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Original Article

IgG4-related hypophysitis: A monocentric experience from North India

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ABSTRACT

Background: Immunoglobulin (Ig)G4-related disease is a systemic fibroinflammatory disease characterized by dense infiltration of IgG4-positive plasma cells in the affected tissue(s) with or without elevated plasma levels of IgG4. Hypophysitis itself is a very rare disease with reported prevalence in the operative specimens are around 0.2–0.88%. IgG4-related hypophysitis (IgG4-RH) may account for a substantial percentage of cases previously regarded as idiopathic hypophysitis.

Methods: This study is a registry-based, retrospective, and cohort study from a tertiary care hospital in North India. The medical records and clinical data of biopsy-proven and suspected IgG4-RH patients registered were retrospectively analyzed. Treatment outcome of cases was also explored during this analysis.

Results: Two thousand and six sellar area space-occupying lesions have been operated-on since 2006, among them only four patients had IgG4-RH on histopathological specimen. One case was diagnosed on clinical suspicion. Mean age of the patients was 31.8 ± 6.32 years. Most frequent presenting complaint was headaches. Extracranial manifestations were present in four patients. The most common pituitary dysfunction was cortisol deficiency. 18 F-fluorodeoxyglucose positron emission tomography (18F FDG PET) was helpful in three cases for diagnosis of hypophysitis and other organ involvement. Classical histological findings with storiform fibrosis, obliterative phlebitis seen in two cases, and IgG4-positive plasma cell infiltration were positive in four cases. Surgery was the primary modality of treatment in all four cases. Only one patient received steroids as a primary therapeutic modality.

Conclusion: IgG4-RH is rare. High index of suspicion is required to diagnosis the case precisely. FDG PET is helpful in diagnosing hypophysitis and extrapituitary lesions.

Keywords: Autoimmune hypophysitis, Immunoglobulin G4-related disease, Immunoglobulin G4-related hypophysitis, Pituitary stalk thickening

INTRODUCTION

Immunoglobulin G 4-related disease (IgG4-RD) is a systemic fibroinflammatory disease characterized by dense infiltration of immunoglobulin (Ig)G4-positive plasma cells in the affected tissue(s) with or without elevated plasma levels of IgG4.[16] Pathologically, it is characterized by "storiform fibrosis, obliterative phlebitis, infiltration of IgG4 positive plasma cells, and

mild eosinophilia."[28] It is a spectrum of the autoimmune phenomenon; clinical presentation may be multisystem in nearly 50% of cases and may be limited to single-organ involving either the pancreas or retroperitoneum or the salivary gland in the remaining percentages. The involvement of multiple organs may be synchronous or metachronous. As a part of sclerosing fibrosis, it often leads to tumefactive lesions and organ dysfunction.[22,23] In 2001, Hamano and colleagues described a spectrum of pancreatitis designated as sclerosing pancreatitis spuriously associated with IgG4-positive plasma cells infiltration. Later on, it was considered as an autoimmune pancreatitis Type 1.[13] After this observation, several other systemic diseases have been considered as a part of this process, that is, Mikulicz disease, chronic sclerosing sialadenitis Kutner's tumor, Riedel's thyroiditis, mediastinal fibrosis, retroperitoneal fibrosis (Ormond's disease), peri-aortitis, idiopathic hypocomplementemia tubulointerstitial nephritis, multifocal fibrosclerosis, and inflammatory pseudotumor.[5,25]

The incidence of IgG4-RD remains unknown. This is due to challenges in making the diagnosis as the disease is often unrecognized or misdiagnosed due to its rarity. The disease mostly occurs in an elderly male patient with a range of 5^{th}–7^{th} decade. Male to female ratio ranges from 1.6: 1 to 4:1 in different cohorts.[24]

Autoimmune hypophysitis itself is a very rare disease, reported prevalence in the operative specimens is around 0.2–0.88%.[9,14] Hypophysitis related to IgG4-RD is noted only in <5% of cases.[7] The first report of the central nervous system involvement by IgG4-RD occurred in the context of hypophysitis. IgG4-RD may account for a substantial percentage of cases previously regarded as idiopathic hypophysitis. Even after an extensive search of the literature, cumulative numbers of IgG4-RD hypophysitis are relatively rare. Most of the cases were reported from Japan and United Kingdom. The reason for this scarcity of data is understandable, based on diagnostic difficulty, the feasibility of biopsy, and specific diagnostic criteria were not available until recently.[17]

Objective

The aim of the study was to describe the clinical manifestation, management, and outcome of IgG4 related hypophysitis (IgG4-RH), retrospectively.

Design and setting

A registry-based, retrospective, and cohort study from a tertiary care hospital in North India.

MATERIALS AND METHODS

The medical records and clinical data of biopsy-proven and suspected IgG4-RH patients registered in the Postgraduate Institute of Medical Education and Research, Chandigarh between 2006 and 2022 were retrospectively analyzed. Treatment outcome of cases was also explored during this retrospective analysis. Each and every case was dealt with by a multidisciplinary team, consisting of an endocrinologist, a neurosurgeon, a pathologist, and a radiologist. Demographic data, clinical presentation, radiological data, hormonal profile, and serum IgG4 level were assessed at the presentation. Posttherapy visual and endocrinological outcomes and imaging features were analyzed. A trend of demography, presentation, biochemical, and imaging characteristics has been discussed as a cluster. Further brief description of each case has been made along with treatment and outcome till the last follow-up. Basic statistical methods were applied only as the cumulative number of cases was too small for any advance statistics.

RESULTS

Two thousand and six sellar area space-occupying lesions (SOL) have been operated-on since 2006, among them only four patients had histopathology proven IgG4-RH. One case was diagnosed on clinical suspicion, which was presented with pituitary stalk thickening and was not biopsy-proven. After considering all organ manifestations, 154 biopsy-proven IgG4-RD had been reported from this institute.

Three of those five patients were female. The mean age of the patients was 31.8 ± 6.32 years, varied from 16 years to 38 years in this cohort. The median duration of symptoms was 12 months (6 months–20 years).

Most frequent presenting complaint was headaches seen in three cases. Among female patients, all three of them had menstrual abnormality in the form of amenorrhea or oligomenorrhea. Infertility after 17 years of marriage was the presenting complaint in one female patient. Other manifestations were short stature, diminution of vision, and poor development of secondary sexual characteristics.

Extracranial manifestations were present in five patients, consisting of pelvic adhesion, pancreatitis, retroperitoneal fibrosis leading to hydronephrosis and renal failure, and primary testicular failure in one patient each. Adamantinomas craniopharyngioma was associated with IgG4-RD in one patient.

The most common pituitary dysfunction was cortisol deficiency, which was presented in three out of those five patients, followed by hyperprolactinemia present in two patients. One patient presented with central diabetes insipidus and one had primary hypogonadism.

Sellar SOL was the imaging findings in three of the patients, one patient presented with only supra sellar SOL, thickening of the pituitary stalk was present in four of the patients, and

one of them had only thickened stalk as the sole imaging finding. One of the patients had craniopharyngioma, loss of pituitary bright spot was evident only in one patient.

The maximum tumor volume reported was 21.57 cc, cavernous sinus extension was present in one patient. Classical histological findings with storiform fibrosis, obliterative phlebitis present in two cases, and IgG4-positive plasma cell infiltration were positive in four cases. IHC for IgG4 cells was positive in four cases with two cases having IgG4/IgG index >40%.

Serum IgG4 was elevated in two cases, one of them was not biopsy-proven. That case was diagnosed radiologically with magnetic resonance imaging (MRI) and 18 F-fluorodeoxyglucose positron emission tomography-computed tomography (18F FDG PET-CT) which was suggestive of stalk thickening and elevated serum IgG4 level and treatment response. Surgery was the primary modality of all four cases, followed by anti-inflammatory therapy. Only one patient received steroids as a primary therapeutic modality. All 5-patient had stable disease with assigned therapy till the publication of this data. One patient diagnosed on the basis of clinical suspicion and IgG4 level showed satisfactory outcomes in her pituitary hormone profile and menstruation cycle following therapy. Although the desired outcome in the form of fertility was not achieved.

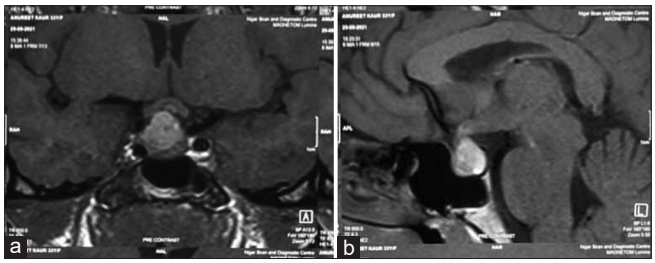

Figure 1: (a) Magnetic resonance imaging (MRI) of sella coronal section showing sella, supra sellar space, and occupying lesions. T1 hyperintense (b) sagittal section T1 contrast-enhanced MRI showing nonhomogenous contrast uptake, suggestive of apoplexy.

Individual case reports

Patient 1, presented with 6-month history of headache and oligomenorrhea. After 4 months of initial complaints, she developed diplopia both in primary gaze and in lateral gaze. Anterior pituitary hormone profile was normal with no features suggestive of diabetes insipidus. Visual field assessment and fundoscopy were normal. Structural imaging suggested altered posterior pituitary bright spot with a sellar SOL measuring 13.5 × 20 mm, with supra-sellar extension with thickening of pituitary stalk. Her excision biopsy specimen was positive for lymphoplasmacytic infiltration, but at that time, IgG4-RD was not suspected due to lack of knowledge of the condition. Nearly 2 years after initial presentation, she developed accelerated hypertension with fatigue and low-grade fever. Laboratory assessment revealed elevated urea and creatinine with ultrasonographic evidence of retroperitoneal fibrosis leading to hydronephrosis with postrenal Acute kidney injury. The diagnosis was subsequently confirmed by 18 F FDG PET-CT. Her pituitary biopsy was reviewed and finally retrospectively diagnosed as IgG4-RD. Later on, she was put on pulse methyl prednisolone followed by maintenance dose of oral prednisolone on which she was responded. (This case has already been published as case report elsewhere).[3]

Patient 2 presented with headache and amenorrhea for 1 year before contact to this hospital and treated as migraine elsewhere. She had high prolactin level with low cortisol and normal thyroid and gonadotrophin levels. Her visual acuity, fundoscopy, and field of vision were normal. Structural imaging showed a sellar mass of 1.8 × 1.3 × 1.3 cm with suprasellar extension and impingement on right sided optic chiasma, there was evidence of hemorrhage with in the lesion and posterior bright spot was intact [Figures 1a and 1b]. She underwent trans-sphenoidal surgery and gross total excision of tumor tissue. Biopsy from the lesion showed lymphoplasmacytic infiltration with IgG4 positive cell >10% and IgG4/IgG + plasma cell >40% with obliterative phlebitis and storiform fibrosis [Figures 2a-c]. Her serum IgG4 level was below 135 mg/dL. Later

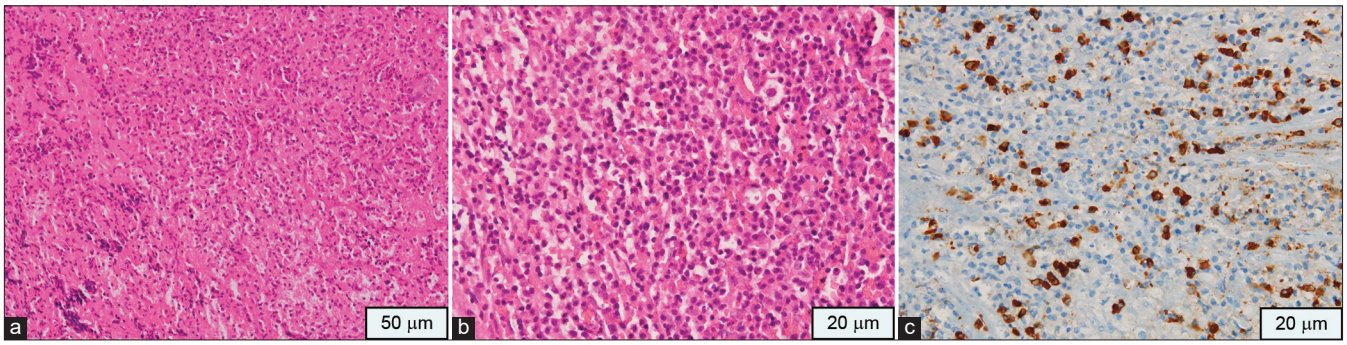

Figure 2: (a) Biopsy shows pituitary parenchyma with heavy inflammatory infiltrate (Hematoxylin and Eosin, ×100), (b) The inflammation is comprising of numerous plasma cells and histiocytes (Hematoxylin and Eosin, ×200). (c) Many IgG4 positive plasma cells are seen in brown stain (Immunohistochemistry, ×400).

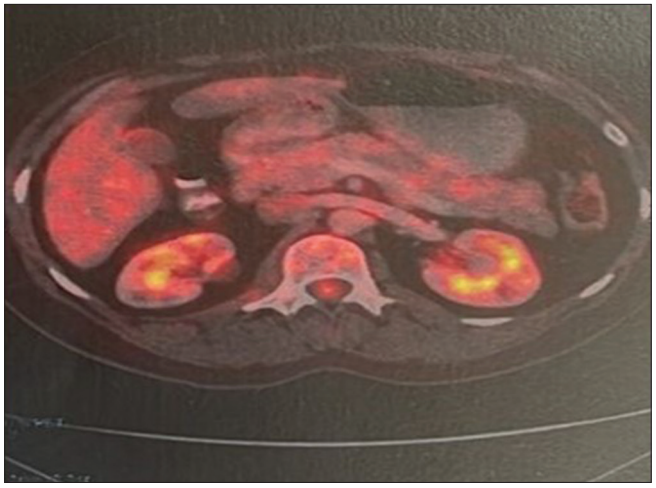

Figure 3: 18 F-fluorodeoxyglucose positron emission tomography/computed tomography showing differential tracer uptake in the pancreas as compared to background.

on, 18F-FDG PET-CT was done that showed inflammatory pancreatic lesion [Figure 3]. She was put on inflammatory dose of glucocorticoids with gradual tapering.

Patient 3 had progressive diminution of vision in the right eye associated with intermittent headache of 1 year duration. He also noticed deceleration in growth velocity, and the lack of development of secondary sexual characteristics. He had panhypopituitarism and visual problem in the form of right sided optic atrophy. MRI of sella showed a 3.8 × 3.5 × 3.1 cm mass with thickening of pituitary stalk and intact posterior bright spot. Excision biopsy showed adamantinomatous craniopharyngioma with part of pituitary and dura showing lymphoplasmacytic infiltration with immunohistochemistry positive for IgG4 plasma cells and fibrosis (This case is published as case report in elsewhere).[19]

Patient 4 was 34-year-old male. He was non-diabetic and had nasal obstruction with bilateral progressive loss of vision. He was also complaining of short stature and hearing impairment. He had low testosterone with elevated luteinizing hormone and follicle-stimulating hormone and low insulin-like growth factor-1. MRI showed an SOL of 1.8 × 3.3 × 1.7 cm, intensely enhancing, lobulated, suprasellar, and left para-sellar mass involving the pituitary stalk and infundibulum. There was the involvement of cavernous sinus too. Immunohistochemistry of excision biopsy specimen revealed 20–25 IgG4- positive plasma cells/high-power field, with an IgG4 to IgG ratio of >40%. A section from the dura overlying the sphenoid bone also revealed similar findings. IgG4 immunostaining highlighted 15–17 cells/high-power field (21% of total IgG-positive cells). His serum IgG4 level was 225 mg/dl (This case is published as case report in elsewhere).[15]

Patient 5 had infertility and oligomenorrhea at presentation. Her symptoms were thought to be contributed by

Table 1: Demographic, clinical, radiological, and histopathological presentation of cases.

Patient Number	Age	Gender	Duration of illness	Nature of hypopituitarism	Tumor size	Thickening of stalk	Posterior pituitary bright spot	Lymphocytic Infiltration	Storiform fibrosis	IgG4/ IgG	IHC for IgG4 cell	Serum IgG4 level	Extra pituitary manifestation
1	34 years	Female	6 months	No pituitary hormone deficiency or excess	1.43 cc	Present	Present	Present	Absent	>40%	Positive	227 mg/dl	Retroperitoneal fibrosis leading to ureteric obstruction and hydronephrosis.
2	33 years	Female	1 year	Hyporcortisolism and Hyperprolactinemia	1.60 cc	Absent	Present	Present	Present	>40%	Positive	<135 mg/dL	Pancreatitis
3	16 years	Male	1 year	Hyporcortisolism, Hypothyroidism, Hypogonadism, Low IGF1, Hyperprolactinemia	21.57 cc	Present	Present	Present	Absent	Absent	Positive	<135 mg/dL	Adamantinomas craniopharyngioma
4	34 years	Male	20 years	Low IGF1, low testosterone with high LH and FSH	5.28 cc	Present	Present	Present	Present	Absent	Positive	Not done	Primary testicular failure
5	38 years	Female	17 years	Hyporcortisolism, Diabetes Insipidus	No tumor	Present	Absent	N/A	N/A	N/A	N/A	155 mg/dL	Pelvic adhesion

IGF-1: Insulin like Growth factor 1, LH: Leutinizing hormone, FSH: Follicular stimulating hormone, N/A : Not available

hyperprolactinemia, pelvic adhesion, and ovarian dysfunction. Her MRI and 18 F FDG PET-CT showed thickening of the stalk with normal remaining pituitary. Serum IgG4 level was >135 mg/dL. She was put on Prednisolone 1 mg/kg body weight as an inflammatory dose with gradual tapering. She showed a satisfactory response and resume her menstruation. Summary of patients depicted in Table 1.

DISCUSSION

The prevalence of IgG4-RH was 0.2% among patient presented with sellar area SOL in our study. There was slight female preponderance as three out of five patients were female.

Mean age of presentation of IgG4-RH was 31.8 ± 6.32 years, which is far younger than the most of the described cohorts. Most common clinical presentation of IgG4-RH was headache in our cohort which was similar to the findings of the previous studies.[1] As per the second presenting complaint is concerned, vision problem was reported in the majority of the cohort. On the contrary, menstrual irregularity was the second most common presenting complaint among our patients. One of our patients presented with infertility of 17 years duration.

There is no fixed pattern of pituitary deficiency described in the literature in relation to IgG4-RH.[8] Most of the cohort mentioned adrenocorticotropic hormone (ACTH) deficiency leading to secondary hyporcortisolism as the predominant pituitary hormone deficiency, followed by gonadotrophin deficiency and thyrotropin deficiency.[12] In our study, some of the findings were similar to prior studies such as ACTH deficiency followed by hyperprolactinemia. Diabetes insipidus was present only in one of our cases. The pituitary function was normal in one case and one case had hypergonadotropic hypogonadism secondary to testicular failure.

Our study was in contrary to most of the cohort that showed a median age of presentation of 6th decade with male preponderance with ration ranging from 1.6:1 to 4:1.[1,18]

In contrary to our study, Bhargava *et al*. found different results, where they analyzed a cohort of eight patients, finding as the most common hormone deficiency being thyroid stimulating hormone (TSH), followed by ACTH and then gonadotrophin deficiency. In their cases, postoperative endocrine function did not improve and most of their patients permanently required pituitary hormone replacement therapy.[4]

Except that fifth case, all other cases were diagnosed retrospectively after neurosurgical intervention and histopathology findings. Only fifth case was suspected clinically and a therapeutic trial of prednisolone was given with satisfactory response. Indication for neurosurgical intervention was similar for all other sellar and supra sellar lesion, such as visual impairment, stalk compression, hypofunctioning of pituitary, and diagnostic uncertainty.

Radiologically, MRI is considered to be the best modality of investigation.[6] MRI could retrieve various pathological hall mark findings, like SOL at sella and suprasellar region, stalk thickening, loss of posterior pituitary bright spots, and postinflammatory empty sella.[6] However, the strongest predictor of an inflammatory process in a background of suitable clinical context is stalk thickening.[11] Among the available modality, we found 18F FDG PET scan as a useful modality, as three out of five patients were diagnosed with the help of this both prospectively and retrospectively. The diagnosis of the disease in one organ would also allow screening for systemic involvement in other organs, especially with use of FDG PET scan.

In this present study, except for one case, all other cases had SOL at the sellar region, maximum tumor volume encountered was 21.57 cc, stalk thickening was present in 4 cases (80%), and the posterior pituitary bright spot was absent in one case, which was presented with central diabetes insipidus.

Criteria devised by Leporati *et al*. which is now widely accepted to diagnose IgG4-RH, have been used in this study. At present, this is the only pituitary-specific clinical diagnostic criteria.[17] They proposed five diagnostic criteria for IgG4-RH and the diagnosis can also be made without a definitive histopathological examination (Supplementary Table).

Four of our patients had biopsy proven disease and they were fitting to the Criteria 1 and the fifth patient was suspected clinically, she had elevated IgG4 levels, thicken pituitary stalk in MRI, and clinical as well as imaging response to glucocorticoids. We have made a diagnosis for the fifth case on the basis of fulfillment of criteria 2, 4, and 5.

If we consider American college of Rheumatology (ACR)/European league against rheumatism (EULAR) classification criteria published in 2019 for IgG4-RD, four out of five cases fulfilled the criteria with a score of >20, only the fifth case was not fulfilling the criteria.

ACR/EULAR 2019 criteria were not specific for IgG4-RH. Considering the rarity of the disease pituitary involvement was not incorporated in the organ system checklist of this criteria.[24]

Pathogenesis of the condition was unclear but an autoimmune mechanism or chronic infection has been proposed as a possible cause.[27] Autoantigens to proopiomelanocortin and growth hormone have been suggested in some studies and anti-pituitary antibodies have been reported in some cases. IgG4 plasma cells are usually not present in the pituitary and

mere presence of IgG4 positive plasma cell does not make the diagnosis of IgG4-RH. Lot of other condition can produce such a biopsy picture such as lymphocytic hypophysitis, early stage of granulomatous hypophysitis, and hypophysitis secondary to infective etiology. Serum IgG4 levels are often but not always elevated in IgG4-RH. It is not particularly useful as it is not specific, it neither correlated with disease activity and nor has it any therapeutic monitoring benefit;[2,10] moreover, they can also be elevated in other conditions.[20,21] In our case series, only two of our patients had elevated serum IgG4 level.

Although there is no standard treatment protocol for IgG4-RD, steroid is considered as a cornerstone of therapy. We have treated our two patients with steroids, one as primary modality and other as second line after excision biopsy. They were started on anti-inflammatory dose of steroid and subsequently tapered off in 6 months. Patient 2 had pancreatitis as a part of systemic manifestation treated with prednisolone. The latest review emphasizes a pituitary biopsy to diagnose IgG4-RH. In all cases of IgG4-RH, steroid sparing agents such as Mycophenolate mofetil and Rituximab may be tried.

Isolated IgG4-RH was seen in 36% cases by Amirbaigloo *et al*. and in 65% from the German Pituitary Tumor Registry.[1,26] In our cohort 3 patients (60%) had extrapituitary involvement in the form of pancreatitis, retroperitoneal fibrosis, and pelvic adhesion as a part of the disease. Two out of those three cases presented simultaneously with pituitary involvement and in one case extrapituitary involvement happened after almost a decade.

Considering our experience, IgG4-RH is rare and indistinguishable from other causes of hypophysitis unless biopsy is done. As the understanding of IgG4-RH getting better, people considering it as differential diagnosis of hypophysitis. We emphasize a multi-disciplinary approach for proper diagnosis and management of this rare disorder.

Limitation

The shortfalls of our study are retrospective nature and small sample size. Even if this is a monocentric study, our center has a large referral base.

CONCLUSION

IgG4-RH is an incompletely understood rare disease. It is being increasingly recognized due to greater awareness among physicians, serum IgG4 assay, and repeat staining of histological samples previously labeled as unspecified and add into the diagnosis. It is prudent to get an extrapituitary screening imaging done with FDG PET if hypophysitis is suspected. If the serum IgG4 concentration is >140 mg/dL and if trial of glucocorticoids resolves the presenting symptoms, then IgG4-RH is highly probable. In case, there is a failure of resolution of symptoms with glucocorticoids or if there is any surgical indication or diagnostic uncertainty and serum IgG4 concentrations are not elevated, an early pituitary biopsy should be sought. If there is an extrapituitary organ involvement found on initial screening, then a biopsy of the affected organ should be sought to make a diagnosis. FDG PET should be considered as an important modality of investigation in suspected cases of IgG4-RD.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY TABLE

Supplementary Table 1: Criteria for diagnosing IgG4 related hypophysitis (Leporati *et al*)

Criterion 1	Pituitary histopathology; mononuclear-infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with more than 10 IgG4-positive cells/HPF.
Criterion 2	Pituitary MRI; sellar mass and/or thickened pituitary stalk.
Criterion 3	Biopsy-proven involvement in other organs; association with IgG4-positive lesions in other organs.
Criterion 4	Serology; increased serum IgG4 (> 140 mg/dL).
Criterion 5	Response to glucocorticoids; shrinkage of the pituitary mass and symptom improvement with steroids.

Diagnosis of IgG4-RH is established when any of the following is fulfilled: Criterion 1 OR Criteria 2 and 3 OR Criteria 2, 4 and 5. (Leporati P, Landek-Salgado MA, Lupi I, Chiovato L, Caturegli P. IgG4-Related Hypophysitis: A New Addition to the Hypophysitis Spectrum. J Clin Endocrinol Metab. 2011 Jul; 96 (7):1971–80.)