Case study

Hypophysitis presented as inflammatory pseudotumor in immunoglobulin G4-related systemic disease

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Summary
Immunoglobulin (Ig) G4–related systemic disease is a recently characterized entity. The best-known manifestation is pancreatitis. Other systemic involvements are also described. Three cases of this disease with hypophysyal involvement have been reported in the literature, all diagnosed clinically. We herein present the first case of IgG4-related hypophysitis diagnosed histopathologically. The patient is a 77-year-old Chinese man with a pituitary tumor. Histologic examination of the resected tumor showed hypophysitis with features of inflammatory pseudotumor. Clinical review showed history of pancreatitis and cholecystitis 4 years ago. The pancreatic biopsy and gall bladder specimens obtained previously had the same pathologic features of inflammatory pseudotumor. Immunohistochemistry highlighted abundant IgG4-positive plasma cells in all 3 specimens. Serum IgG4 level was also elevated. A diagnosis of IgG4-related systemic disease was confirmed. This is the first case of intracranial inflammatory pseudotumor shown to be associated with IgG4-related systemic disease.

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1. Introduction

Hypophysitis is a rare inflammatory disorder, which can mimic pituitary tumor clinically and radiologically [1]. The causes are heterogeneous and can be idiopathic or secondary to other systemic diseases. Hypophysitis featuring inflammatory pseudotumor (IPT) has not been described pathologically. A subgroup of IPT is associated with immunoglobulin (Ig) G4–related systemic disease. This autoimmune disease has a variety of clinical manifestations depending on which organ systems are involved [2,3], but they all share the same histopathologic features of IPT, which consist of dense lymphoplasmacytic infiltration with sclerosis and phlebitis [4]. One specific feature is the presence of abundant IgG4-secreting plasma cells in the infiltrates. The serum IgG4 level during the active phase of the disease is also elevated. IgG4–related systemic disease with hypophysitis has been described, but the cases were all diagnosed clinically [5-7]. We describe here the first case of pathologically proven IgG4-related hypophysitis with features of IPT. This is also the first reported case of intracranial IPT associated with this systemic autoimmune disease.

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2. Case report

A 77-year-old Chinese man presented with blurred vision for several months. Physical examination showed a pale optic disc. Computer tomographic scan and magnetic resonance imaging showed a pituitary tumor (1 × 1 × 0.8 cm) with suprasellar extension and optic nerve compression. Laboratory tests revealed hypogonadism, with a low testosterone level (1.48 nmol/L; reference range, 12.00-34.00 nmol/L), but other pituitary hormones were within the normal range. Transphenoidal tumor resection was performed, and the visual symptoms subsided after surgery. The patient was then prescribed hydrocortisone and thyroxine replacement therapy. Pathologic examination showed hypophysitis with features of IPT. Clinical review showed a medical history of obstructive jaundice 4 years before this episode. Computer tomographic imaging showed a prominent pancreatic uncinate process with suspected distal common bile duct and ampulla of Vater tumor. The tumor was biopsied, and pancreatitis was diagnosed at that time. Choledochojunostomy and cholecystectomy were performed. Retrospective examination of the pancreatic biopsy and cholecystectomy specimen showed the same pathologic features of IPT. The serum IgG and IgG4 level was measured using blood preserved before steroid replacement therapy. The IgG4 serum level was elevated (720 mg/dL; reference range, 0-291 mg/dL), and the IgG serum level was normal (13.3 g/L; reference range, 7.51-15.55 g/L), with a ratio of IgG4 to IgG of 0.54. The diagnosis of IgG4-related systemic disease was confirmed.

3. Pathologic findings

Two pieces of tan-colored tissue specimens, each measuring 4 to 5 mm, were received for pathologic examination. One was submitted for frozen section, and the other was submitted for permanent section. Microscopic examination showed prominent plasmacytic infiltration with a sprinkle of lymphocytes and an area of sclerosis (Fig. 1A and C). The plasma cells showed no atypia, and there was no granulomatous inflammation, significant histiocytic infiltration, or

Fig. 1  Histopathology of the pituitary tumor showed dense plasmacytic infiltration (A), residual nests of adenohypophyseal cells (B), and area of sclerosis (C). Immunohistochemistry for IgG4 highlighted numerous positive plasma cells (D).
phlebitis evident. Residual pituitary tissue was noted (Fig. 1B). Immunohistochemistry for the κ (Dako Cytomation, Glostrup, Denmark; dilution, 1:120000) and λ light chains (Dako; dilution, 1:80000) showed no restriction, signifying polytypic plasma cells. Grocott silver stain for fungal organisms and polymerase chain reaction for mycobacterial tuberculosis were negative. Retrospective pathologic examination of the pancreatic biopsy showed periductal, lobular, and septa plasmacytic and lymphocytic infiltration. Sclerosis was evident, and the gall bladder showed similar marked inflammatory infiltration. Immunohistochemistry for IgG4 (Zymed, San Francisco, CA; dilution, 1:1000) showed abundant positive plasma cells in the pituitary (Fig. 1D), pancreatic, and gall bladder specimens.

4. Discussion

IgG4-related systemic disease has emerged as a distinct clinicopathologic entity recently [2,3]. The history of this systemic disease started with autoimmune pancreatitis (AIP), which was described decades ago [4], but it was not until 2001 that an association was first reported between the serum level of IgG4 and AIP [8]. Histologically, AIP is characterized by a prominent lymphoplasmacytic infiltration that can be ductocentric and lobulocentric in distribution and associated with sclerosis and phlebitis [2]. The predominant plasma cell in the infiltrate is of IgG4 immunophenotype. It is now recognized that this is a systemic autoimmune disease, which can recur and affect multiple organ systems, including the salivary gland, breast, lung, liver, gall bladder, bile duct, kidney, and retroperitoneum [2,3,9]. The pituitary gland is a rare site of involvement. Three previous cases of hypophysitis have been reported in the English literature [5-7]. They all presented with hypopituitarism, were associated with other systemic involvement (Table 1), and were diagnosed by imaging and clinical correlation. The current case is the first report with histopathologic correlation.

The present case has typical demographic and clinical features of IgG4-related systemic disease, namely, an adult male with pseudotumor affecting multiple organs. The patient presented with both hypopituitarism and a tumor producing visual impairment. The histologic features consisted of dense plasmacytic infiltration with an area of sclerosis. Phlebitis was rather inconspicuous. The features are those of IPT, which is a heterogeneous group of diseases [10]. IPT has different names, such as plasma cell granuloma and inflammatory myofibroblastic tumor. Central nervous system IPTs have been described. Jeon et al [11] reviewed the largest series of intracranial IPT, but no attempt has been made to investigate the possible linkage with IgG4-related systemic disease and characterize the plasma cell immunophenotype. Other isolated cases of IPT involving the pituitary gland have been reported [12,13]. It would be interesting to review the clinical features and examine the plasma cell immunophenotype of those cases. A finding of intracranial IPT should prompt the search for the features of this systemic autoimmune disease.

The other differential diagnoses of pituitary IPT include plasmacytoma involving the pituitary gland and various other causes of hypophysitis. Plasmacytoma can present as a sellar mass [14]. The pituitary gland is densely infiltrated by atypical plasma cells, and immunohistochemistry shows light-chain restriction. The diagnosis can be confirmed by demonstrating clonal rearrangement of the immunoglobulin gene. Hypophysitis is a heterogeneous group of diseases that can be primary or secondary. Primary hypophysitis is composed of 3 clinicopathologic entities: lymphocytic, granulomatous, and xanthomatous hypophysitis [1]. Lymphocytic hypophysitis is a well-characterized entity classically affecting adult females during late pregnancy or the

<table>
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<tr>
<th>Case</th>
<th>Reference</th>
<th>Clinical features and laboratory test</th>
<th>Outcome</th>
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| 1    | Van der Vliet et al [6] | 66/F  
Hypophysitis with central hypothyroidism; sellar mass on imaging  
Also involved submandibular gland, lung, pancreas, and retroperitoneum  
Elevated serum IgG4  
No surgical biopsy done | Responded to steroid treatment |
| 2    | Tanabe et al [5] | 71/M  
Hypophysitis with panhypopituitarism; pituitary swelling on imaging  
Also involved submandibular gland, mediastinum, and retroperitoneum  
Elevated serum IgG4  
Histopathologic examination of submandibular gland and retroperitoneal biopsy showed characteristics | Responded to steroid treatment |
| 3    | Yamamoto et al [7] | 70/M  
Hypophysitis with hypopituitarism; swelling of pituitary stalk on imaging  
Also involved lacrimal and submandibular glands  
Elevated serum IgG4  
Histopathologic examination of submandibular gland biopsy showed characteristics | Responded to steroid treatment |
early postpartum period. Patients usually present with hypopituitarism, and there is predominant lymphocytic infiltration, forming follicles with a minor population of plasma cells. Granulomatous and xanthomatous hypophysitis can be readily differentiated from IPT. Infectious causes of secondary hypophysitis are rare today. Other systemic secondary causes include neurosarcoïdosis, Wegener’s granulomatosis, and Langerhan cell histiocytosis. Rosai-Dorfman disease (RD) can present in the sellar region, forming a tumor mass, and the plasmacytic infiltration is admixed with large foamy histiocytes [15]. These Langerhan cells are characterized by lymphophagocytosis and are positive for S-100 protein.

Correct diagnosis of IgG4-related systemic disease has important prognostic and therapeutic implications. This disease can recur and affect different organ systems. On the other hand, it is treatable and extremely sensitive to steroid therapy. The tumefactive nature means that the patient may undergo invasive diagnostic and treatment procedures. A definitive diagnosis will spare the patient unnecessary invasive clinical procedures and therapeutic interventions.

In conclusion, we have reported a case of hypophysitis in IgG4-related systemic disease featuring pituitary IPT pathologically. Hypophysitis is a rare manifestation. Intracranial IPT is heterogeneous, and IgG4-related systemic disease should be considered in the differential diagnosis.

References