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Atypical IgG4 related hypophysitis revealed by submandibular sialadenitis: a case report

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Objective. IgG4-related disease is a fibro-inflammatory multisystemic condition with lesions mimicking tumors. Involvement of the hypophysis is rare and the first case of IgG4-related hypophysitis was described in 2004. Typically, it is revealed by sellar mass effects, hypopituitarism, and diabetes insipidus. In the present paper, we report a case of IgG4-related hypophysitis revealed by submandibular sialadenitis.

Case Report. The subject was a 52-year-old patient presented with swelling of the submandibular gland. His complaints were decreased libido, anorexia, and weight loss for three months. Hormonal assessment found mild hyperprolactinemia, hypogonadotropic hypogonadism, and central hypothyroidism. Pituitary magnetic resonance imaging showed heterogeneous enlargement of the pituitary gland with diffuse gadolinium enhancement. The submandibular gland biopsy revealed submandibular sialadenitis with positive immunohistochemistry to IgG4. Diagnosis of IgG4-related hypophysitis was made based on Leporati criteria 2 and 3. Glucocorticoid therapy was prescribed for this patient, but without improvement of the pituitary function. In fact, the effectiveness of steroid therapy on the pituitary swelling is proven and already represents the fifth diagnostic criterion of Leporati. However, the improvement of the pituitary functions is uncertain.

Conclusion. The present case illustrates an atypical presentation of IgG4-related hypophysitis without tumor syndrome or diabetes insipidus. Continuous monitoring of the pituitary function is needed during the long-term follow up given that improvement of the hormonal deficiencies is uncertain.

Keywords: IgG4-related disease (IgG4-RD), IgG4-related hypophysitis (IgG4-RH), hypopituitarism, diabetes insipidus

IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition with tumor-like lesions of unknown etiology, but characteristic histopathological features (Nambiar and Oliver 2023). Dysregulated immunity with expansion of $CD4^+$ cytotoxic T lymphocytes is a key hallmark of the disease (Wallace et al. 2024). Environmental exposures and genetic factors increase the risk for IgG4-RD.

The disease causes organ enlargement that mimics a tumor and can affect major salivary and lacrimal glands, orbits, pancreas, bile ducts, retroperitoneum, lungs, kidneys, and aorta (Perugino and Stone 2020). In 2019, a multidisciplinary group assembled by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) has developed a set of classification criteria (2019

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ACR/EULAR classification criteria for IgG4-RD) that help to better define the disease (Wallace et al. 2024). Endocrine manifestations are rare and mainly concern pancreas (diabetes mellitus secondary to type 1 autoimmune pancreatitis), thyroid, and hypophysis (Bashier et al. 2015).

IgG4-related hypophysitis (IgG4-RH) is an uncommon manifestation of IgG4-RD and represents a rare etiology of hypophysitis less than 5% of cases. It may either be isolated or a part of multisystemic disease (Leporati et al. 2011). The majority of the cases reported involved middle-aged or elderly men presenting with various degrees of hypopituitarism and diabetes insipidus (Bashier et al. 2015).

The management of IgG4-RH include glucocorticoid therapy as the first choice of treatment and hormone replacement therapy for pituitary deficiencies (Lojou et al. 2020). The efficacy of steroid therapy on pituitary swelling is widely reported, but the effect on pituitary functions is still controversial (Lojou et al. 2020; Nishi et al. 2021).

In this paper, we report the case of a male patient with IgG4-RH revealed by swelling of the salivary glands.

Case presentation

A 52-year-old male was admitted to our Department of Endocrinology and Internal Medicine with left submandibular gland swelling. He had a history of the type 2 diabetes mellitus treated by oral antidiabetic drugs. He reported anorexia with 7 kg weight loss, dyspnea, and decreased libido for three months. However, there was neither polyuria-polydipsia syndrome nor visual disturbances. Physical examination revealed left submandibular swelling, bilateral cervical lymphadenopathy, bilateral gynecomastia, reduced pilosity, and normal thyroid exam.

His initial laboratory tests indicated the presence of biological inflammatory syndrome and an increased plasma gamma globulin level of 56 g/l (7–18 g/l), good glycemic control (HbA1c: 7%, 53 mmol/mol), and no electrolyte imbalance were found.

Hormonal examination showed hyperprolactinemia, hypogonadotropic hypogonadism, and central hypothyroidism. The hypothalamic-pituitary-adrenal axis (HPA), explored by an adrenocorticotropic hormone (ACTH) stimulation test, was intact. Table 1 presents the results of the patient's hormonal examination.

Thoracic and abdominal CT scan found interstitial pneumopathy, hepatomegaly, and diffuse enlarged lymph nodes. Pituitary magnetic resonance imaging (MRI) showed heterogeneous enlargement of the pituitary gland with diffuse gadolinium enhancement suggesting the diagnosis of hypophysitis (Figures 1A, B). The posterior pituitary bright spot was present. A remarkably high plasma IgG4 level of 36.7g/l (range 0.04–0.87g/l) was found and the submandibular gland biopsy revealed submandibular sialadenitis with positive immunohistochemistry to IgG4 at 80% (Figures 2A, B).

The diagnosis of IgG4-RH was made based on Leporati criteria. The patient was treated with prednisone at a dose of 1 mg/kg per day, with a gradual decrease of 10 mg each month and levothyroxine 100 µg/day for his central hypothyroidism. Cabergoline was also prescribed at a dose of 1 mg/week without improvement of his sexual dysfunction. For this reason, we added 250 mg of testosterone enanthate every month. A follow-up pituitary MRI and reassessment of pituitary functions is planned in 6 months.

Table 1
Results of the patient's hormonal examination

Hormone test	Value	Reference range
Prolactin (µg/l)	50	<20
FSH (mUI/ml)	2	3–10
LH (mUI/ml)	1.1	3–7
Testosterone (nmol/l)	6.5	10.4–34.6
TSH (µUI/ml)	2.5	0.4–4.0
T4 (pmol/l)	7	12–22
Baseline cortisol (nmol/l)	262	138–496
Cortisol after cosyntropin stimulation test 0.25mg (nmol/l)	689	>496

Abbreviations: FSH – follicle-stimulating hormone; LH – luteinizing hormone; T4 – free thyroxin; TSH – thyroid stimulating hormone.

Discussion

IgG4-RD is a multisystemic condition. Involvement of the pituitary gland is rare and was initially described in 2004 (Li et al. 2019). In a systemic literature review, it accounted for 1.5 % of cases (Brito-Zeron et al. 2014). A slight male predominance has been reported (Li et al. 2019). Unlike lymphocytic, hypophysitis is usually diagnosed in young females in association with late pregnancy or the post-partum period. The age of onset of IgG4-RH is over sixty (Li et al. 2019). The majority of reported patients were Asian (Lojou et al. 2020).

As IgG4-RH is a part of IgG4-RD, assessment of endocrine function is needed even in the absence of clinical manifestations. In fact, adrenal insufficiency

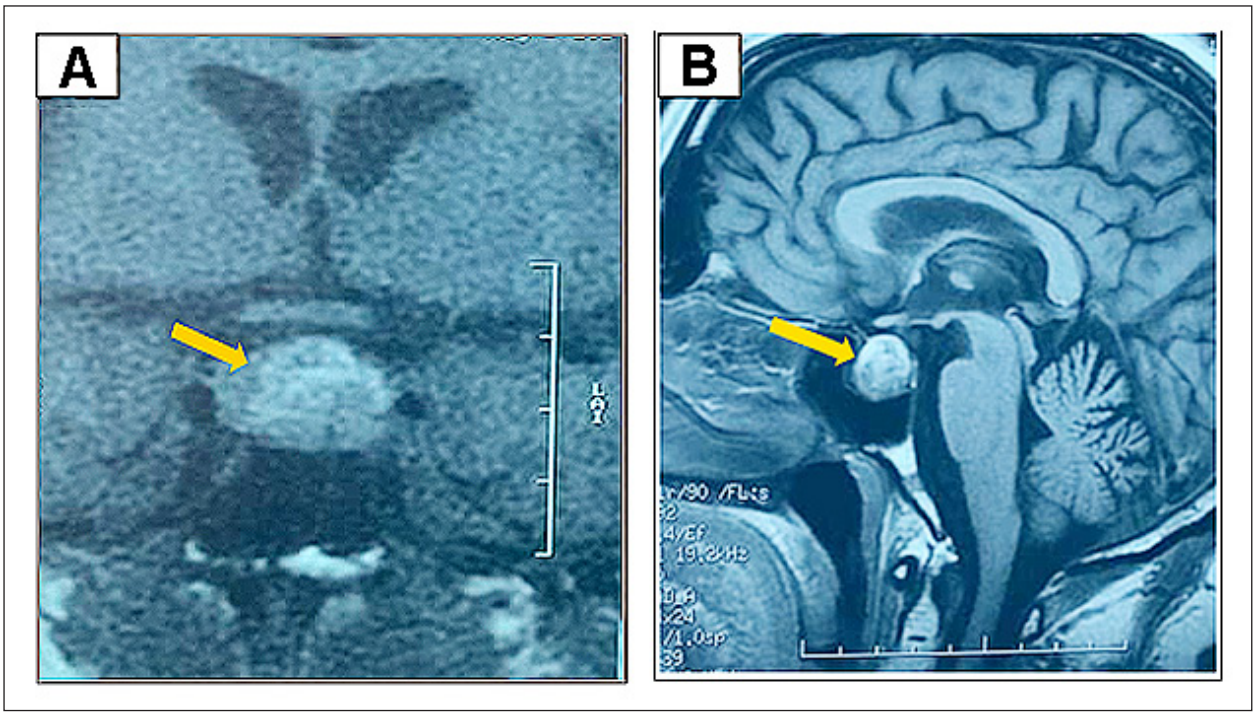

Figure 1. Pituitary magnetic resonance imaging (MRI): coronal T1 weighted image after gadolinium showing symmetrically enlarged pituitary gland with diffuse enhancement (**A**) and pituitary MRI: sagittal T1 weighted sequence after gadolinium showing globular enlarged pituitary gland with heterogeneous gadolinium intake and bright spot of posterior pituitary (**B**).

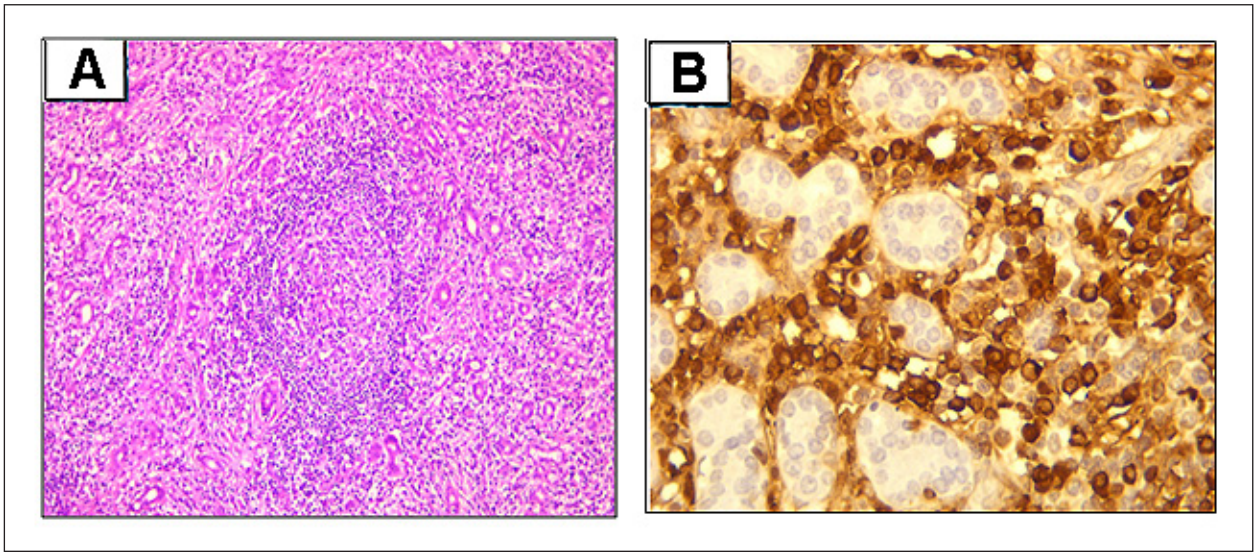

Figure 2. Biopsy of the left submandibular gland (HE ×100): the lobules of submandibular gland are dissociated by a dense inflammatory infiltrate with fibrosis (**A**) and biopsy of the left submandibular gland (HE ×400): intense immunoreactivity for IgG4 in plasma cells (**B**).

is life-threatening condition that needs to be recognized early. In this case, ACTH stimulation test was normal. The clinical presentation of IgG4-RH is non-specific. Symptoms and signs can be divided into sellar mass effects (headaches, visual dysfunction), anterior hypopituitarism symptoms (fatigue, weakness, weight loss, erectile dysfunction, and irregular menses) and central diabetes insipidus

(polyuria and polydipsia) (Amirbaigloo et al. 2021; Bhargava et al. 2022). The most common symptoms at diagnosis were headache (50%), polyuro-polydipsic syndrome (45%), sexual dysfunction (37.5%), asthenia (36%), and visual impairment (25%) (Lojou et al. 2020; Bhargava et al. 2022).

Anterior hypopituitarism with various combinations has been reported. The most common deficiency is central hypogonadism and the sequence of pituitary axis dysfunction is as follows: gonadotropic, adrenal, thyrotropic, somatotropic, and prolactin, which is different from lymphocytic hypophysitis characterized by more frequent adrenal and thyrotropic axis deficiencies (Khare et al. 2015; Li et al. 2019).

Hyperprolactinemia is not specific and can be found in all types of hypophysitis. It is a sign of compression and/or infiltration of pituitary stalk (Amirbaigloo et al. 2021). Central diabetes insipidus was frequently reported (75% of cases) (Lojou et al. 2020). However, in our case, there was no polyuria or polydipsia and the posterior pituitary light spot was easily identified on T1 weighted MRI.

IgG4-RH has the same MRI characteristics as any other etiology of hypophysitis. Usually, MRI shows asymmetrical or more frequently symmetrical pituitary gland hypertrophy in an intact sella turcica (Lojou et al. 2020; Amirbaigloo et al. 2021). Typically, the lesion is iso-hypointense in both T1 and T2 weighted sequences (Lv et al. 2022). Homogeneous and obvious gadolinium enhancement is characteristic and may be associated with the inflammatory process (Lv et al. 2022; Naik et al. 2023). Thickening of the stalk and loss of the posterior pituitary spot were seen in the most reported cases, especially in patients with central diabetes insipidus (Bhargava et al. 2022).

It is important to distinguish IgG4-RH from pituitary macroadenoma to avoid unnecessary surgical treatment (Lv et al. 2022). Usually, macroadenoma invades the surrounding area and the degree of enhancement is lower than that of hypophysitis (Lv et al, 2022; Naik et al 2023). Sometimes, an empty sella may be found, this can be the direct outcome of the inflammatory process or the result of glucocorticoid therapy (Amirbaigloo et al 2021; Bhargava et al. 2022).

To establish the diagnosis, we have used the criteria described by Leporati et al. (2011). Criterion 1 is based on pituitary biopsy showing mononuclear infiltration of the pituitary gland, rich in lymphocytes, and plasma cells with more than 10 IgG4 positive cells/hpf. The second criterion is the presence of a sellar mass and/or thickened pituitary stalk on MRI. Criterion 3 is biopsy-proven involvement in other organs. Criteria 4 and 5 are elevated serum IgG4 levels (>140 mg/dl) and a rapid reduction of the pituitary mass and symptom improvement with steroids. Diagnosis of IgG4-RH is made when any of the following is fulfilled criterion 1 or criteria 2 and 3 or 2, 4, and 5. In our case, criteria 2, 3, and 4 were present at the time of diagnosis. Based on 2019 ACR/EULAR classification criteria, in this case, the patient presented "28" points allowing the diagnosis of IgG4-RD (Dense lymphocytic infiltrate "+4", serum IgG4 concentration > 5× upper limit of normal "+11", One set of glands involved "+6" and immunostaining of "+7").

The management of IgG4-RH includes replacement therapy of pituitary deficiencies and specific management of hypophysitis. Steroid therapy is the first line option with an initial dose of prednisone of 0.6 mg/kg/day for 1–2 months (Takagi et al. 2020). The dose can be tapered to a maintenance dose of 2.5–5 mg/day over a period of 2–3 months (Li et al. 2019).

Swelling of the pituitary gland is responsive to steroid therapy, but the prognosis of pituitary function after the treatment remains unclear (Nishi et al. 2021). An initial improvement in pituitary deficiencies may be seen, but it may be transient (Nishi et al. 2021). In addition, disease relapse is frequent. In this case, physician might consider a maintenance dose for an extended period (up to three years), rituximab or other immunosuppressant (Boharoon et al. 2020; Nishi et al. 2021). New available agent as inebilizumab, an anti-CD19 antibody that depletes CD19-expressing B cells, reduced the risk of flares of IgG4-RD and increased the likelihood of flare-free complete remission at 1 year (Stone et al. 2025).

The present case reported illustrates an atypical presentation of IgG4-RH without sella mass effects or diabetes insipidus. The pituitary functions must be well assessed at the time of diagnosis and monitored during long term follow-up because improvement is uncertain and may even be transient.

Conflicts of interest: *The authors declare no conflicts of interest.*

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