REVIEW

Pituitary and Stalk Lesions (Infundibulo-hypophysitis) Associated with Immunoglobulin G4-related Systemic Disease: an Emerging Clinical Entity

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Abstract. Inflammatory lesions of the pituitary gland are rarely encountered. Recently, the concept of immunoglobulin G4 (IgG4)-related systemic disease was proposed in Japan, and more than 20 cases have been reported as possibly associated with infundibulo-hypophysitis since 2000. We herein review such case reports in the published literature and in the abstracts of scientific meetings. Almost all cases involved middle-aged to elderly men presenting with various degrees of hypopituitarism and diabetes insipidus and demonstrating a thickened pituitary stalk and/or pituitary mass. These structures shrank remarkably in response to glucocorticoid therapy, even in a lower dose range similar to that prescribed as a replacement for adrenocortical insufficiency. Some of the anterior pituitary insufficiencies were also resolved by glucocorticoid administration. The presence of IgG4-related systemic disease and an elevated serum IgG4 level before glucocorticoid therapy were the main clues to a correct diagnosis of IgG4-related infundibulo-hypophysitis. Autoimmunity is suggested but not yet established to play a role in the pathogenesis for IgG4-related systemic disease. The fact that hypertrophic pachymeningitis and para-sinusitis accompanied some cases suggested that both sellar and parasellar structures are involved in the chronic inflammation. We therefore classify this disorder not as a variant form of primary autoimmune hypophysitis but as a secondary form of infundibulo-hypophysitis associated with IgG4-related systemic disease.

Key words: Secondary hypophysitis, Immunoglobulin G4, Multifocal fibrosclerosis, Hypopituitarism, Diabetes insipidus

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INFLAMMATORY LESIONS of the pituitary and pituitary stalk are rarely encountered. However, due to the availability of magnetic resonance (MR) imaging, so-called lymphocytic hypophysitis has been reported more frequently in Japan than in Western countries [1]. Infundibulo-hypophysitis may be categorized into three groups according to the involved tissues: adenohypophysitis, infundibulo-neurohypophysitis and panhypophysitis [2]. An autoimmune mechanism is thought to be involved in adenohypo-

physitis and infundibulo-hypophysitis. However, panhypophysitis may be heterogeneous; that is, it may be primary or secondary as a direct result of systemic infectious or inflammatory processes or as a result of local processes such as a ruptured Rathke cleft cyst, craniopharyngioma, or germinoma. Chronic inflammation of parasellar structures such as seen in hypertrophic pachymeningitis or Tolosa-Hunt syndrome may spread into the pituitary gland. Rare cases associated with multifocal fibrosclerosis have been reported [3, 4].

Recently, the new concept of immunoglobulin G4 (IgG4)-related systemic disease was proposed from the close observation of autoimmune pancreatitis (AIP) and lymphoproliferative diseases [5, 6]. Involvement of the pituitary gland may be recognized as a possible extra-pancreatic manifestation of AIP. More than 20 cases have been reported since 2000. In the present

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article, we review these case reports and summarize the clinical features of IgG4-related infundibulo-hypophysitis. We also discuss the relationship to autoimmune hypophysitis and the possible pathogenesis of IgG-4 related disease.

1. IgG4-related systemic disease

IgG4-related sclerosing disease is a systemic disease characterized by extensive infiltration of IgG4-positive plasma cells and T-lymphocyte into various organs [5]. Clinical manifestations are apparent in the pancreas, bile duct, gallbladder, salivary gland, retroperitoneum, kidney, lung, and prostate, in which organ tissue fibrosis with occlusive phlebitis is pathologically induced. Most IgG4-related sclerosing diseases have been found to be associated with AIP, but IgG4-related diseases without pancreatic involvement have been reported. Some inflammatory pseudotumors may be involved in this disease. The disease occurs predominantly in elder men, is frequently associated with lymph node swelling, and responds well to glucocorticoid therapy. Serum IgG4 levels and immunostaining with anti-IgG4 antibody are useful for making a diagnosis.

Multifocal fibrosclerosis is an uncommon fibroproliferative systemic disorder with multiple manifestations, including sclerosing cholangitis, salivary gland fibrosis, retroperitoneal fibrosis, Riedel's thyroiditis, and fibrotic orbital pseudotumor [7]. As the histopathological findings of these disorders are similar - i.e., fibrotic changes with lymphoplasmacytic infiltration and occasional phlebitis - it is suggested that they are all interrelated and probably different manifestations of a common disorder of fibroblastic proliferation. The histopathology of the extrapancreatic lesions associated with AIP strongly suggests that multifocal fibrosclerosis is an IgG4-related sclerosing disease [8].

2. Pituitary and stalk lesions (infundibulo-hypophysitis) associated with IgG4-related systemic disease

Chronic inflammatory diseases of the pituitary gland, inflammatory pseudotumor [9] or plasma cell granuloma [10] have been described, and several cases of pituitary lesion associated with retroperitoneal fibrosis have been reported [3, 4]. More recently, a new

disease entity consisting of hypophysitis associated with IgG4-related systemic disease has been described [11-14]. We surveyed the case reports involving this entity both in the published literature and in the abstracts of scientific meetings since 2000. Inclusion criteria for the survey were the presence of pituitary and stalk lesions associated with at least one IgG4-related systemic disease or multifocal fibrosclerosis, and/or the biopsy-proven inflammatory pseudotumor of the pituitary mass infiltrated with IgG4-positive plasma cells.

There were 22 such cases (Table 1: [11-34]). Twenty-one cases were male and only one was female. The age distribution was as followed; 2 patients were in their 40s, 4 in their 50s, 8 in their 60s, and 8 in their 70s. The median age was 64 years. Whether the observed extreme male predominance is the characteristics for the IgG4-related hypophysitis or not remains to be determined, since the male: female ratio of AIP was reported as 2.77:1 [35].

1) Clinical manifestations

Symptoms related to the hypothalamic-hypophyseal system were general malaise (11 cases), headache (6 cases), visual disturbances including impaired eye movement (6 cases), fever (5 cases), polyuria (6 cases), appetite loss (4 cases), weight loss (4 cases), and decreased libido (3 cases). General malaise, loss of appetite and weight loss was closely related with ACTH deficiency.

2) Pituitary function

Various degrees of anterior pituitary hormone deficiency were observed in 19 cases, and central diabetes insipidus was observed in 12 cases. Eleven cases had both hypopituitarism and diabetes insipidus. Masked diabetes insipidus was diagnosed in 3 cases. Diabetes insipidus may have preceded the development of hypopituitarism in 4 cases.

Isolated hypogonadism, isolated central hypothyroidism, and isolated ACTH deficiency were observed in 2 patients, one patient and one patient, respectively. Another 15 cases had combined anterior pituitary hormone deficiencies. Decreased secretion of LH/FSH (15 cases), ACTH (14 cases), TSH (12 cases), GH (8 cases) were documented. It is unclear whether specific combinations of pituitary hormone deficiencies may

Table 1. Reported cases of pituitary and stalk lesion associated with IgG4-related systemic diseases (since 2000)

Case	Age/Sex	Pituitary function DI Hypopituitarism	MRI	IgG/IgG4 (mg/dL)	IgG4-related lesions	Ref.	Report
1	53/M	DI Hypopituitarism	Stalk	—/—	Dura Orbita Parasinus Lung	15	Kishimoto (2000)
2	43/M	DI Hypopituitarism	Stalk	—/—	Retroperitoneum	16	Braun (2001)
3	66/M	DI Hypopituitarism	Stalk	6060/—	Mikulicz Pelvis Lung Parasinus	17	Sumitani (2003)
4	42/M	Hypopituitarism	Stalk	1400/—	Dura Retroperitoneum	18	Fukuda (2003)
5	65/M	DI Hypopituitarism	Stalk Pituitary mass	3277/—	Mikulicz Dura	19	Katabami (2003)
6	66/F	Hypopituitarism	Pituitary mass	—/485(20-250)	Pancreas Retroperitoneum Salivary Lung	20	van der Vliet (2004)
7	71/M	Hypopituitarism	Stalk Pituitary mass	3015/405	Salivary Retroperitoneum Lymph node	11	Tanabe (2006)
8	70/M	Hypopituitarism	Stalk	—/2220	Mikulicz	12	Yamamoto (2006)
9	75/M	Hypopituitarism	Stalk - Pituitary mass	6040/—	Pancreas Eye Lung	13	Taniguchi (2006)
10*	62/M	Hypopituitarism	Pituitary mass	1330/720 (0-291)	Pancreas Gallbladder	14	Wong (2007)
11	61/M	DI Hypopituitarism	Stalk	—/—	Peritoneum Cholangitis	21	Sommerfield (2008)
12	73/M	Hypothalamic dysfunction	Stalk	1581/22 (4.8-105)	Retroperitoneum Pancreas	22	Miyoshi (2008)
13	55/M	DI Hypopituitarism	Stalk	2701/1860	Parasinus Retroperitoneum	23, 24	Isaka (2008)
14	62/M	DI Hypopituitarism	Stalk	1990/292 (<135)	Pancreas Lung Lymph node Retroperitoneum	25	Tsuboi (2008)
15*	68/M	—	Stalk - Pituitary mass	—/elevated	Kidney Lymph node	26	Yamamoto (2008)
16*	77/M	DI Hypopituitarism	Stalk	2370/229	Dura	27, 28	Uehara(2008) Tsukada(2009)
17*	59/M	DI Hypopituitarism	Stalk - Pituitary mass	1515*/111*	Pancreas Orbita Eye Lymph node Retroperitoneum Lung Kidney Thyroid	29	Taji (2009)
18	70/M	DI Hypopituitarism	Stalk - Pituitary mass	—/949	Liver Mikulicz Lung	30	Ando (2009)
19	58/M	DI	Stalk	—/466*	Retroperitoneum Dura	31	Ueda (2009)
20	77/M	DI Hypopituitarism	Stalk Pituitary mass	—/1950	Pancreas Liver Lymph node Salivary	32	Takeuchi (2009)
21*	72/M	Hypopituitarism	Stalk - Pituitary mass	—/—	— (Pituitary alone)	33	Mizutani (2009)
22	64/M	Hypopituitarism	—	—/—	Retroperitoneum Lung Mikulicz	34	Yoneda (2009)

case*: case with pituitary biopsy

DI: diabetes insipidus

Stalk: stalk thickening or mass on the stalk; Stalk - Pituitary mass: united large mass formation in the pituitary and stalk

—: not described

IgG/IgG4*: under steroid therapy, (): reference ranges

Fig. 1. MR imaging of the pituitary in a patient with IgG4-related infundibulo-hypophysitis [33]. T1-weighted gadolinium enhanced imaging (A: coronal section, B: sagittal sections).

exist, since provocative tests to examine the pituitary hormone reserve were not used in every patient. Three cases with hyperprolactinemia were reported. Altered hypothalamic regulation of pituitary hormone secretion was demonstrated in one case [22].

3) MR imaging of the pituitary

A thickened pituitary stalk or mass formation on the stalk was observed in 18 cases, and some of the thickening took place at the level of infundibulum or the proximal end of the stalk. On the other hand, a swelling of the pituitary gland or mass formation in the pituitary was present in 10 cases. Among these 10 cases, 2 showed a pituitary mass alone, and 3 showed both a thickened stalk and pituitary mass occurring simultaneously. The other 5 cases showed a united large mass formation involving both the pituitary and stalk (Fig. 1).

The “bright” signal seen in the posterior portion of the pituitary on T1-weighted imaging was absent in the cases involving central diabetes insipidus and in several cases without clinical diabetes insipidus.

Hypertrophic pachymeningitis was found in 5 patients and orbital lesion including pseudotumor formation was in 2 cases. Para-sinusitis was observed in 3 cases.

4) Laboratory findings

Seven of the 9 patients who were tested for C-reactive protein were found to be positive. Elevated levels of serum immunoglobulin G and serum IgG4 were observed in 7 of 9 cases and in 12 of 13 cases in

which they were assessed, respectively. A normal serum level of IgG4 was observed only in patients receiving steroid therapy [29]. Serum levels of IgG4 promptly decreased to reference range after initiation of steroid therapy [21]. Clinical manifestations and laboratory findings did not seem to differ between the cases with and without IgG4 measurement.

In the two cases in which FDG-PET was performed, uptake was observed in both the pituitary gland and other involved lesions [11, 23].

5) Histopathology of pituitary lesion

Pituitary biopsy was performed in only 5 cases via a transsphenoidal approach or transcranial approach. The inflammatory pseudotumor of the pituitary was densely infiltrated with both lymphocyte and plasma cells and fibrous changes were demonstrated in all cases. The plasma cells were stained positive by IgG4 immunostaining (Fig. 2).

6) Associated IgG4-related systemic disease

Various IgG4-related systemic diseases are associated with pituitary and stalk lesion. Among these, retroperitoneal fibrosis was the most prevalent disease (n=10), followed by Mikulicz disease and salivary gland lesions (n=8), pulmonary lesions (n=8), pancreatic lesion (n=6), and lymph node swelling (n=5).

Systemic diseases preceded the pituitary lesions in 11 patients, the two occurred simultaneously in 8 cases, and the pituitary lesion preceded the systemic disease in 2 cases. An isolated pituitary lesion not as-

Fig. 2. Histopathology of the pituitary gland in a patient with IgG4-related infundibulo-hypophysitis [33]. A: HE staining, B: IgG4 immunostaining.

Table 2. Clinical characteristics of pituitary and stalk lesions associated with IgG4-related systemic diseases.

1. Preponderance of the disease amongst elderly males
2. Presented with various degrees of hypopituitarism and diabetes insipidus
3. MRI demonstrated a thickened pituitary stalk and/or pituitary mass
4. Thickened stalk and pituitary mass shrank in response to glucocorticoid therapy
5. Some of the anterior pituitary insufficiencies were resolved by glucocorticoid therapy
6. Presence of IgG4-related systemic diseases
7. Elevated serum IgG4 levels before glucocorticoid therapy
8. Some cases accompanied with pachymeningitis or para-sinusitis, suggesting that both sellar and parasellar structures were involved in the chronic inflammation

sociated with any systemic IgG-4 related disease was described in one patient [33].

7) *Effect of glucocorticoid therapy*

Various kinds and doses of glucocorticoid were used for replacing adrenocortical insufficiencies or actively treating the pituitary mass and/or accompanying hypertrophic pachymeningitis, AIP or other lesions. Some of the anterior pituitary insufficiencies were resolved by glucocorticoid even in a lower dose range similar to that prescribed as a replacement for adrenocortical insufficiency. In most cases of diabetes insipidus, glucocorticoid therapy did not lead to remission. As for the pituitary mass and the stalk thickening, almost all lesions shrank during glucocorticoid therapy. However, several cases showed a relapse of the pituitary mass when the doses of glucocorticoid were

decreased. Serum levels of IgG and IgG4 promptly decreased to normal ranges after glucocorticoid therapy.

8) *Summary of clinical features*

Table 2 provides a summary of the clinical features of the IgG4-related pituitary and stalk lesion. Almost all cases involved middle-aged to elderly men presenting with various degrees of hypopituitarism and diabetes insipidus and demonstrating a thickened pituitary stalk and/or pituitary mass. These structures shrank remarkably in response to glucocorticoid therapy. Some of the anterior pituitary insufficiencies were also resolved by glucocorticoid administration. The presence of IgG4-related systemic diseases and the elevated serum IgG4 levels before glucocorticoid therapy were the main clues to a correct diagnosis of IgG4-related infundibulo-hypophysitis. Several cases were

Fig. 3. Involvement of pituitary gland with hypophysitis (conceptual figures).
Shaded area represents the involved tissues.

accompanied with pachymeningitis and para-sinusitis, suggesting that both sellar and parasellar structures were involved in chronic inflammation.

3. Relationship to other forms of hypophysitis (Fig.3)

Primary hypophysitis is of unknown etiology and is classified on a histopathological basis as lymphocytic, granulomatous, or xanthogranulomatous hypophysitis [36-38], whereas secondary hypophysitis occurs as a direct result of systemic infectious or inflammatory processes or as a result of local processes such as a ruptured Rathke cleft cyst, craniopharyngioma, adenoma, or germinoma.

Primary hypophysitis may also be categorized into adenohypophysitis, infundibulo-neurohypophysitis, and panhypophysitis based on the tissues involved. Adenohypophysitis typically affects females during the puerperal period and presents a pituitary mass and hypopituitarism, whereas patients with infundibulo-neurohypophysitis typically show diabetes insipidus with a posterior pituitary mass or thickened pituitary stalk.

Both entities are regarded as autoimmune-mediated. On the other hand, panhypophysitis involves both lobes of the pituitary gland, which has a different developmental origin, suggesting that it may not arise solely from an autoimmune mechanism. Inflammation of the anterior or posterior lobe of the pituitary may spread out over the whole pituitary [37]. There are several case reports of panhypophysitis showing an aggressive behavior and invading into the cavernous sinus or hypothalamus and causing cranial nerve paralyses [39]. Whether these types of lymphocytic hypophysitis belong to the same category as other types of hypophysitis is currently unknown.

Chronic parasellar inflammation such as those in hypertrophic pachymeningitis, cavernous sinusitis or Tolosa-Hunt syndrome have been reported to be accompanied by hypopituitarism and/or diabetes insipidus [40]. We have previously reported three such cases but did not measure the subjects' IgG or IgG4 levels [41]. Both sellar and parasellar structures were involved in the chronic inflammation in the cases of IgG4-related hypophysitis with pachymeningitis, para-sinusitis, and/or orbital pseudotumor. The previously reported cases of pituitary lesion associated with

multifocal fibrosclerosis were considered to belong the same category as the currently reviewed cases of IgG4-related pituitary diseases.

Cases of isolated pituitary lesions or cases in which onset of diabetes insipidus preceded the other lesions by several years present a challenge for diagnosis. It is recommended that the measurement of serum IgG4 levels be included in the panel during the initial workup for investigating hypopituitarism and/or diabetes insipidus.

4. Pathogenesis

The pathogenesis of IgG4-related systemic disease is currently under intensive investigation [5]. Elevated serum IgG4 and dense infiltration of IgG4-positive plasma cells in various organs suggest that IgG4 plays a major role in the pathogenesis, although the trigger for IgG4 elevation has not been clearly established.

There are increased numbers of activated CD4+ and CD8+ T cells bearing HLA-DR in the pancreas of AIP patients. An inhibitory molecule, cytotoxic T-lymphocyte antigen 4 (CTLA-4), which is expressed on activated memory T cells and CD4+CD25+ regulatory T cells (Tregs), acts as a negative regulator of T cell responses [42]. The soluble isoform of CTLA-4 is reported to be elevated in patients with AIP, enhancing immune responses by blocking the interaction of CD80 on antigen-presenting cells and CTLA-4 on T cells. Tregs are thought to be associated with various autoimmune diseases [43]. Miyoshi *et al.* [44] have observed that the number of circulating naïve Tregs is decreased in the peripheral blood of the patients with AIP, whereas the number of memory Tregs is significantly increased. Prominent infiltration of Tregs has been observed in the liver of patients with sclerosing cholangitis. These findings suggest that regulatory functions of T cells, such as CTLA-4 and Tregs, are involved in the development and pathophysiology of AIP [45].

Given the preponderance of the disease amongst elderly males and the dramatic responses to oral steroid therapy, the pathogenesis may not involve an autoimmune mechanism but rather other mechanisms, such as an allergic reaction. Zen *et al.* [46] have reported that the expression of T helper 2 (Th2) cytokines and regulatory cytokines (IL-10 and transforming growth factor-beta) was up-regulated in the affected tissues of patients with IgG4-related pancreatitis and cholangitis. They have suggested that the predominant Th2

and regulatory immune reactions in this disease reflect an allergic mechanism.

In conjunction to the above mentioned pathogenesis of IgG4-related systemic disease, we should cite two important observations regarding autoimmune hypophysitis. Mirocha *et al.* [47] have observed two separate entities of primary hypophysitis; one entity involves an autoimmune process with Th 17 cell dominance and lack of Tregs, and the other entity involves a process in which Tregs seem to control the immune response, which may not be self- but foreign-targeted. Another important observation is that of drug-induced hypophysitis. Inhibitory antibodies directed against CTLA-4 cause disruption of immune tolerance to antigens on cancer cells and were associated with anti-tumor activity in melanoma and renal cell carcinoma [48]. Anti-CTLA-4 antibody therapy has been associated with autoimmune hypophysitis, and high dose glucocorticoid treatment resulted in markedly improved symptoms and partial recovery of hypopituitarism [49].

5. Summary and conclusion

We have reviewed case reports of possible infundibulo-hypophysitis associated with IgG4-related systemic diseases and described their common clinical features. We consider this disorder not as a variant form of primary autoimmune hypophysitis but as a secondary form of hypophysitis associated with IgG4-related systemic disease. Only 5 cases demonstrated histological proof of inflammatory pseudotumor on pituitary biopsy. Therefore, we should accumulate similar cases of suspected hypophysitis by measuring serum IgG4 levels and try to investigate their histopathology in order to clarify the possible immune- or allergy-mediated pathogenesis.

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