sclerosing cholangitis. However, this was also unlikely, because MRCP...
did not reveal concurrent AIP or bile duct stenosis (9).

The association of IgG4 with sclerosing diseases was first recognized in 2001, when Hamano et al (5) reported that patients with AIP had elevated serum IgG4 levels. Soon thereafter, the examination of pancreatectomy specimens from patients with AIP revealed that the pancreas and surrounding tissues had been infiltrated by increased numbers of IgG4+ plasma cells (7). Tissues from other organs affected by sclerosing cholangitis and multifocal fibrosclerosis were also found to show infiltration by IgG4+ plasma cells (8). Kamisawa et al (9, 10) proposed the concept of an IgG4-related autoimmune/sclerosing disease that encompassed these conditions. Since then, the association of IgG4 with diseases involving numerous organs has been recognized; these diseases may occur in isolation, in various combinations and in the absence of AIP.

IgG4-related diseases occur predominantly in men and are more common in the fifth and sixth decades of life. Patients often exhibit hypergammaglobulinaemia and elevated serum IgG and IgG4 levels (11, 12). Histological examination of involved tissue reveals characteristic features that include lymphoplasmacytic inflammation, fibrosis, obliterator phlebitis and increased numbers of IgG4+ plasma cells. Clinically, IgG4-related diseases often present as a mass-like lesion that can be confused with a malignancy. However, these diseases, which are believed to be autoimmune in nature, respond well to corticosteroid therapy. The recognition of IgG4-related conditions is important to avoid unnecessary surgical procedures.

Several cases of IgG4-related disease accompanied by hypophysitis as a CNS lesion have been reported (6, 13-19), but only four documented cases of IgG4-related pachymeningitis have been described to date (20-23). Fortunately, all four case reports included histopathological data.

The clinical and demographic characteristics of the five (including ours) cases of IgG4-related disease with hypertrophic pachymeningitis are shown in Table 1. This patient sample is composed of two women and three men, with an age range of 37-75 years. Sites of dural lesions were classified broadly into intracranial and spinal dura mater; the intracranial lesions tended to be distributed extensively within the cranium and the spinal lesions were also distributed extensively in the thoracic vertebral region. The mean ages of patients with spinal and intracranial pachymeningitis were 41.5 ± 4.5 and 63.3 ± 8.2 years, respectively; hence, the latter tended to be older.

Symptoms varied among the patients with intracranial lesions. For example, some presented with multiple cranial nerve palsy symptoms, such as facial dysesthesia, deafness, paresis, and ophthalmoplegia, in addition to headache and fever, as observed in the present case (case 5) and case 3. Patients also had symptoms such as anorexia, nausea, vomiting, and impaired consciousness, as in case 2. In patients with spinal lesions (cases 1 and 4), progressive bilateral weakness of the lower limbs and disturbances in touch and pain sensations were considered spinal cord compression signs and symptoms.

Serum IgG4 levels were measured in only two patients prior to the initiation of steroid therapy. In both cases, the serum IgG4 level prior to steroid therapy was >135 mg/dL. Elevated serum IgG4 levels have been defined as >135 mg/dL in the diagnostic criteria proposed recently by Masaki et al (24) for IgG4+ multiorgan lymphoproliferative syndrome (MOLPS). These authors also established a pathological di-

Figure 4. Findings of bronchoscopy and a transbronchial biopsy specimen at diagnosis and after steroid treatment (A, D) Bronchoscopic findings of bronchoscopy before and after steroid therapy. Several elevated lesions in both bronchi were associated with irregular tracheobronchial stenosis (A, arrow). Following steroid therapy, the elevated lesions and tracheobronchial stenosis disappeared (D, arrow). (B, C, E, F) Histological findings of a transbronchial biopsy specimen from a left B6h elevated bronchial lesion before and after steroid therapy. Dense infiltration of lymphocytes and plasma cells (B) was demonstrated on a Hematoxylin and Eosin (H&E) staining slide (400×) and predominantly IgG4+ plasma cells, shown immunohistochemically (C; 400×), tended to subside following steroid therapy (E, F).
agnostic criterion: infiltration of IgG4+ plasma cells into tissue (IgG4+/IgG+ plasma cells >50%) with fibrosis or sclerosis. Pathological examination of the dura mater was performed in four cases other than those described herein. The ratio of IgG4+ to IgG+ plasma cells in dura mater tissues was reported for two cases, and the majority of plasma cells were described as IgG4+ in the other two cases. Therefore, one may reasonably regard all four cases as fulfilling the diagnostic criteria for IgG4+ MOLPS. Moreover, lymphoplasmacytic infiltration, with fibrosis or sclerosis, was evident in the dura mater tissues of all four patients. Thus, the findings were not inconsistent with IgG4+ MOLPS. Although, the results of routine cerebrospinal fluid (CSF) examinations were available for only the present case and case 2. Although our case showed a significantly increased number of monocytes and increased protein level in the CSF, the case 2 results were normal.

Lindstrom et al (25) identified 10 cases of unexplained lymphoplasmacytic meningeal inflammation among the files of cases examined and/or treated at their institution during the past decade, and then evaluated specimens from those cases using immunohistochemical stains for IgG4 and IgG. The average number of IgG4+ plasma cells per HPF was calculated. The authors defined cases with >10 IgG4+ cells/HPF as IgG4-related, and thereby showed that five of the study cases met these criteria. The mean number of IgG4+ cells/HPF was 36.2 (range, 11.8-54.2), and the average percentage in the IgG4-related cases was 42% (range, 24-60%). All cases exhibited the typical histological features of IgG4-related disease, including lymphoplasmacytic inflammation, fibrosis and phlebitis. The following description of IgG4-related pachymeningitis has been published: “Due to the lack of international standards for the histological diagnosis of extra-pancreatic IgG4-related disease, we recommend the use of the consensus criteria for AIP of ≥10 IgG4-positive cells/HPF as the minimum criterion for the diagno-
sis (26, 27)” (25). Of the cases summarised in Table 1, the number of IgG4+ plasma cells in dura mater lesions has been reported for only two cases, both of which reported an excess of 10 IgG4+ cells/HPF. The authors (25) also stated that “We should emphasize, however, that clinical and laboratory data are essential for making the definitive diagnosis of IgG4-related meningeal disease. Biopsy can be used to rule out other conditions and confirm the diagnosis, so that corticosteroid therapy can be initiated”. This statement again emphasises the need for an integrated assessment.

With respect to extracranial and extraspinal involvement, three of five patients had various lesions involving the salivary glands and the lungs, whereas the other two patients had hypertrophic pachymeningitis alone; these findings indicate the importance of including IgG4 syndrome in the differential diagnosis, even for cases with hypertrophic pachymeningitis alone (Table 1).

All patients but one (Case 1 in which it was unclear whether or not steroid therapy was administered) responded rapidly to steroid therapy and showed clinical improvement (Table 1); the patients’ courses were thus not inconsistent with IgG4-related disease. In cases with spinal dura mater lesions (Cases 1 and 4), the inflammatory mass was removed by laminectomy because these patients presented with symptoms requiring acute care surgery, such as systemic paresis. The treatment of IgG4-related pachymeningitis requires the use of systemic corticosteroids. Although no controlled prospective studies of the use of corticosteroids to treat IgG4-related pachymeningitis have been conducted, clinical experience suggests that such treatment accelerates the recovery in patients with pachymeningitis. High doses (prednisolone: 1 mg/kg/day) should be used, with a gradual reduction according to the patient’s clinical response. Other disorders, such as malignant tumours and infections, cannot be ruled out in patients with a solitary spinal cord lesion, and emergency surgical intervention may be inevitable for

### Table 1. The Clinical and Demographic Characteristics of the Five Cases of IgG4-related Disease with Hypertrophic Pachymeningitis

<table>
<thead>
<tr>
<th>Case</th>
<th>Report</th>
<th>Age (years)/sex</th>
<th>Site of dural lesions</th>
<th>IgG4 (mg/dL)</th>
<th>Extent of IgG4+ plasma cell infiltration in dural lesions</th>
<th>Extracranial and extraspinal involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chan et al. [20]</td>
<td>37/M</td>
<td>Spinal dura from thoracic vertebrae T5-T10</td>
<td>N/A</td>
<td>&gt;310/HPF (IgG4+/IgG+ plasma cells &gt; 85%)</td>
<td>Bilateral submandibular gland swelling</td>
</tr>
<tr>
<td>2</td>
<td>Riku et al. [21]</td>
<td>75/M</td>
<td>Diffuse intracranial dura mater involvement, encompassing especially the tentorium cerebelli and falx cerebri in the dorsal region</td>
<td>N/A</td>
<td>The majority of plasma cells were IgG4+.</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Kosakai et al. [22]</td>
<td>54/F</td>
<td>Dura mater of the orbital apex, from the parasellar area to the middle skull base</td>
<td>251</td>
<td>Many plasma cell infiltrates (IgG4+/IgG+ plasma cells &gt; 50%)</td>
<td>Nodular lesion in the right lung, interstitial nephritis</td>
</tr>
<tr>
<td>4</td>
<td>Choi et al. [23]</td>
<td>46/F</td>
<td>Mass in the epidural space between T9 and T11</td>
<td>90*</td>
<td>&gt;20/HPF, diffuse infiltration of IgG4-bearing plasma cells</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Present case</td>
<td>70/M</td>
<td>Diffuse intracranial dura mater involvement of the supra- and infratentorial and cerebellar tentorial regions</td>
<td>2,600</td>
<td>N/A</td>
<td>Elevated lesions of the bronchial mucous membrane, interstitial pneumonia, paravertebral soft tissue around the thoracic vertebrae, bilateral salivary gland swelling, mediastinal lymphadenopathies</td>
</tr>
</tbody>
</table>

*Displayed 6 weeks after steroid therapy. F: female; M: male; N/A: not available; HPF: high-power field.
the dual purposes of diagnosis and treatment if symptoms are progressive.

Although we could not perform a histological analysis of the thickened dura mater in our patient, we believe that the findings would be identical to the pathological findings of the bronchus and parotid gland because all affected organs responded similarly to steroid therapy, and we recognised the existence of many plasma cells that are generally not evident in the cytological examination of the cerebrospinal fluid. Other systemic diseases, such as sarcoidosis and ANCA-associated vasculitis (including Wegener’s granulomatosis), can be excluded in a differential diagnosis by histological findings, high serum IgG4 levels and negative serological markers such as ANCA and ACE. For this reason, the cause of multiple cranial nerve palsy, presenting with hoarseness in the present case, was considered to be hypertrophic pachymeningitis due to IgG4-related disease.

Taniguchi et al (28), first reported interstitial pneumonia (IP) as a lesion of the respiratory system associated with AIP. According to their report, imaging disclosed ground-glass attenuation and honeycombing, and a transbronchial lung biopsy showed alveolar IgG4+ cell infiltrates. Since then, not only IP, but also a wide variety of other disease states, such as organising pneumonia (OP) (29), inflammatory pseudotumour (IPT) (30), lymphomatoid granulomatosis-like nodules (31), mediastinal lymphadenopathy (32) and involvement of pleural effusions (33), have become generally recognised to develop concurrently with AIP. Zen et al (34) summarised nine cases of IPT, showing that marked IgG4+ cell infiltration was characteristic of plasma-cell type IPT. However, only one case of the pulmonary lesion of central airway stenosis in IgG4-related disease has been reported (35). In the present case, IP, pulmonary hilar and mediastinal lymphadenopathy, and intrapulmonary nodular opacity suggestive of IPT, as well as the extremely rare finding of central airway stenosis, were documented. Dense laminar lymphocyte and plasma cell infiltrates were observed on the mucosal surfaces of elevated lesions, and the majority of the infiltrating cells proved to be IgG4+. Therefore, these lesions were considered to be attributable to IgG4-related disease. Steroid therapy dramatically improved the central airway stenosis and other abnormal lung findings, as well as the pachymeningitis and other lesions. Accordingly, the central airway stenosis and all other abnormal pulmonary manifestations found in the present case were considered to be IgG4-related lesions.

Lung hilar and mediastinal lymph-node swelling are characteristic of sarcoidosis, multicentric Castleman’s disease and malignant lymphoma; central airway stenosis has also been reported to be a clinical manifestation of sarcoidosis (36). In sarcoidosis, granulomas and serum ACE elevations are often observed (37); however, in the present case, no granulomatous change was detected in the central airway specimens and the ACE value was normal. Sato and colleagues (38) gave the following description: “Multicentric Castleman’s disease sometimes occurs with abundant IgG4-positive cells and elevated serum IgG4 levels. Therefore, these two diseases cannot be differentially diagnosed versus IgG4-related disease by immunohistochemical staining alone. Laboratory findings, especially the IL-6 [interleukin] level, CRP [C-reactive protein] level and platelet count, are important for differential diagnosis of these two diseases”.

In the case documented here, multicentric Castleman’s disease seemed unlikely because the CRP level and platelet count remained normal throughout the clinical course. The possibility of malignant lymphoma can probably be ruled out because the patient responded remarkably well to steroid therapy alone and remission was maintained solely by prednisolone administration (5 mg/day), although a histopathological differential diagnosis is difficult due to the lack of a lymph node biopsy.

Thus, IgG4-related disease should be included in the differential diagnosis of cases with hypertrophic pachymeningitis and/or elevated lesion(s) of the bronchus (even if solitary) associated with central airway stenosis. Because we currently lack international standards for the diagnosis of extra-pancreatic IgG4-related disease, we consider that the diagnosis of IgG4-related pachymeningitis may be achieved by a comprehensive assessment based on the following points: 1) elevated serum IgG4 level (>135 mg/dL), 2) infiltration of IgG4+ plasma cells into lesions (≥10 IgG4+ plasma cells/HPF) with fibrosis or sclerosis, 3) a good response to steroid therapy, 4) involvement of other IgG4-related disease such as AIP, MD, retroperitoneal fibrosis and IgG4-related sclerosing cholangitis, and 5) exclusion of other diseases that could cause hypertrophic pachymeningitis. However, at present, reports of patients with IgG4-related pachymeningitis have been restricted to Asia. Additional cases must be investigated to establish the disease concept of IgG4-related pachymeningitis and determine the long-term prognosis of this disease with treatment.

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

References


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