Recently advances in endocrinological and neuro-radiological expertise have greatly facilitated the early detection of pituitary lesions. Technical refinements of transsphenoidal microsurgery have also provided a safe and effective approach to the sellar tumor or mass, and broadened the indications. Previously, rare cases of pathological processes involving the intrasellar cavity and the pituitary gland were identified only dependent on autopsy materials. Nowadays, with the increasing number of transsphenoidal microsurgery, these diseases have been delineated in the clinical setting and emerge as a distinct pathological entity to be included in the differential diagnosis of sellar lesions. Primary granulomatous hypophysitis (PGH) is a rare chronic inflammatory disease of pituitary gland. Literature review demonstrated its low incidence in population. Within three large surgical series of more than 6000 sellar tumors, only 8 cases of PGH were identified [1-3]. Here, we report a case of PGH which was treated by microsurgical transsphenoidal approach and analyze the cases from the relative literatures, trying to know the characteristics of this disease.

**Case Reports**

A 56-year-old female presented with 4 months history of headache and 2 months history of polyuria and polydipsia. On physical examination, the visual fields, fundoscopic and neurological examinations were unremarkable. Endocrinological evaluation showed secondary hypothyroidism and hypocorticalism: TSH < 0.01 μIU/mL (normal: 0.3-5); free triiodothyronine (T3) 3.3 pmol/L (normal: 3.5-6.5); free thyroxine (T4) 9.8 pmol/L (normal:11.5-23.5); ACTH 6.4 pg/mL(normal :0-46); cortisol 3.6 μg/dL at 8am (normal: 5-25). A water deprivation test revealed diabetes insipidus of central origin. MRI showed a symmetric sellar mass, with 15 mm in height, which abutted the optic...
and definite, the patient was further undergone cutaneous, skeletal, visceral, and laboratory examinations for systemic granulomatous disease such as tuberculosis, syphilis, sarcoidosis, brucellosis, and histiocytosis X. Due to no significant evidences of systemic granulomatous disease were found, the final diagnosis was definitely primary granulomatous hypophysitis.

The postoperative course was uneventful. Although the resection was limited, repeatedly MRI scanning in 3 months following surgery revealed almost normal pituitary soft tissue without evidence of the lesion (Fig. 3). Desmopressin acetate was able to be withdrawn in 1 month later and glucocorticiod and thyroxine therapy were able to be gradually withdrawn in 3 months. No

Fig. 1 Preoperative coronal MRI showed a symmetric sellar mass, measuring 15 mm in height, which abutted the optic chiasm. The mass was isointensity with gray matter on T1-weighted (A) and T2-weighted (B) images and had heterogeneous enhancement after the administration of gadolinium (C and D).

The mass was isointensity with gray matter on T1-weighted and T2-weighted images and shown in heterogeneous enhancement after the administration of gadolinium (Fig. 1). The diagnosis of pituitary adenoma and secondary hypopituitarism was made. She underwent surgical exploration via the transsphenoidal approach after preoperative prednisolone, thyroxine and desmopressin acetate replacement. Surgical exploration showed the whole pituitary fossa was occupied by a fibrous and yellowish mass adherent to the adjacent dural mater and only partial resection was achieved. Histological examination revealed a non-necrotizing granulomatous lesion with chronic inflammation (Fig. 2). Once the histological diagnosis was clear...
Here, such 37 patients, add the case of ours, total 38 patients with PGH were analyzed together. In addition, Gutenberg et al. [23] reported 6 cases of PGH among a series of 31 patients with primary hypophysitis (21 lymphocytic, 6 granulomatous, and 4 xanthomatous cases). However, the author did not describe the details of each patient respectively, so such 6 patients did not include in our analysis.

Although it is generally thought no gender predilection in PGH [6, 24], the real ratio of male to female among these 38 reviewed cases was closely to 1:2 (12:26). The mean age of these patients at presentation was 46.1 years old (range from 16 to 76 years old), and the female was 44.7 years, younger than the 49.2 years old mean age of male.

Clinical presentation of PGH is variable and comprises four main categories of symptoms: sellar compression, hypopituitarism, diabetes insipidus, and hyperprolactinemia. In the total 38 patients, headache was the most common symptom, present in 23 cases (60.5 %). Followed by symptoms related to diabetes insipidus in 10 cases (26.3 %), visual field impairment in 9 cases (23.7 %), vomiting in 8 cases (21.1 %), nausea in 7 cases (18.4 %), extraocular muscle paralysis in 6 cases (15.8 %) and febrile in 5 cases (13.2 %).

All of the 38 reported patients presented with endocrinological abnormality. The incidence of diabetes insipidus was 34.2 % (13 of 38 cases) and hyperprolactinemia was 31.6 % (12 of 38 cases). Details of anterior pituitary function were available in 34 patients. Based on the available biochemical results, the incidences of insufficiency of gonadal, adrenal, thyroid and growth hormone axes were 76.5 % (26 of 34 cases), 61.8 % (21 of 34 cases), 50 % (17 of 34 cases) relapse occurred in 2 years of follow-up.

**Review of the Literature**

PGH is so rare that only case reports but no series were published by now. Thus, in clinic, there are no plenty of population-based data to calculate the real incidence of PGH. However, some authors estimated its rate might be less than 1% of all pituitary disorders with a population incidence of 1 in 10 million per annum [3, 4]. Searching in PubMed via the key words of ‘hypophysitis’, and ‘primary’ or ‘idiopathic’, we found 21 literatures published from 1985 to 2009 and 37 patients with PGH were reported [1, 2, 4-22].
headache and visual disturbance, are the most common and usually the initial complaint. Headache is considered to be induced by distension and distortion of the dural mater and diaphragma sellae due to the expanding pituitary mass. Visual abnormalities, including visual field defect and decreased acuity, are secondary to compression of optic chiasm. Lateral expansion of the mass into the cavernous sinus could compress III, IV or VI cranial nerves, resulting in diplopia and subsequently ocular misalignment [26]. All of the 38 reported patients were presented with endocrinological abnormality, in partial or complete deficit of the posterior and/or anterior pituitary hormones. These defects can lead to the classic signs and symptoms of diabetes insipidus, hypogonadism, hypoadrenalism, and hypothyroidism.

Imaging appearances of the three primary hypophysitis types are very similar. The striking CT features are an intrasellar mass with cystic areas and ring enhancement [12-14]. Currently, MRI plays a crucial role in the diagnosis of primary hypophysitis because it has distinct advantage over CT for imaging the pituitary and sellar regional lesions. The MRI findings of primary hypophysitis include: (1) Diffuse, ill-defined, symmetrical enlargement of pituitary tissue; (2) Pituitary stalk thickened, but not deviated or unidentifiable; (3) Sellar floor usually intact; (4) Mostly isointensity with gray matter on T1 weighted image, marked homogeneous or heterogeneous enhancement by gadolinium and a strip of enhanced tissue along the dura mater (the so-called ‘dural tail’); (5) Delayed complete contrast enhancement of the whole pituitary in dynamic MRI (>90 sec) [1, 4, 8-12, 29-32]. Among these unusual MRI scan findings, three imaging signs – pituitary diffuse enlargement and marked enhancement and pituitary stalk thickening, are perhaps the strongest predictor of primary hypophysitis.

**Differential Diagnosis**

To diagnose PGH, we should exclude secondary granulomatous hypophysitis. The etiology of secondary granulomatous hypophysitis includes infection (tuberculosis, syphilis, fungal), systemic inflammatory conditions (sarcoidosis, Wegener’s granulomatosis, Takayasu’s arteritis, Crohn’s disease, histiocytosis X) and foreign body reactions (ruptured Rathke’s cyst, mucocoele). In these patients, pituitary symptoms are not isolated but are always associated with a general inflammation, and presenting in specific abnormalities.
of chest X-ray, or biological inflammatory examination. Cheung et al. [4] have summarized the distinguishing features among the different types of primary hypophysitis, but the authors also pointed out the clinical and radiological presentation are similar among them and mentioned that the definite diagnosis is only based on pathological findings. Histologically, lymphocytic hypophysitis is characterized by diffusely inflammatory infiltration of the pituitary, predominant lymphocytes with occasional plasma cells and macrophages, and sometimes neutrophilic and eosinophilic polymorphonuclear cells with a variable degree of fibrosis [4, 9, 18, 26, 27]. Granulomatous hypophysitis is characterized by necrotizing granulomas that are formed by collections of histiocytes, multinucleated giant cell, and variable numbers of lymphocytes and plasma cells [4, 9, 18, 26, 27]. Xanthomatous hypophysitis, the least common form of primary hypophysitis, is characterized by the presence of lipid-rich foamy histiocytes with variable numbers of lymphocytes [4, 10, 26, 37].

Although some PGH with typical clinical and radiological presentation, such as diabetes insipidus and pituitary diffuse enlargement and pituitary stalk thickening, can be easily differentiated from a pituitary adenoma, PGH mimicking pituitary adenomas has been widely reported. Mild hyperprolactinaemia is common in granulomatous hypophysitis patients due to the compression of the pituitary stalk or the inflammatory process itself preventing the inhibitory regulation of prolactin release by hypothalamic dopamine. However, PRL concentrations are usually much lower than those of prolactinoma patients. Both hypophysitis and non-functioning pituitary adenoma can cause pituitary expansion and a variable degree of hypopituitarism, but the degree of pituitary failure of hypophysitis patients is out of proportion to the degree of lesion volume. In patients with PGH, hypopituitarism may be present with small mass or even unenlarged pituitary, while in patients with tumor it is unusual to see such a degree of panhypopituitarism except when the mass is very large. Headache, nausea and vomiting and posterior pituitary involvement are more common presentations of PGH than pituitary adenomas and the course of PGH is more rapid than in the usual cases of pituitary tumor. Diabetes insipidus rarely accompanies a pituitary adenoma, due to compression of the stalk, but in granulomatous hypophysitis it is one of the most frequent complications, due to infiltration of the stalk.

### Treatment

The natural history of inflammatory hypophysitis, including PGH, is incompletely understood yet and its treatment is still controversial. Satisfactory response to high-dose steroid therapy or anti-inflammatory and immunosuppressive (methotrexate, cyclosporine A, azathioprine) treatments have been widely reported [2, 9, 18, 26]. Conservative management with close clinical observation has also been advocated as the primary therapeutic option based on the disease’s often benign and transient course and spontaneous remission may occur [44]. Transsphenoidal surgery is, however, both diagnostic and therapeutic and, therefore, should be performed in cases with progressive compression, especially for those whose clinical and radiological presentation is not typical and diagnosis is not confirmed. In fact, majority of reported PGH and approximately half of the primary hypophysitis were misdiagnosed as pituitary adenomas preoperatively [2, 9, 18, 26]. Histopathological findings of pituitary biopsy remain the gold standard for diagnosing primary hypophysitis. Surgery provides live tissue for histological diagnosis and can rapidly decompress the mass lesion, thereby resolving headache and visual deficits immediately [1, 11, 22]. Furthermore, surgery and definitive histological diagnosis may obviate the unnecessary use of high-dose steroid therapy and facilitate the appropriate treatment of other conditions such as infection or neoplasm. A pituitary experienced neurosurgeon would remove abnormal tissue and preserve normal-looking tissue to minimize the risk of hypopituitarism. If primary hypophysitis is suspected, an intraoperative histology on frozen sections is recommended to confirm the diagnosis and avoid extensive unnecessary surgery because hypopituitarism may occur or be worsened following extensive surgery.

Surgery had poor effect on improving the preexisting endocrine defects. Most patients required long-term replacement with one or more hormones. Pituitary deficiencies in inflammatory hypophysitis result from cell destruction, so it is not surprising that hormone dysfunction respond less favorably to surgical therapy. Thus, to treat primary hypophysitis, hormone replacement is required in most cases and long-term follow up is very important.

### Conclusion

PGH is a rarely occurred inflammatory disease of
unknown etiology. The clinical presentations and radiological signs are helpful for the diagnosis of PGH. The outcome of surgery for PGH is favorable for histological diagnosis and immediate mass reduction, but hormone replacement is required in most cases and long-term follow up is very important.

References

Primary granulomatous hypophysitis


