

BACKGROUND

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated collection of disorders that share certain radiological, pathological and clinical features. The pathogenesis of IgG4-RD is currently unknown yet research suggests that aberrantly functioning CD4⁺ cells are associated with the development of both autoimmune and allergic pathologies.

Based on endocrinological behaviour, hypophysitis can be divided into three types: Adenohypophysitis and infundibulo-neurohypophysitis which are considered to be autoimmune mediated and panhypophysitis (involving both lobes of the pituitary gland) which is suggestive of systemic infection or an inflammatory process.¹

Since 2000 there are more than 20 reported cases worldwide which relate infundibulohypophysitis with IgG related systemic disease. The majority of these cases involve middle aged men presenting with diabetes insipidus, hypopituitarism, thickened pituitary stalk +/- pituitary mass.

This is an interesting case of a patient who only presented with flu like symptoms yet was found to have plasma cells positive for IgG4 on biopsy of his suspected Küttner's Tumour (chronic sclerosing sialadenitis) and abnormal thickening and enhancement of the infundibulum on MRI head.

CASE REPORT

A 57-year-old gentleman presented with bilateral painless submandibular swelling, and flu like symptoms. A biopsy from the enlarged submandibular gland showed chronic sclerosing sialadenitis with lymphoplasmacytic infiltration (Image 1 and 2). Immunohistochemistry showed plasma cells positive for CD79a and IgG4, and a combination of CD4 and CD8 positive lymphocytes (Image 3 and 4). IgG4 levels were significantly raised (3.16 g/L NR < 1.3g/L).

A diagnosis of IgG4 related disease was made. Chest and abdominal CT imaging did not reveal involvement of other organ systems. Treatment with a reducing dose of oral prednisolone over 6 months resulted in a reduction of IgG4 levels to 2.27 g/L but no significant change in the ultrasound appearance of the submandibular glands. A 6 month trial of hydroxychloroquine was also ineffective. IgG4 levels have increased over time (IgG4 > 3.44 g/L Sept 2014).

In October 2014 the patient complained of recent onset of severe thirst and frequent urination. Initial investigations showed serum and urine osmolalities of 309 mosm/kg and 116 mosm/kg respectively. A subsequent water deprivation test confirmed a diagnosis of central diabetes insipidus. Anterior pituitary function was normal apart from hypogonadotropic hypogonadism (LH 2.7 U/L; FSH 1.8 U/L; testosterone 4.4 nmol/l). MR imaging showed a normal pituitary gland but with abnormal thickening and enhancement of the infundibulum (figure 1).

A diagnosis of IgG4 related hypophysitis was made and the patient responded well to desmopressin. Testosterone replacement is currently under consideration.

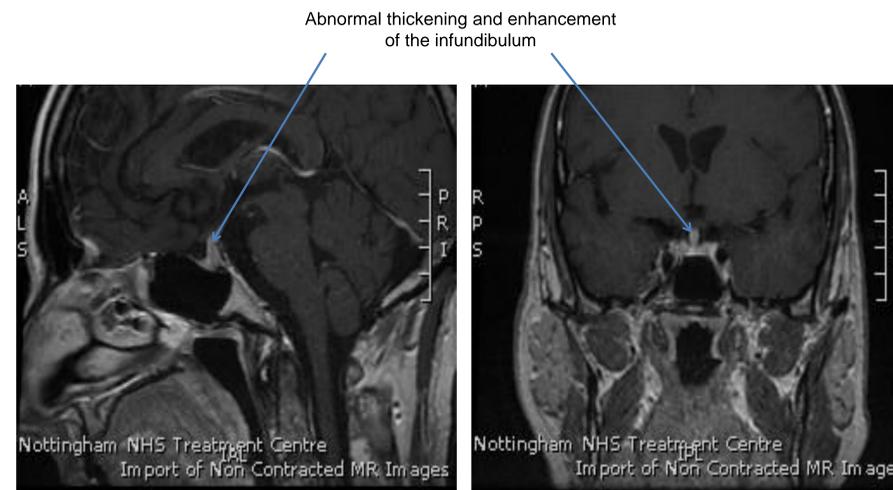


Fig. 1. MR imaging of the pituitary in this patient with IgG4-related hypophysitis. T1-weighted gadolinium enhanced imaging (sagittal section and coronal section)

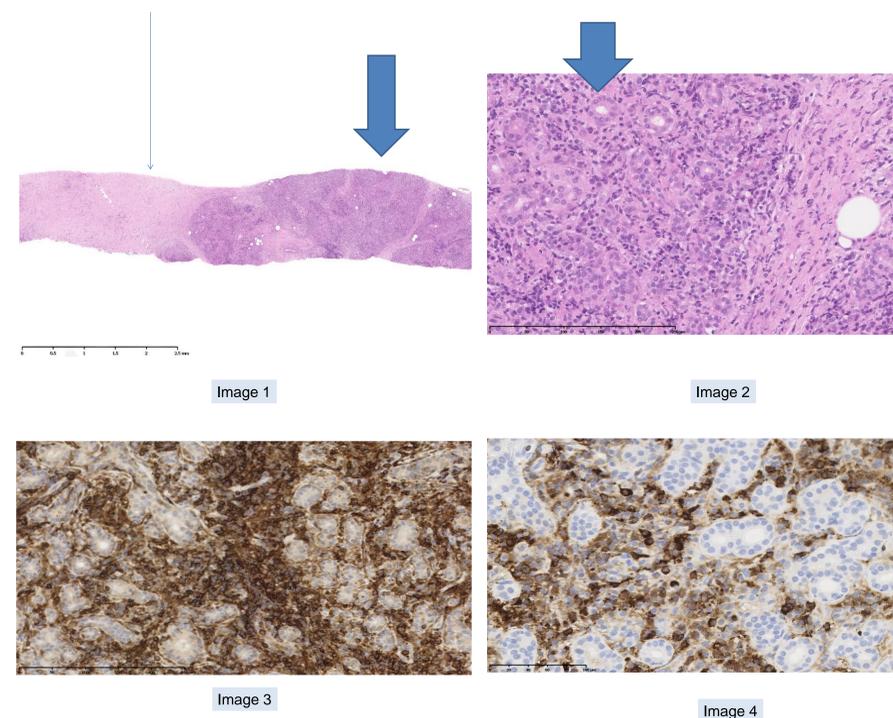


Fig. 2. Histopathology of Submandibular Gland in this patient

Image 1: H&E X20 Low power view of submandibular gland biopsy showing thick fibrous bands (long arrow) with lobules of acini surrounded by inflammation including lymphocytes and plasma cells (short arrow)
Image 2: H&E X200, High power view showing acini (arrow) surrounded by chronic inflammation consisting of lymphocytes and plasma cells
Image 3: CD79a stain highlighting plasma cells and some lymphocytes
Image 4: IgG4 staining plasma cells surrounding acini

DISCUSSION

A review by Shimatsu et al looked at 22 cases of hypophysitis associated with IgG4 related systemic disease since 2000¹. The median age was 64, with a male: female ratio of 21:1. He discovered that clinical manifestations related with the hypothalamic-hypophyseal system included general malaise, visual disturbance, fever, headaches and polyuria whilst those related to ACTH deficiency included weight loss, loss of appetite, and general malaise. Anterior pituitary hormone deficiency and central diabetes insipidus were found in some patients.

The case series highlighted that IgG4 related systemic diseases can occur before, during or after pituitary lesions are present. This gentleman had salivary gland involvement yet other common systemic diseases include retroperitoneal fibrosis, Mikulicz disease, pulmonary and pancreatic lesions².

MR imaging of the pituitary in hypophysitis can be highly useful. This can manifest as a thickened pituitary stalk or mass formation on the stalk or thickening at the level of the infundibulum or proximal end of pituitary stalk. Laboratory findings of elevated levels of serum immunoglobulin G and serum IgG4 can support diagnosis, as can raised CRP. As shown on figure 2 the histopathology of an affected organ usually demonstrates infiltration with lymphocytes and IgG4 positive plasma cells. Some of these features have been included into a classification criteria by Leparati and colleagues.³

In the majority of reported cases steroid treatment has been found to replace adrenocortical insufficiency as well as shrink pituitary mass and stalk thickening associated with IgG4 related hypophysitis yet in this gentleman this was not the case.⁴ This could be owing to the presence of diabetes insipidus, as a case series demonstrates that for most patients with diabetes insipidus, glucocorticoid therapy does not lead to remission.¹

CONCLUSIONS

- This case study underlines the need to investigate with measurement of serum IgG4 levels and histopathological analysis in elderly males with hypophysitis.
- Observable features to identify include raised serum IgG4 and infiltration of IgG4 positive plasma cells such as that found in the submandibular gland, as identified in this case.
- The patient population, mostly elderly, makes it less likely to be an autoimmune process yet further research is warranted to ascertain whether the pathogenesis is immune or possibly allergy mediated.

REFERENCES

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