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Granulomatous hypophysitis: experience with eight surgical cases of a single center

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Abstract

Background: Although primary hypophysitis is not uncommon, a granulomatous etiology of hypophysitis is relatively rare. Radiological and diagnostic characteristics of several isolated cases have been described to date. However, to the best of our knowledge, surgical treatment of eight cases of granulomatous hypophysitis confirmed by histopathology has not yet been reported.

Methods: A retrospective study was performed to review cases of granulomatous hypophysitis from November 2003 to November 2013 in our neurosurgical department. Only eight out of 1345 operations were diagnosed with granulomatous hypophysitis.

Results: The cohort included two men and six women. The most common manifestations reported were headache, fatigue and polyuria. All six female patients presented with either menstrual disorders or amenorrhea. Seven of eight patients suffered polyuria. Two patients suffered bitemporal hemianopsia. One was accompanied with eosinophilic granuloma of the skull. Prolactin levels were increased in six patients, four of them were noted to have thyroid axis imbalances, one was noted to be deficient in the gonadotropin axis and two were deficient in the adrenal axis. The lesion demonstrated homogenous enhancement and an abnormally thickened pituitary stalk. A histological diagnosis of granulomatous hypophysitis was established in all eight patients, who were treated surgically. Characteristic granulomas formed by epithelioid histiocytes and multinucleated giant cells were observed.

Conclusion: Pure glucocorticoid therapy is less effective than surgical intervention and has not been recommended for the treatment of granulomatous hypophysitis. Although replacement therapy can relieve associated symptoms, we conclude surgical intervention, particularly minimally invasive surgery via a transsphenoidal approach, to be mandatory in establishing a diagnosis and reducing the size of the inflammatory mass. Adjuvant corticosteroids therapy is recommended.

Keywords: Pituitary, Transsphenoidal surgery, Replacement

Background

Inflammatory hypophysitis is a rare disease characterized by focal or diffuse inflammatory infiltration and destruction of the pituitary gland [15]. The precise incidence of this disorder remains unknown and early descriptions consisted primarily of individual case reports [6–8]. Granulomatous involvement of the pituitary gland occurs even more rarely. This entity may be occasionally mistaken for a pituitary neoplasm, such as an adenoma. Unlike lymphocytic hypophysitis, which predominantly affects females, young women in late pregnancy or the postpartum period, granulomatous hypophysitis appears to have no gender predilection and the average age at diagnosis is greater than 40 years. The majority of cases are primary, and are characterized by a predominance of epithelioid histiocytes and multinucleated giant cells. Secondary hypophysitis may occur in patients with systemic conditions, such as Takayasu's disease [17], ruptured intrasellar Rathke's cleft cyst [1, 11], Wegener's granulomatosis [4], Crohn's disease [3], thyroiditis and lymphocytic adrenalitis [13]. Pressure symptoms and visual impairment may arise from the development of a sellar mass lesion, mass effect, and involvement of the pituitary stalk, ensuing pituitary destruction may result in endocrine dysfunction.

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Although some lymphocytic hypophysitis cases have been reported to exhibit spontaneous partial or complete recovery of function [10], self-limited cases of the disease have not yet been published. The natural history of granulomatous hypophysitis is unpredictable. Typically, patients progress from initial symptoms related to the mass effect of the inflamed, enlarged gland, to development of hypopituitarism as the gland is destroyed via inflammation. While the standard management for granulomatous hypophysitis remains controversial, accepted regimens includes transsphenoidal removal of the intrasellar mass and administration of corticosteroid therapy. Stereotactic radiotherapy has also been successfully used [14]. As we known, the important reviews and case reports on granulomatous hypophysitis are only involved in one or two cases after since 1980s [2], however, only one single center in India reported six cases with granulomatous hypophysis diagnosed after biopsy in 2004 [2]. This article describes a single medical center's experience with eight patients suffering from granulomatous hypophysitis in which all of the patients were diagnosed and surgically treated. Which shares the important experience and evidence in treatment of granulomatous hypophysitis with surgery and steroids.

Methods

The patients who underwent surgery for pituitary lesions from November 2003 to November 2013 in our center were analyzed retrospectively. Only eight out of 1345 operations over the last 10 years were performed for granulomatous hypophysitis. The cohort of non-infective inflammatory pituitary lesions included two men and six women with the mean (±SD) age of 36 ± 12.1 years (range 16–57 years). A thorough history was obtained and physical examination was performed in all patients. All patients had undergone radiological evaluation of the sellar region with contrast-enhancement magnetic resonance imaging (CE-MRI). Neuro-ophthalmological evaluation including computerized perimetry was performed. Endocrinological assessment at presentation included basal cortisol at 8 a.m., adrenocorticotropic hormone (ACTH), thyroid hormone profile (T3, T4, TSH), luteinizing hormone (LH), follicular stimulating hormone (FSH), testosterone (T), estradiol (E2), prolactin (PRL). IgG4, an immunologic marker, was also measured in selected patients.

All eight patients underwent surgical excision of the lesion, which was confirmed to be granulomatous hypophysitis on histopathology. Postoperatively, they were evaluated after three months, with imaging profiles and hormonal status were re-assessment.

Results

Clinical profile

The cohort included two men and six women with the mean (±SD) age of 36 ± 12.1 years (range 16–57 years) and reported duration of symptoms ranging from 5 to 24 months. The most common manifestations of these patients were headache, fatigue, polyuria and menstrual disorders in females. All six female patients presented with either menstrual disorders or amenorrhea (case 1, 2, 3, 5, 6, 7). One male patient had erectile dysfunction (ED) (case 4). Seven of eight patients suffered polyuria (except case 6), and the 24 h output of urine was determined to be about nine liters in one patient (case 1). The preoperative endocrine level in serum revealed that only two patients (case 5, 6) had normal levels. Two patients suffered bitemporal hemianopsia (case 1 and 2), and other patients were with normal vision. One was accompanied with eosinophilic granuloma of the skull (case 2). Additionally, prolactin levels were increased in all other six patients, four of them were noted to have thyroid axis imbalances (case 1, 2, 3, 4), one was noted to be deficient in the gonadotropin axis (case 1) and two were deficient in the adrenal axis (case 1, 2) (summarized in Table 1).

Table 1 Clinical and endocrine profiles

Case No.	Sex	Age(years)	Clinical manifestation	Duration of symptoms(months)	Hormone deficiencies	Visual field defects	Accompanied skull lesion
1	F	34	Headache, polyuria, weight loss, menstrual disorder	5	T3,T4,FSH,LH,P,E2, ACTH, cortisol, hyperprolactinaemia	Bitemporal hemianopsia	*N
2	F	57	polyuria, weight loss, menstrual disorder	24	T3,T4,ACTH, hyperprolactinaemia	Bitemporal hemianopsia	eosinophilic granuloma of the skull
3	F	32	polyuria, fatigue, amenorrhea	24	T3,T4, hyperprolactinaemia	*NL	N
4	M	35	polyuria, *ED	6	T3,T4, hyperprolactinaemia	NL	N
5	F	16	polyuria, dwarfishness, amenorrhea	7	NL	NL	N
6	F	48	Amenorrhea, weight loss	6	NL	NL	N
7	F	32	Polyuria, menstrual disorder	9	hyperprolactinaem	NL	N
8	M	34	polyuria, ED	8	T3,T4, hyperprolactinaemia	NL	N

*_ED_ erectile dysfunction, _NL_ normal level; _N_ no

Table 2 Radiological Profile

Case No.	T1	T2	Contrast enhancement	Stalk	Radiology	Size(mm)
1	Iso/hypo-intensity	Iso/hyper-intensity	Ring-like	Thickened	Suprasellar extension	22×20×18
2	Hypo-intensity	Hyper-intensity	Heterogenous	Thickened	Suprasellar extension	20×18×21
3	Hypo-intensity	Iso-intensity	Homogenous	Thickened	Suprasellar extension	11×9×9
4	Hypo-intensity	Iso-intensity	Homogenous	Thickened	Suprasellar extension	10×5×5
5	Hypo-intensity	Iso-intensity	Homogenous	Thickened	Suprasellar extension	13×4×6
6	Hypo-intensity	Hyper-intensity	Homogenous	Thickened	Suprasellar extension	13×6×6
7	Hypo-intensity	Iso-intensity	Homogenous	Thickened	Suprasellar extension	18×13×12
8	Hypo-intensity	Iso-intensity	Homogenous	Thickened	Suprasellar extension	15×5×6

All eight patients had a sellar mass extending into the suprasellar region that appearing on long T1, long T2 and contrast enhanced on MRI. The lesion typically demonstrated marked, homogenous enhancement (except case 1, 2), although heterogeneous (case 2) and ring-like enhancement (case 1) was also noted. An abnormally thickened pituitary stalk was noted in all patients, and the mean size of the seller mass in our patients was 15.3 mm in the longest diameter (summarized in Table 2).

Treatment and outcome

All eight patients underwent excision of the lesion via transsphenoidal approach, except one who had a transcranial approach due to an initial diagnosis of hypophysial abscess (case 1). Intraoperatively, the surgeon found the difficulty in transsphenoidal resection due to adhesion of lesions and the dura mater. The appearance of lesions was mostly gray-white and firm, with a moderate vascular supply. There was no obvious borderline between delineating the lesion from pituitary tissue. Postoperatively, six patients still manifested with symptomatic hypopituitarism and underwent treatment of varying duration involving hormonal replacement therapy, with the exception of one recovery immediately after surgery (case 6). In one patient hypopituitarism remained permanent (case 1), and long-term hormone replacement was instituted. Headache resolved in all patients, diabetes insipidus and menstrual disorders improved or resolved entirely in all symptomatic patients, one still reported amenorrhea (case 5). The patient with ED preoperatively had not improved (case 4). And the patients with vision impairment were both improved after surgery. There were no recurrences of hypophysitis at follow up postoperatively to date (summarized in Tables 3 and 4).

Pathologic profile

A histological diagnosis of granulomatous hypophysitis was obtained in all eight patients who underwent surgery. Microscopic examination revealed preservation of anterior pituitary acini separated by inflammatory cells infiltrate exclusively composed of lymphocytes and

Table 3 Management and Diagnosis

Case No.	Initial diagnosis	Management	Pathological diagnosis	Operation complication
1	Hypophysis abscess	Initial craniotomy surgery	Granulomatous hypophysitis	Panhypopituitarism
2	*PA with Rathke's cleft cyst and eosinophilic granuloma of the skull	Initial trans-sphenoidal surgery	Granulomatous hypophysitis and eosinophilic granuloma of the skull, Rathke's cleft cyst	None
3	PA	Initial trans-sphenoidal surgery	Granulomatous hypophysitis	None
4	PA	Initial trans-sphenoidal surgery	Granulomatous hypophysitis	None
5	PA	Initial trans-sphenoidal surgery	Granulomatous hypophysitis	None
6	PA	Initial trans-sphenoidal surgery	Granulomatous hypophysitis	None
7	Hypophysitis	Initial trans-sphenoidal surgery	Granulomatous hypophysitis	None
8	PA	Initial trans-sphenoidal surgery	Granulomatous hypophysitis	None

*PA Pituitary adenoma

Table 4 Clinical and Endocrine Outcome

Case No.	Clinical symptom	Endocrine function	Duration(months) of hormonal replacement	Recurrence	Follow up(months)
1	No headache, improved polyuria	Hypopituitarism	Long term	None	
2	None	*NL	12m	None	
3	None	NL	4m	None	
4	No polyuria, *ED	NL	3m	None	
5	No polyuria, amenorrhea	NL	6m	None	
6	None	NL	None	None	
7	None	NL	5m	None	
8	None	NL	None	None	

**ED* Erectile dysfunction, *NL* Normal level

plasma cells. Characteristic granulomas formed by epithelioid histiocytes and multinucleated giant cells were also observed. One case was deemed to be associated with a Rathke's cleft cyst (case 2) (summarized in Table 3).

Representative cases

Case 1

A 35-year-old female was admitted to our department presenting with headache, polyuria, fatigue and menstrual abnormalities for five months. Past medical and family history were unremarkable. Physical examination showed bitemporal hemianopsia. The preoperative endocrine levels in serum revealed insufficiency of the thyroid, gonadotropin and adrenal axes, with increased levels of prolactin. The urine volume per 24 h was about nine liters. A sellar contrast enhancement MRI was performed (Figs. 1, 2 and 3).

According to semiology, disease history and radiological characteristics, the patient underwent a craniotomy via subfrontal approach due to the initial diagnosis of hypophysial abscess. Intraoperatively, a sellar cystic lesion was noted with moderate vascular supply. Visualization of the lesion revealed yellow fraction pus within the cyst and milky-white wall (Fig. 4 left). After the lesion was resected, a histological examination revealed necrotizing granulomas composed of perinecrotic epithelioid histiocytes, lymphocytes and occasional multinucleate giant cells (Fig. 4 right).

The postoperative MRI showed the lesion was disappeared (Fig. 5). However, the symptoms of polyuria and hypopituitarism were still present. Fortunately, the patient responded well to a pharmacological dose of hormonal replacement. Dose reduction resulted in exacerbation of her symptoms after one year. Finally, we decided to administer long-term hormonal replacement to control her symptoms.

Case 2

A 57-year-old female was admitted to our department complaining of polyuria, weight loss and a menstrual disorder for the past 24 months. Past medical and family

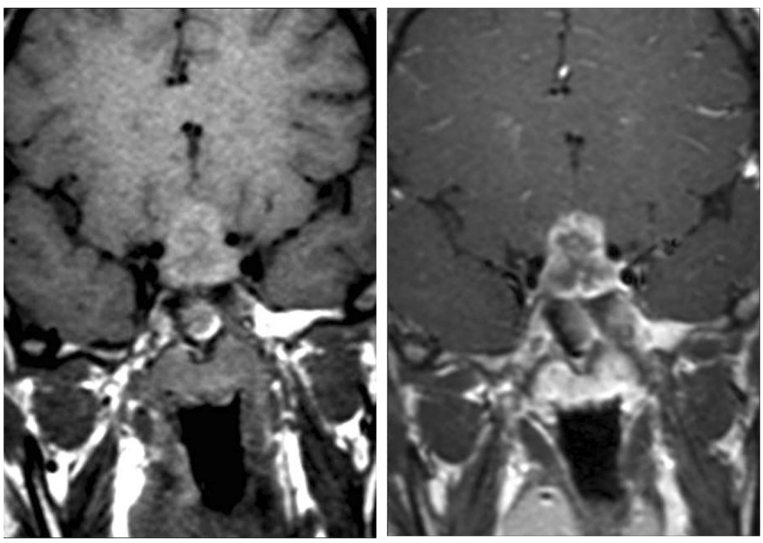

Fig. 1 A coronal T1-weighted image (left) revealed a iso/hypo-intense sellar lesion with a su-prasellar extension. A gadolinium enhanced image (right) demonstrated an enhancing lesion with a hypointense center

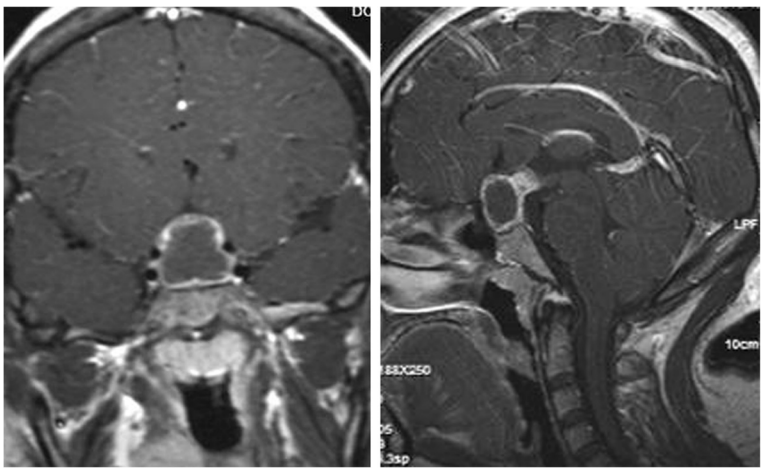

Fig. 2 T1-weighted coronal (left) and sagittal (right) MRI with contrast demonstrated an intra-sellar and suprasellar mass lesion and thickening of the pituitary stalk with ring-like enhancement

history were unremarkable. The preoperative serum endocrine levels revealed thyroid and adrenal axis insufficiencies, but increased of levels of prolactin. A sellar contrast enhancement MRI, regular cerebral MRI and plain brain X ray were performed (Figs. 6, 7 and 8).

According to semiology, disease history and radiological manifestations, the preoperative diagnosis of the patient was pituitary adenoma with Rathke's cleft cyst and an eosinophilic granuloma of the skull. Transsphenoidal surgery was therefore planned for the intrasellar lesion and a craniotomy was deemed appropriate for the skull lesion, these two surgeries were performed under one anesthesia session. Intraoperatively, the surgeon also found difficulty in resection of the intrasellar lesion due to dural adhesion. Mass visualization revealed a gray-white color and firm appearance, moderate vascular supply, and a lack of obvious borderline between the lesion and pituitary tissue. Both intracranial and skull lesions were completely resected, with a histological examination confirming the diagnosis (Fig. 9).

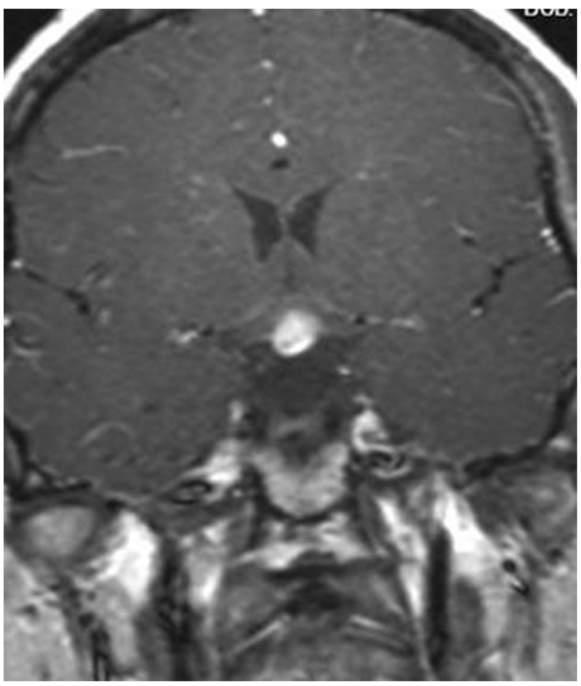

Fig. 3 Coronal T1-weighted with contrast MRI showed 'bright spot' in tuber cinereum of the hypothalamus

The postoperative sellar MRI revealed the lesion as resolved (Fig. 10). Additionally, the symp-toms of polyuria and hypopituitarism state improved. Hormone replacement dosage was gradually diminished until she received a dose of hormonal replacement for 1 year. Symptom resolution was reported after surgery.

Discussion

Clinicopathological features

Granulomatous hypophysitis is a rare inflammatory process, accounting for less than 1 % of all pituitary lesions [12]. The disease appears to have no gender predilection and the average age at diagnosis is greater than 40 years [2]. The mean age at diagnosis in our patients was 34.5 years in males and 36.5 years in females.

Patients often present with a headache. Other symptoms may include hypopituitarism, diabetes insipidus, hyperprolactinemia, and symptoms associated with chiasmal compression. Seven of our patients had clinical evidence of diabetes insidipus at presentation. Hyperprolactinemia was observed in six patients, and attributed to either stalk compression by the expanding lesion or due to direct involvement of the stalk.

While preoperative diagnosis is important, diagnosis is most often made postoperatively. There are no reliable

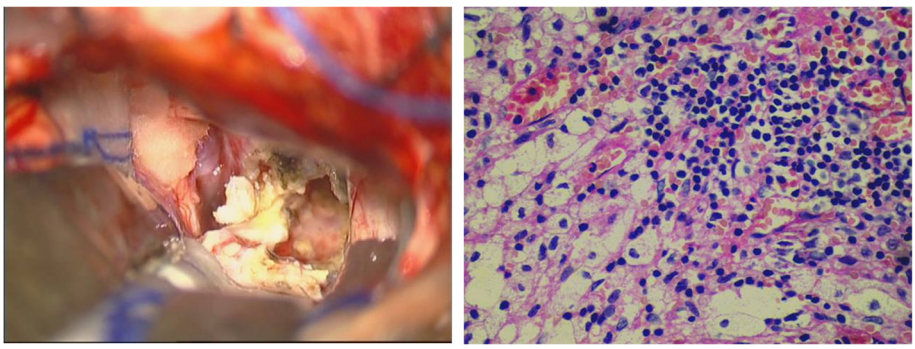

Fig. 4 The image of the lesion at operation (left). The image of histological examination (right) revealed necrotizing granulomas composed of perinecrotic epithelioid histiocytes, lymphocytes and occasional multinucleate giant cells

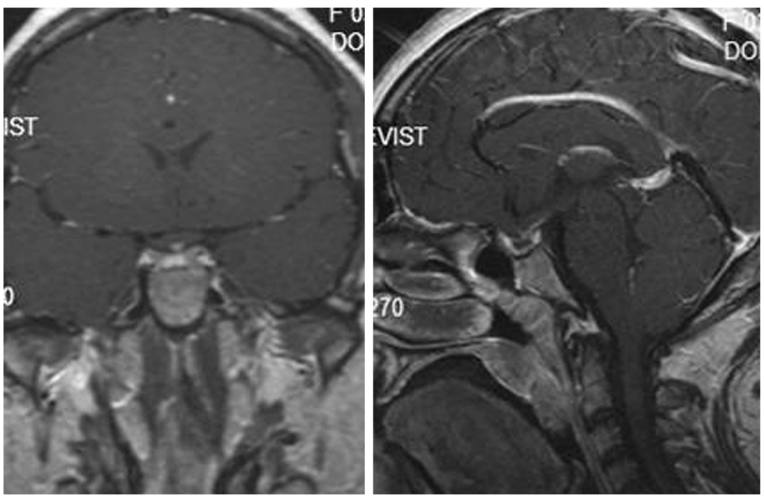

Fig. 5 T1-weighted coronal (left) and sagittal (right) MRI with contrast demonstrated the sel-lar/suprasellar mass lesion was disappeared 3 months after surgery

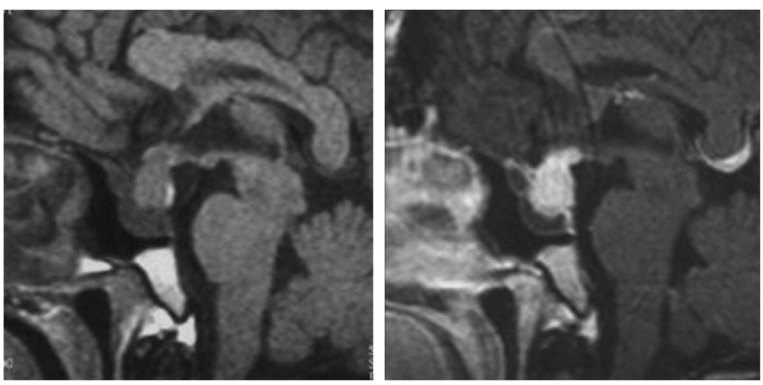

Fig. 6 Sagittal T1-weighted (left) and contrast (right): A tumor-like lesion involving the pitui-tary distinct enhancement up to the suprasellar region. Extension of mass along a thickened pitui-tary stalk into the hypothalamus

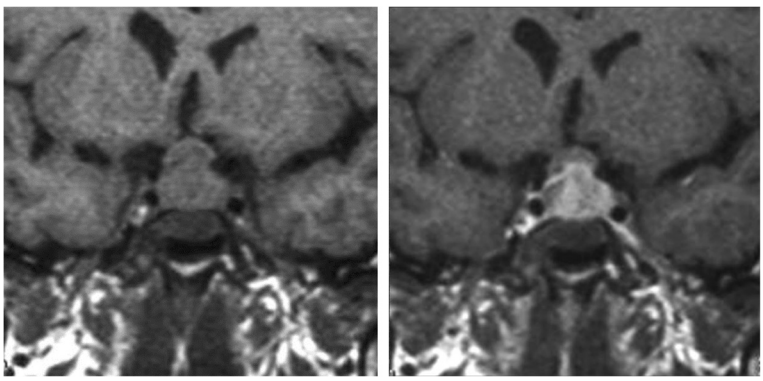

Fig. 7 Coronal T1-weighted (left) and contrast (right): Sellar/suprasellar mass, isointense T1 and hyper/hypo-intense in T2 to white matter, with mass effect on the undersurface of the optic chiasm. Mass demonstrates heterogenous enhancement

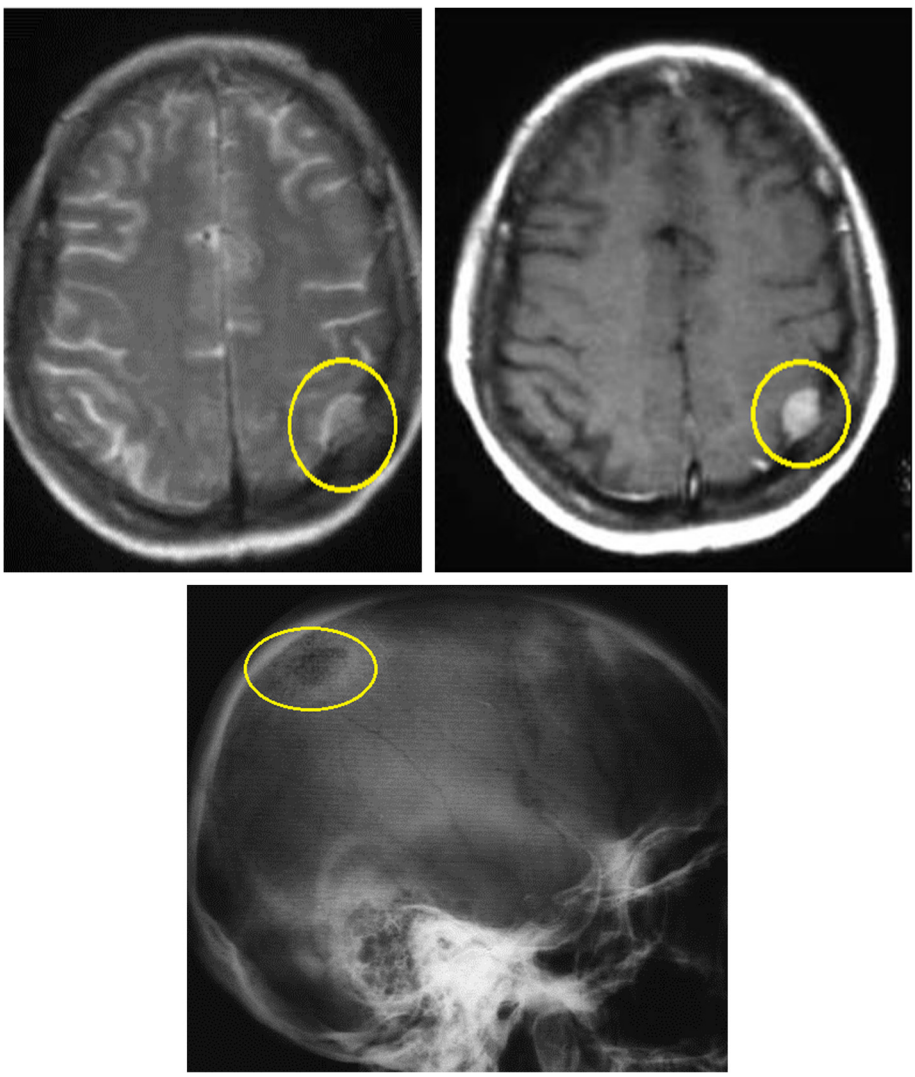

Fig. 8 Axonal T2 (upleft) and T1 (upright) MR showed the iso/hyper-intensity lesion in the left parital skull. Advanced cerebral plain X ray (down) confirmed the skull lesion (yellow circle)

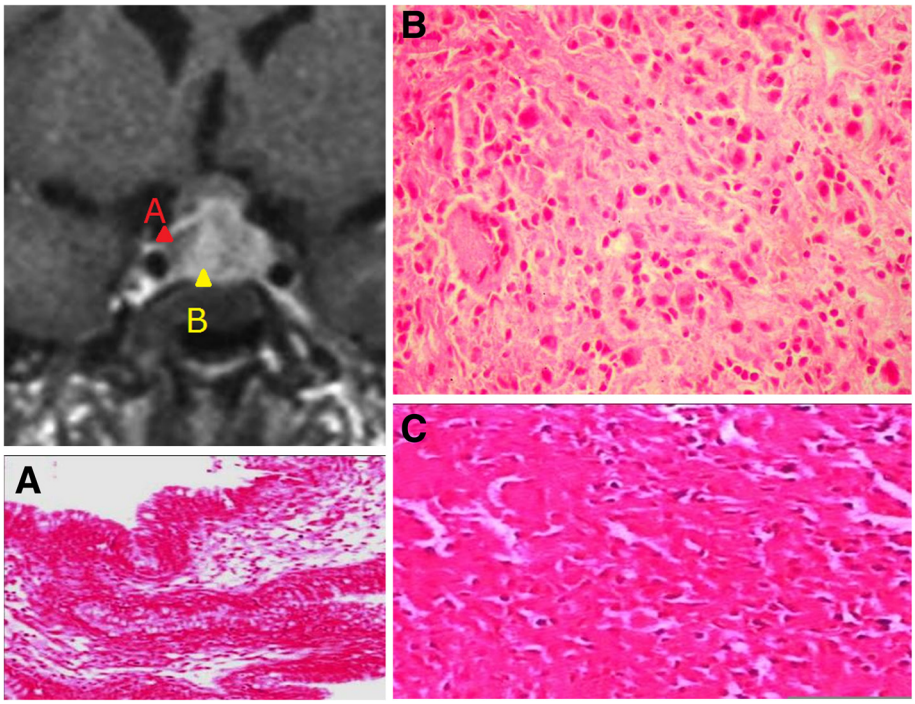

Fig. 9 The image of histologic examination and relative MR (upleft). **A**: Rathke's cleft cyst; **B**: show granulomatous hypophysitis of epitheloid macrophages and multinucleated giant cells. **C**: Eosinophilic granuloma of the skull. HE stain showing granuloma with epitheloid macrophages and multinucleated giant cells

clinical or radiological findings that can differentiate this condition from pituitary adenoma. A diagnosis of pituitary adenoma based on clinical and radiological profiling was made in all except two patients, where diagnoses of hypophysitis was considered. Granulomatous hypophysitis may also be associated with foreign body reactions, such as a ruptured Rathke's cleft cyst (case 2) or a mucocoele.

Imaging characteristically demonstrates a sellar mass with a tongue-like, suprasellar extension. The lesion may contact or infiltrate the basal hypothalamus. Pituitary stalk thickening is often a prominent feature. The lesion usually shows marked, homogenous enhancement, although heterogeneous and ring-like enhancement may also manifest. However, enhancement with contrast in granulomatous hypophysitis is very variable and it can not be used as a reliable distinguishing feature with pituitary adenomas. And other most common findings are dural enhancement and sphenoidal sinus mucosal thickening.

The key diagnostic feature of necrotizing granulomatous hypophysitis is a marked mononuclear infiltrate within

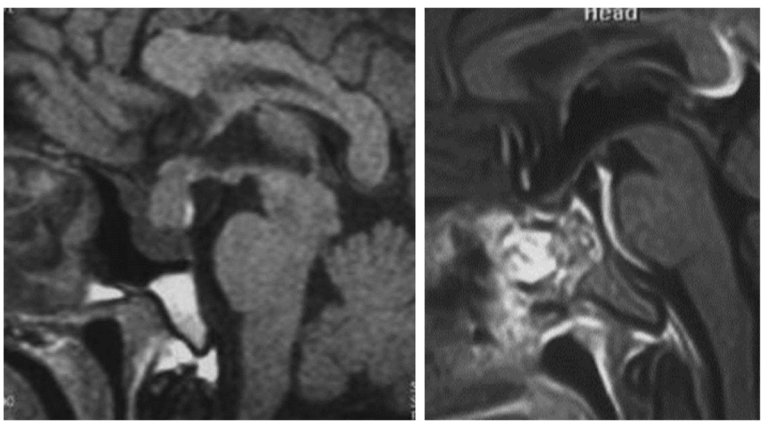

Fig. 10 T1-weighted sagittal (left) and with contrast (right) MRI demonstrated the sel-lar/suprasellar mass lesion was disappeared 3 months after surgery

pituitary tissue showing significant necrosis. Histologic examination revealed necrotizing granulomas composed of perinecrotic epithelioid histiocytes, lymphocytes and occasional multinucleate giant cells. Anterior pituitary showed partial necrosis with infiltration by numerous macrophages, necrotic areas were marked. T cell infiltrates with high numbers of cytotoxic T cells were found in the anterior pituitary. It is difficult to demonstrate the etiology of granulomatous hypophysitis immunohistochemically. The differential diagnoses considered included tuberculosis, sarcoidosis, fungal infection, syphilis, granulomatous autoimmune hypophysitis, Langerhans cell histiocytosis, and Erdheim-Chester disease.

In our cases, preoperative clinical suspicion of hypophysitis was not strong enough to end in biopsy or treatment with steroids. So all patients underwent surgical excision of the lesion, and the mass effects were immediately improvement after procedure.

Management

Considering the inflammatory nature of granulomatous hypophysitis, high-dose corticosteroid therapy may present a cornerstone therapeutic option in select cases. Some authors have reported satisfactory responses to high dose steroid therapy and methotrexate injection [5, 9, 16, 18, 19]. The diagnosis of all cases was lymphocytic hypophysitis. Although few studies reported the tentative glucocorticoid could be performed for diagnostic strategy, poor responses or high recurrence rates following steroid withdrawal have also been reported, and the adverse effects of long-term steroid therapy should also be weighed when considering this treatment option. We therefore conclude that glucocorticoid therapy is less effective in granulomatous hypophysitis. Mass enlargement seems inevitable when glucocorticoid dosage is being tapered. An ambivalent response to glucocorticoids should be expected in granulomatous hypophysitis.

Thanssphenoidal surgery, being both diagnostic and therapeutic, should therefore, be performed in cases with progressive compression or those in whom radiological and/or clinical progression occurs during conservative medical management. Surgical intervention is mandatory in establishing the diagnosis and reducing the size of the inflammatory mass, which could compress surrounding neural structures. Follow-up corticosteroid therapy is beneficial. All patients in our cohort with surgical excision of the lesion continued with steroids treatment, no recurrences have been noted during the follow up.

It is crucial to avoid overzealous resection of potentially viable pituitary tissue. However, the variable natural history of this condition makes it is difficult to accurately assess efficacy of nonsurgical treatments.

Selch et al. reported a good efficacy of stereotactic radiotherapy for two cases of recurrent lymphocytic hypophysitis [14]. Although we have no experience with stereotactic radiotherapy in the treatment in granulomatous hypophysitis, we believe this treatment modality may present a noninvasive treatment option for patients with granulomatous hypophysitis, particularly if the disease is recurrent after surgery or resistant to corticosteroids.

Conclusion

As a single center, our experience in treating eight patients with primary granulomatous hypophysitis has demonstrated the clinical characteristics of a rare inflammatory process. Radiology demonstrates a sellar mass with a tongue-like suprasellar extension. Pure glucocorticoid therapy is less effective and has not been recommended in granulomatous hypophysitis. Hormone replacement therapy can alleviate some symptoms. However, surgical intervention, (i.e. minimally invasive transsphenoidal surgery), is mandatory to establish the diagnosis and reduce the size of the inflammatory mass. Corticosteroid therapy is recommended as a suitable adjuvant therapy postoperatively.

Abbreviations

SD: Standard deviation; CE-MRI: Contrast enhancement magnetic resonance imaging; ACTH: Adrenocorticotropic hormone; T3: Thyroxine 3; T4: Thyroxine 4; TSH: Thyroid stimulating hormone; LH: Luteinizing hormone; FSH: Follicular stimulating hormone; T: Testosterone; E2: Estradiol; PRL: Prolactin; IgG4: Immunoglobulin G4; ED: Erectile dysfunction.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YX drafted the first manuscript and made a contribution to acquisition and interpretation of data. LL, T-HW, YYZ, XXC and JM performed the clinical work-up and literature search. GL revised the language and grammar of the manuscript. YX and GL revised the manuscript that let to the final approval of the current submission. All authors read and approved the final manuscript.

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