A case series of atypical features of patients with biopsy-proven isolated IgG4-related hypophysitis and normal serum IgG4 levels

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Abstract

Background IgG4-related hypophysitis is a rare clinical entity that forms part of an emerging group of multi-organ IgG4-related fibrosclerotic systemic diseases. The rare prevalence of the disease, presenting features that overlap with other sellar pathologies, and variable imaging features can make preoperative identification challenging.

Purpose and methods We report three cases of isolated IgG4-related hypophysitis with atypical clinical and imaging features that mimicked those of pituitary apoplexy and other sellar lesions. Additionally, we review the literature of IgG4-related hypophysitis to provide context for individual patient data described herein.

Results All patients presented with symptoms that mimicked those of pituitary apoplexy and visual disturbance, and MRI findings suggestive of pituitary macroadenoma, Rathke's cleft cyst and craniopharyngioma. The clinical presentation warranted surgical decompression, resulting in rapid symptomatic improvement. Preoperative high-dose followed by postoperative low-dose glucocorticoid replacement therapy was administered in all cases. Histopathology showed dense infiltrate of IgG4 cells. Post-operative follow-up monitoring for 12-26 months revealed normal serum IgG4 levels with no other organ involvement, while endocrinological testing revealed persistent pituitary hormone deficiencies.

Conclusions Our cases highlight the importance of considering IgG4-related hypophysitis in the differential diagnosis of solid and cystic sellar lesions presenting acutely with pituitary apoplexy symptoms. Existing diagnostic criteria may not be sufficiently precise to permit rapid and reliable identification, or avoidance of surgery in the acute setting. In contrast to other reports of the natural history of this condition,

despite the severity of presenting features, the disease in our cases was pituitary-restricted with normal serum IgG4 levels.

Introduction

Primary hypophysitis is a rare disease entity that has a reported estimated incidence of 1 case per 9 million persons per year [1], whereas clinically relevant hypophysitis is even rarer, accounting for 0.24 to 0.88% of all pituitary surgical cases [2]. Histopathologically, the disease is sub-classified into lymphocytic, granulomatous, xanthomatous, necrotizing, or IgG4-related hypophysitis, with lymphocytic being the most common subtype characterized by diffuse lymphocytic infiltration due to an autoimmune phenomenon [2].

IgG4-related hypophysitis is a newly described subtype of hypophysitis that forms part of an emerging group of multi-organ IgG4-related fibrosclerotic systemic diseases characterized by a combination of dense infiltration of IgG4-positive plasma cells into the pituitary gland, thickening of the pituitary stalk, diffuse infiltration of the pituitary with lymphocytes, and fibrosis with a “storiform” pattern [3-5]. Previous studies have reported its prevalence to range between 5% and 30% of hypophysitis cases [6,7]. However, Bernreuther *et al*. [8] recently reported that its prevalence could be as high as 41% in histologically confirmed hypophysitis cases, suggesting that this disease may have been previously underestimated [6].

The first case of IgG4-related hypophysitis with both clinical and histopathologic evidence was described in 2007 by Wong *et al.* [9] in an elderly Chinese male, where they found that the pituitary lesion had a dense lymphoplasmacytic infiltrate among adenohypophysial cells, and fibrosis with immunohistochemical staining for IgG4, and kappa/lambda light chains demonstrating a significant number of polyclonal plasma cells in the pituitary. Because pituitary biopsy is required for definitive diagnosis but often avoided due to its invasive nature, Leporati *et al.* [10] in 2011 devised new diagnostic

criteria without the need for biopsy by taking into consideration of MRI findings, serologic results, and response to glucocorticoid therapy **(Table 1)**. These criteria have since become widely adopted, and the number of case reports of IgG4-related hypophysitis in the literature has gradually increased in recent years.

As the disease can involve part of or the entire pituitary gland, the extent and severity of pituitary hormone deficiencies and presenting symptoms may vary. Symptoms commonly associated with IgG4-related hypophysitis include headache, vomiting, nausea, visual field defects, fatigue, fever, weight loss, hypopituitarism, and/or diabetes insipidus [4,9-20]. Additionally, imaging features of hypophysitis can be challenging to differentiate to those of a pituitary adenoma with concurrent cystic components, sellar cysts, and non-endocrine sellar tumors [21], thus making hypophysitis an important disease entity to consider in the differential diagnosis of sellar lesions.

Herein, we present morphologic and immunohistochemical findings of three cases of IgG4-related hypophysitis with atypical clinical and imaging features mimicking those of pituitary apoplexy. Case 1 is an elderly male that presented with adrenal crisis, whereas Cases 2 and 3 were young females with MRI features suggestive of Rathke's cleft cyst and craniopharyngioma, respectively. In all three cases, there was no evidence of involvement of other organs on CT imaging, and postoperative serum IgG4 levels remained within the normal range after more than 12 months of follow-up.

Case reports

Case 1

A 71-year-old Caucasian man with no known medical history presented to the emergency department (ED) in May 2015 with sudden frontal headache, pains behind his left eye, generalized weakness, diplopia, profound fatigue, nausea and vomiting. On admission, the patient was clinically dehydrated with a supine blood pressure of 131/86 mmHg and standing of 115/75 mmHg. Ophthalmological examination revealed a disconjugate gaze and left oculomotor abnormality. MRI revealed a solid pituitary mass measuring 19 x 10 x 14 mm that filled the sella turcica and extended superiorly along the infundibulum abutting the optic chiasm **(Figures 1A and 1B)**. Laboratory evaluation revealed hyponatremia (serum sodium 120 mmol/L), secondary adrenal insufficiency (ACTH stimulation test: baseline cortisol 3.5 μg/dL, 30-min cortisol 10.8 μg/dL, and 60-min 14.3μg/dL), secondary hypogonadism (total testosterone < 3 ng/dL, LH < 0.01 mIU/mL, and FSH < 0.01 mIU/mL), and secondary hypothyroidism (TSH 0.39 uIU/mL and free thyroxine 0.6 ng/dL). Based on the biochemical evidence of hyponatremia and hypocortisolemia, he was treated with intravenous hydrocortisone 100 mg and rehydrated with intravenous 0.9% normal saline. In light of the severity of his presenting symptoms, surgical decompression via a transsphenoidal approach was emergently performed the following day. At surgery, the pituitary gland was diffusely fibrotic without evidence of tumor or infarction. He received intravenous hydrocortisone (100 mg twice a day) on the day before and the day of surgery. Intravenous hydrocortisone was discontinued at post-operative day two, oral hydrocortisone (20 mg/day) and levothyroxine were initiated, and he was discharged home on these doses. By this time, the patient reported significant improvement of headaches and visual symptoms. Histopathologic examination of the sellar lesion demonstrated dense infiltration of B lymphocytes, IgG4-positive plasma

cells and eosinophils, with focal regions of interstitial fibrosis **(Figures 1E-1G)**. An ACTH stimulation test performed 7 days post-operatively revealed persistent secondary adrenal insufficiency, indicating the need for him to continue on hydrocortisone replacement (20 mg/day). In July 2015, CT imaging of the chest, abdomen and pelvis showed no evidence of fibrosclerosis elsewhere. In August 2015, because of low morning testosterone levels, intramuscular testosterone cypionate was initiated, and he was continued on oral hydrocortisone (20 mg/day) and levothyroxine. In December 2015, MRI was performed 7 months after surgery that demonstrated post-surgical changes, residual tissue of the pituitary gland, and persistent thickening of the infundibulum **(Figure 1C and 1D)**. Serum IgG4 levels were measured in June 2015 (28 days after initial presentation when he had received his first dose of intravenous hydrocortisone), December 2015 and October 2016, which were all within the normal range **(Figure 4)**. Two years after he first presented to the ED, repeat CT of the chest, abdomen and pelvis continue to show no extracranial involvement, and he is currently treated with oral hydrocortisone (20 mg/day), levothyroxine, and testosterone cypionate.

Case 2

A 24-year-old Caucasian woman with a history of multiple sclerosis and recurrent migraines was incidentally found to have a pituitary cystic mass measuring 13 x 16 x 11 mm on routine MRI in July 2015. She had recurrent headaches that were thought to be due to her migraines, but presented to the ED in January 2016 with severe throbbing headaches, diplopia and visual blurring. MRI was performed that demonstrated enlargement of the cystic pituitary mass, now measuring 20 x 19 x 11 mm. The mass was

protruding superiorly from the pituitary fossa causing a mass effect on the optic chiasm **(Figures 2A and 2B)**. She was treated empirically with intravenous hydrocortisone (100 mg) at anesthesia induction and transsphenoidal resection of the sella lesion was performed emergently, where a firm pituitary mass was noted. The dose of intravenous hydrocortisone was decreased to 50 mg/day at post-operative day 1, and converted to oral hydrocortisone (20 mg/day) at post-operative day 2. Within 2 days postoperatively, her headaches and visual symptoms improved, but she developed diabetes insipidus and secondary hypothyroidism, and was discharged home on desmopressin and levothyroxine, together with hydrocortisone (20 mg/day). Histopathologic examination of the sellar lesion demonstrated marked infiltration of the adenohypophysis by a mixed inflammatory infiltrate consisting of lymphocytes (B and T cells), histiocytes, neutrophils, eosinophils, plasma cells, and focal regions of interstitial fibrosis. Also present were separate "lakes" of acellular colloid but no epithelium, suggestive of a Rathke's cleft cyst, and dense infiltration of IgG4-positive plasma cells **(Figures 2C-2E)**. Because of the histopathologic findings, serum IgG4 levels were measured 6 days after she had received her first dose of intravenous hydrocortisone, and at regular intervals **(Figure 4)**, which were all within normal limits. CT of the chest, abdomen and pelvis showed no evidence of fibrosclerosis elsewhere. Six weeks after surgery, repeat neuroendocrine laboratory evaluation revealed normal hypothalamic-pituitary adrenal axis and hydrocortisone was discontinued. However, she continued to have secondary hypothyroidism, persistent diabetes insipidus, and low IGF-I levels. She underwent an insulin tolerance test that confirmed the diagnosis of adult GH deficiency and was started on GH replacement therapy. Postoperative MRI 6 weeks after surgery demonstrated

resolution of the cystic pituitary mass, and repeat CT of the chest, abdomen and pelvis performed 18 months after she initially presented to the ED continue to show no extracranial involvement. Currently, she remains on levothyroxine, desmopressin and GH.

Case 3

A 24-year-old Indian woman presented to the ED in July 2016 with a 7-month history of worsening headaches, malaise, nausea, diplopia and visual blurring, polydipsia and polyuria. She was previously diagnosed with Hashimoto's thyroiditis in November 2015 and reported sudden cessation of her menstrual cycles in January 2016. MRI demonstrated a partially cystic, suprasellar mass measuring 12 x 15 x 20 mm with solid expansion of the infundibulum measuring 13 x 13 x 10 mm. There was also a cystic component in the right hypothalamus measuring 7 x 9 x10 mm that was compressing the optic chiasm **(Figures 3A and 3B)**. Laboratory evaluation revealed secondary adrenal insufficiency (ACTH stimulation test: baseline cortisol 1.4 μg/dL, 30-min cortisol 10.4 μg/dL), secondary hypogonadism (LH 0.4 mIU/mL and FSH 2.7 mIU/mL), secondary hypothyroidism (TSH 0.90 uIU/mL and free thyroxine 0.2 ng/dL), and diabetes insipidus (serum osmolality 299 mosm/kg and urine specific gravity 1.007). She was treated with intravenous dexamethasone 4 mg at anesthesia induction and surgical decompression via transsphenoidal approach was performed in July 2016. At surgery, the pituitary gland was diffusely fibrotic without evidence of tumor and multiple cysts were present. At post-operative day 1, oral hydrocortisone (30 mg/day), levothyroxine, and desmopressin were initiated, and she was discharged home on these doses. Around this time, her headaches

and visual symptoms improved significantly, but her diabetes insipidus worsened before stabilizing upon increasing the doses of desmopressin. Histopathologic examination of the sellar lesion demonstrated dense inflammatory infiltrate of the adenohypophysis with IgG4-positive plasma cells, eosinophils, and focal regions of collagen-rich fibrosis **(Figures 3D, 3E and 3F)**. Because of the histopathologic findings, serum IgG4 levels were measured 7 days after she had received her first dose of intravenous dexamethasone, and at regular intervals **(Figure 4)**, which were all within normal limits. No evidence of fibrosclerosis was found on CT of the chest, abdomen and pelvis. Six weeks after surgery, repeat neuroendocrine laboratory evaluation revealed persistent panhypopituitarism, and is maintained on hydrocortisone (20 mg/day), levothyroxine, and desmopressin, but she remains amenorrheic. Postoperative MRI 6 months after pituitary surgery demonstrated resolution of the pituitary mass with persistent thickening of the pituitary infundibulum **(Figure 3C)**. Twelve months after she initially presented to the ER, repeat CT of the chest, abdomen and pelvis repeat CT continue to show no extracranial involvement. Currently, she remains on hydrocortisone (20 mg/day), levothyroxine, desmopressin, GH, and daily oral contraceptives.

Discussion

To our knowledge, more than 104 cases of IgG4-related hypophysitis have been described in the literature to date with more than half of the reported cases originating from Japan, raising the possibility of ethnic differences, variability in disease prevalence, and/or increased awareness in certain countries [22]. The majority of all cases of IgG4-related hypophysitis involved middle-aged or older male patients, whereas

females are more prone to acquire isolated IgG4-related hypophysitis than males (52% *vs* 13.6%) [22]. The pathogenesis of IgG4-related hypophysitis remains unclear, but likely related to autoimmunity or chronic infection [23].

In the normal pituitary, IgG4 immunopositive plasma cells are not seen. By contrast, in IgG4-related hypophysitis, in addition to the presence of IgG4-positive cells, polymorphs and eosinophils, areas of fibrosis is also an important morphological characteristic [23]. Therefore, it is important to be cautious when diagnosing IgG4-related hypophysitis with only the presence of IgG4-positive cells in the lesion because IgG4-positive plasma cells can also be detected in other conditions (e.g., inflammatory, infectious, autoimmune, and neoplastic diseases). In fact, there is no clear cut-off criterion for the number of IgG4-positive cells necessary for the diagnosis of IgG4-related disease. The first set of guidelines for the diagnosis of IgG4-related disease proposed in 2011 by Umehara *et al.* [24] emphasized the need for histopathological findings. In 2012, Deshpande *et al.* [25] proposed a set of guidelines based on findings of dense lymphoplasmacytic infiltrates on tissue biopsy with less emphasis on tissue IgG4 counts and IgG4:IgG ratios. However, the guidelines by Umehara *et al*. [24] and Deshpande *et al.* [25] have not been more widely adopted because the diagnostic yield is decreased, particularly for organs that are difficult to biopsy. The criteria proposed by Leporati *et al.* [10] is now widely accepted mainly because pituitary biopsy is not required to establish the diagnosis, and takes into account of other diagnostic factors and response to glucocorticoid therapy. Specifically, pituitary histopathology alone is sufficient to establish the diagnosis (criterion 1), but if these data are not available, pituitary MRI and histopathology of other involved organs (criterion 3) may be used to

establish the diagnosis. If the histopathology of other organs is not available, pituitary MRI (criterion 2) in combination with increased serum IgG4 levels (criterion 4) and response to glucocorticoid therapy (criterion 5) may be used to establish the diagnosis **(Table 1)**. Regardless of which guidelines are used [10,24,25], it is imperative to exercise caution about the applicability of the criteria for diagnosing IgG4-related disease for specific organ sites with limited experience. While the criteria for histopathological diagnosis continue to be re-defined, variability and exceptions to this "rule" exist, such as the absence of storiform-type fibrosis or obliterative phlebitis in certain organs (e.g., lymph node, minor salivary glands, lacrimal glands, and lung) [25]. Given the scarcity of reports documenting pituitary involvement in IgG4-related disease, which defining criteria (clinically and pathologically) that apply will need further investigation. Additionally, there is little known of the natural history of IgG4-related disease to determine whether features such as fibrosis are present at all stages. Furthermore, the influence of glucocorticoid therapy (pre- or post-operative) on the histologic, serum and radiologic features of IgG4-related disease is still not fully understood. Finally, the volume of tissue sampling may also be of concern, as organs like the pituitary may be limited, and could reflect in the histopathologic findings or lack thereof.

Serum IgG4 levels, although helpful, is not a specific diagnostic criterion as these levels can be elevated in various non-inflammatory conditions [26], and can be normal in up to 40% of patients with biopsy-proven IgG4-related disease [27] and in postpartum IgG4-related hypophysitis [28]. As there does not appear to be a direct relationship between serum IgG4 levels and the number or severity of organs involved in patients with systemic disease, changes in serum IgG4 levels is therefore not necessary

for the diagnosis of either comprehensive IgG4-related disease or hypophystis [25]. It is also unclear whether serum IgG4 level reflects disease activity because IgG4 itself is not considered a disease driver since it has been traditionally thought to inhibit rather than induce chronic immune activation [29]. Furthermore, among all of the IgG subclasses, IgG4 is the least abundant. Although in our cases, serum IgG4 levels were not assessed before exposure to glucocorticoid therapy and there was no other detectable organ involvement, the diagnosis of IgG4-related hypophysitis is justified based on the tissue biopsy findings of the presence of dense infiltrates of IgG4-positive cells, polymorphs, eosinophils, fibrotic areas, and rapid symptom improvement with glucocorticoid therapy.

Our cases presented with non-specific acute symptoms that mimicked those of pituitary apoplexy, and because glucocorticoid therapy was required to improve symptoms of adrenal insufficiency, it is unlikely that we would have identified IgG4-related hypophysitis before surgery until the histopathologic results became available. Furthermore, as the half-life of IgG4 is approximately 30 days, it is possible that the increased production of IgG4 rapidly decreased upon initiation of glucocorticoid therapy. Thus, it could be argued that measuring serum IgG4 levels before commencing glucocorticoid therapy may have helped increase the probability of diagnosing IgG4-related hypophysitis pre-operatively.

Glucocorticoids are the first-line treatment for IgG4-related hypophysitis because the disease responds well to this therapy, with concomitant reductions in serum IgG4 levels [10,13,30,31] that can range from days to 3 months [10,11,28,32]. While there is no consensus for the optimum dose, type, and duration of glucocorticoid therapy for this disease, prednisolone at a dose of 0.6 mg/kg/day has been used and continued for 1 to 2

months, with the objective of tapering the dose at a rate of 5 mg/week. In fact, recent studies have reported using low physiological hydrocortisone doses in effectively decreasing serum IgG4 levels and pituitary size [30,31]. The physiological hydrocortisone doses in these reports are comparable to the doses used in our patients, with the exception of the pharmacological doses that we intentionally used to pre-emptively cover for potential adrenal crisis on the day of and the day after surgery. However, if the disease relapses after glucocorticoid therapy is discontinued or tapered [10,32], continuing at the maintenance dose for an extended period, in some cases exceeding 3 years [33,34], or in combination with Rituximab [35], may be required. Because low-dose glucocorticoid replacement doses were used in our cases instead of high therapeutic doses, we cannot exclude the possibility that low glucocorticoid doses may have normalized serum IgG4 levels pre-operatively or that surgical removal of the sellar lesion rapidly decreased IgG4 levels.

The findings of our 3 cases of isolated IgG4-related hypophysitis with no other systemic lesions is somewhat unusual; however, these observations are not totally unique as there have been previous reports, albeit in small numbers, in Japanese patients [6,13,30,36]. In all of these reported cases, the patients were diagnosed by a pituitary biopsy without any other suspected lesions. By contrast, Khong *et al*. [37] also reported a case of a 33-year-old female presenting with hypopituitarism and biopsy-proven IgG4 hypophysitis with normal IgG4 levels and no evidence of other organ involvement. However, our cases differ from those previously reported in several aspects. First, there is a lack of systemic features and other organ involvement. Most patients with this disease present with concurrent or previous involvement of other organs [14-20], thus making it

challenging to confirm the diagnosis without tissue biopsy in the absence of systemic involvement. Second, in contrast to Case 1 which was an elderly male, Cases 2 and 3 were young females, with Case 2 being the first young Caucasian female to be reported with concurrent multiple sclerosis and Case 3 being the first young Indian female. Apart from one recent case report in a 16-year-old female [12], there have been no other reported cases based on tissue diagnosis in females less than 25 years old [4,37]. While considered rare, IgG4-related disease has also been described in the pediatric population, but usually within the context of autoimmune pancreatitis with other systemic manifestations, such as retroperitoneal fibrosis, sialadenitis, and mediastinal adenopathy [18]. Thus, it is possible that previous cases of IgG4-related hypophysitis may have occurred in younger patients but reported as different entities, or that treatment with high-dose glucocorticoids for co-existing systemic symptoms may have effectively treated the hypophysitis and normalized serum IgG4 levels. In line with our 2 young female cases, there are also reports suggesting cases of isolated IgG4-related hypophysitis in young women that are not part of a systemic syndrome [4,37]. Third, preoperative identification of hypophysitis is important for treatment planning. However, the MRI studies of Cases 2 and 3 were misleading because the imaging features suggested those of Rathke's cleft cyst and craniopharyngioma, respectively.

Conclusion

IgG4-related hypophysitis is a rare subtype of hypophysitis that forms part of a spectrum of IgG4-related fibrosclerotic diseases. Currently, majority of cases of IgG4-related hypophysitis [22] fulfilling Leporati's diagnostic criteria [10] have been reported in

publications and presented at scientific meetings, with most of these cases originating from Japan and described in elderly males. Our cases highlight the importance of considering IgG4-related hypophysitis in the differential diagnosis of solid and cystic sellar lesions in not only older men, but also in young females. Furthermore, our cases are important to increase the awareness among clinicians of these atypical clinical features of IgG4-related hypophysitis, and underscore the limitation of set diagnostic criteria and serum IgG4 levels to enable rapid and reliable identification. Because of the severity of the presenting symptoms, surgical decompression may be necessary in the acute setting to relieve the symptoms of neural compression. Our cases experienced rapid improvement in headaches and visual dysfunction, and in keeping with previous studies [7,21], post-operative endocrinologic profiles did not recover over time. Notably in our patients, despite the severity of the clinical presenting features, the disease was pituitary-restricted with normal post-operative serum IgG4 levels. Further studies are needed to search for other biomarkers for diagnosis and/or follow-up, and other imaging modalities such as positron emission tomography-CT for staging of the disease and assessment of other organ involvement [38].

Compliance with ethical standards.

Conflict of interest: The authors declare that they have no conflict of interest.

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Table 1 Summary of Leporati *et al.* [10] diagnostic criteria for IgG4-related hypophysitis.

Criterion 1: Pituitary histopathology Mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with more than 10 IgG4-positive cells per high-power field
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-related hypophysitis is established when any of the following is fulfilled: *Criterion 1* *Criteria 2* and *3* *Criteria 2*, *4*, and *5*

Figure legends

Figure 1

Case 1 post-contrast MRI sagittal and coronal T1-weighted images (A-D), and histopathologic (E-H) findings. *MRI:* Pre-operative images (A and B) demonstrate an enlarged pituitary gland (10 mm craniocaudal) with thickening of the infundibulum. Post-operative images (C and D) show enhancing tissue within the sella, decreased in volume compared to the preoperative examination reflecting post-surgical changes and residual pituitary tissue. Enlarged, avidly-enhancing pituitary infundibulum is unchanged from the pre-operative images (A and B). *Histopathology:* Hematoxylin and eosin, 400x original magnification demonstrate dense inflammatory lymphoplasmacytic infiltrate that composed of mature plasma cells, histiocytes, lymphocytes and eosinophils, with focal regions of interstitial fibrosis (E). High-power IgG immunostain (100x) demonstrate abundant IgG-positive plasma cells diffusely distributed within the infiltrate (F) and significant number of IgG4-positive cells (number of IgG4-positive cells per high power field is > 200; IgG4/IgG ratio estimated 30-40%) (G).

Figure 2

Case 2 post-contrast MRI sagittal and coronal T1-weighted images (A, B), and histopathologic (C-E) findings. *MRI:* Pre-operative images (A and B) demonstrate a lesion with avid peripheral enhancement and heterogeneous contents extending from the sella into the suprasellar cistern, and mildly thickened pituitary infundibulum that attaches to the rostral aspect of the lesion. The optic chiasm is mildly displaced rostrally and has a draped appearance over the lesion.

Histopathology: Hematoxylin and eosin, 400x original magnification demonstrate acini surrounded by moderately dense mixed lymphoplasmacytic inflammation and rare neutrophils and histiocytes (C). Immunostain to IgG, 400x original magnification demonstrate infiltration of IgG-positive cells and eosinophils (arrows), with focal regions of interstitial fibrosis (D). Immunostain to IgG4, 400x original magnification demonstrate acini surrounded by diffuse but variable intensity of IgG4-positive cells (number of IgG4-positive cells per high power field is > 150; IgG4/IgG ratio estimated 30%) (E).

Figure 3

Case 3 post-contrast MRI sagittal and coronal T1-weighted images (A, B), pre-contrast MRI sagittal T1-weighted images (C), and histopathologic (D-F) findings. *MRI:* Pre-operative images (A and B) demonstrate a lesion with a large cystic component extending from the sella into the suprasellar cistern. There is solid expansion of the pituitary infundibulum and a cystic component involving the right hypothalamus and abutting the optic chiasm. Post-operative images (C) demonstrate post-surgical changes with mild thickening of the pituitary infundibulum and minimal residual pituitary tissue at the base of the sella. *Histopathology:* Hematoxylin and eosin, 400x original magnification demonstrate acini surrounded by dense mixed lymphoplasmacytic inflammation, eosinophils and focal regions of collagen-rich fibrosis (D). Immunostain to IgG, 400x original magnification demonstrates acini surrounded by dense infiltration of IgG-positive cells (E). Immunostain to IgG4, 400x original magnification demonstrates acini surrounded by infiltrate of IgG4-positive cells (number of IgG4-positive cells per high

power field is > 200; IgG4/IgG ratio estimated 40%) (F).

Figure 4

Follow-up serum IgG4 levels (mg/dL) of all cases over time *(reference range: 1-291 mg/dL)*.