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Case Report:

Granulomatous hypophysitis: two case reports and literature review

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Abstract: Granulomatous hypophysitis (GRH) is extremely rare and commonly presents with chronic inflammatory of the enlarged pituitary gland. In our study, 66-year-old and 57-year-old women, both Chinese, were diagnosed with GRH presenting preoperatively definite imageology characters as pituitary adenoma. The 66-year-old woman presented with a year of headache, half a year of gradual decrease of visual acuity, and one month of right ptosis. Serum prolactin level was slightly elevated. Screening computed tomography (CT) scanning revealed typical low density mass found on the enlarged sella, which demonstrated invasive extension from the sella to the right cavernous sinus by contrast enhanced magnetic resonance imaging (MRI). Consequently, the patient was diagnosed with probable invasive pituitary adenoma. The other 57-year-old woman complained a light headache and had been previously treated as nonfunctional pituitary adenoma in other hospital. Finally these two patients underwent transsphenoidal microsurgery and were diagnosed with GRH according to postoperative histopathology. They then were treated with steroid. During the follow-up, the clinical symptoms such as headache, visual damage, and ptosis vanished, and the mass of the sellae dramatically shrank on repeated MR images. Clinically and radiologically, GRH is a rare sellar entity easily to be misdiagnosed as a pituitary adenoma. Trans-sphenoidal surgery can decompress the optical nerve or oculomotornerve as a therapeutic strategy, and support biopsy or further pathological diagnosis. However, the hormonal therapy should be emphasized both as diagnostic and therapeutic strategies. Conservative and tentative steroid treatment should be performed in preoperative period without acute nerve damage.

Key words: Granulomatous hypophysitis, Steroid treatment, Imageology, Trans-sphenoidal surgery
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INTRODUCTION

Primary hypophysitis is a rare sellar entity classified histologically into four different subtypes: lymphocytic hypophysitis (LYH), granulomatous hypophysitis (GRH), xanthomatous hypophysitis (XH), and necrotizing hypophysitis (NEH). GRH is extremely rare and presents commonly with chronic inflammatory of the enlarged pituitary gland, initially described by Simmonds in 1917 (Roncaroli *et al*., 1998). Until 1980, the first ante mortem case was reported (Taylon and Duff, 1980). GRH entity, mimicking adenoma, often has clinical manifestation of headache or visual damage, but seldom presents hypopituitarism that is involved more likely in LYH. The gland can be diffusely enlarged in a pyramidal or round shape. A thickened stalk can be defined as the most characteristic feature on sagittal or coronal magnetic resonance imaging (MRI). However, these typical radiological indications occur infrequently (Unlu *et al*., 2006; Vasile *et al*., 1997), which results in the difficulty in differentiating GRH from pituitary adenoma based upon preoperative clinical and imaging data. Therefore, a considerable number of GRH cases were initially misdiagnosed as adenoma and then inappropriately received surgery therapy (Bhansali *et al*., 2004). Indeed, Beressi *et al*.(1994) reported that steroid alone was successfully used to

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treat LYH in 1994. After that, a GRH due to Wegener's granulomatosis allowed successful medical management and helped avoid surgery (Goyal *et al*., 2000). Nonetheless, other researchers insisted that surgery for hypophysitis should not be restricted to patients whose optical nerves had been crushed evidently with a decreased visual acuity. Subsequently, many attempts were made to early explore it surgically in view of the insidious clinical course of the illness (Buxton and Robertson, 2001; Honegger *et al*., 1999). In the present study, two abiogenetic GRH cases were documented, in which systemic granulomatous diseases were ruled out. Diagnosis and therapy strategies were presented, and the literature pertaining to adult GRH was reviewed.

CASE REPORT

In this retrospective study, we reviewed clinic data, endocrinological and radiological examination, operative findings and outcomes of two GRH cases. The clinical data displayed the typical symptoms of invasive pituitary adenoma on computed tomography (CT) and magnetic resonance (MR) images, and the involvement with hypopituitarism on endocrinology. As a result, one case accepted trans-sphenoidal biopsy and partial resection as "pituitary adenoma" and flushing dose steroid management. The other previously diagnosed as non-functional hypophysoma by other hospital received transsphenoidal resection.

Case 1

A 66-year-old female presented with a history of one year of severe headache and half a year of dramatic visual harm. Neurological examination revealed right-acroisa, and the left vision had only a light perception. A CT scanning showed enlarged sella and pituitary gland without calcification. A contrast enhanced MR revealed a diffusely-enlarged, homogeneously-enhanced gland, which bulged upward through the diaphragma sellae in a pyramidal or round shape, and the pituitary stalk at the top of the gland thickened. The marginal part invaded the bilateral cavernous sinus so that the left internal cranial artery was surrounded by the mass (Fig.1). Serum prolactin level was modestly elevated (35.3 ng/ml), but human thyroid stimulating hormone (h-TSH) (0.03 mU/L) and cortisol levels were low due to the hypofunction of the hypophysis thyroid and adrenal axle.

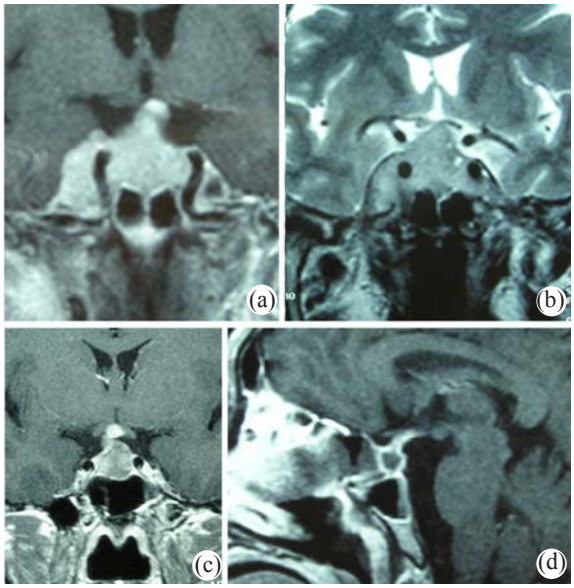

Fig.1 MR images obtained through the pituitary gland show diffusive enlargement and enhancement of the pituitary gland. The gland shows in a pyramidal shape extending to hypophysial stalk from the sellar base. MR images also note the presence of enhanced mucosa in the bilateral sphenoid sinus and enhanced meninges around the sella. (a) Case 1: T1-weighted coronal (450/15/4, repetition time (TR)/echo time (TE)/excitations) MR image; (b) Case 1: T2-weighted coronal (4000/90/3; echo train length, 8) MR image; (c) Case 2: contrast-enhanced T1-weighted coronal (450/15/4) MR image; (d) Case 2: follow-up one year, postoperative MR examination, contrast-enhanced T1-weight sagittal (450/15/4) MR image

The initial diagnosis was an invasive pituitary adenoma and the patient underwent trans-sphenoidal biopsy and microsurgery. Intraoperatively, the character of mass revealed a grey-white, fragile mixture of the eroded bone of the sellar base, but pus- or tubercular cheese-like matter had not been found. Finally, partial resection was performed. To avoid complication, the 'adenoma'-involved bilateral cavernous sinus had to be reserved. No strong evidence supporting pituitary adenoma was confirmed, and the biopsy result of intraoperative cryosections suggested that it might be related to immunity inflammation.

Postoperatively, while waiting for the histopathologic result, the patient was injected with a flushing dose of steroids (methylprednisolone, 120 mg/8 h)

for 2 d and a regular dose of steroids (methylprednisolone, 160 mg/d) for 4 d, and took thyroid hormones. A second MR was performed 6 months later. The mass in the sella was reduced markedly both in size and the degree of contrast enhancement, and the pituitary stalk recovered a normal shape and size (Fig.1). The pathologic diagnosis was clearly a chronic GRH, and additional serologic examinations of tuberculosis and syphilis were negative. A small dose of methylprednisolone (60 mg/d) was added for 7 d after discharge. The medication was tapered off and the headache gradually disappeared. At last, her visual acuity evidently improved and her serum prolactin and TSH stalk became normal.

Case 2

A 57-year-old woman presented with progressive visual damage on the right side and bilateral frontal headache for 4 months. Her visual acuity was 0.1/1.0 at the admission, the diameter of the right pupil was 0.6 cm, and the eyeball was not moveable in any direction. Moreover, the left temporal hemianopia and the paralyses of the right third, fourth, and sixth nerves were detected during a neurological examination. MRI showed a sellar entity, which was suggestive of a pituitary adenoma (Fig.1c). Chest X-ray and CT were not remarkable and no mediastinal adenopathy was noticed. Laboratory endocrinological investigations revealed mild hyperprolactinemia (300 U/L) and mild low thyroid stimulating hormone, but erythrocyte sedimentation rate was normal. A provisional diagnosis hypophysoma was thus made.

On admission, the sellar entity was partially resected via a trans-sphenoidal approach and was found to be a yellowish mass with leathery consistency. Postoperatively, a regular dose of methylprednisolone (160 mg/d) was taken for 3 d, and the patient was discharged with restoration of extraocular muscle function. Hematoxylin and eosin (H&E) stained biopsy sections revealed destruction and infiltration of hypophyseal parenchyma by lymphocytes and plasmocytes, and noncaseating granulomas with giant cells and fibrosis tissue (Fig.2). Staining for acid-fast bacilli, fungi, and spirochetes was negative. An amendatory diagnosis was offered as idiopathic granulomatous hypophysitis. There was no evidence of other systemic diseases. On follow-up, her vision returned to normal with recovery of the right pupil and the normalization of the temporal hemianopia on the left eye. A repeated MRI one year later revealed dramatic resolution of the pituitary entity.

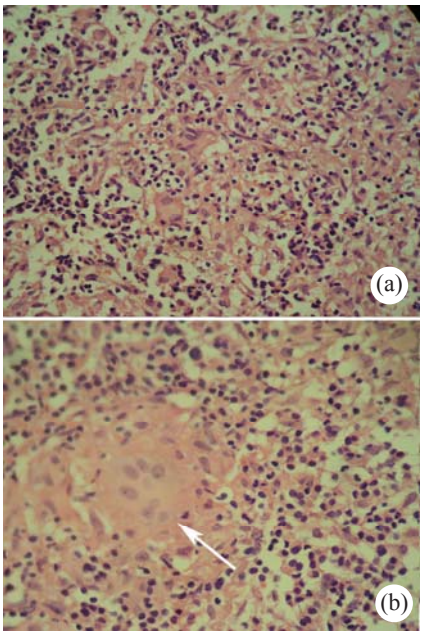

Fig.2 Hematoxylin and eosin (H&E)-stained sections from the biopsy revealed (a) focal replacement of pituitary architecture by a lymphocytic infiltrate (400×), and (b) noncaseating epithelioid cell granulomas with multinucleated giant cells (white arrow, 800×) and areas of fibrosis

An interesting similarity of clinical and imaging signs was found in the two cases, including an old age, female, headache, visual acuity decrease, extraocular muscle paralysis, triangle enhanced sellar mass on coronal MRI, and encroachment to the bilateral cavernous sinus, which supported a diagnosis of "invasive pituitary adenoma." However, histopathology showed a different story. After we reviewed clinic and imaging data, some characteristic signs for GRH were found, such as acute development in the course of disease but less imaging evidence of adenoma hemorrhage, a slight increase of serum prolactin level but insufficient thyroxine or h-TSH, thickening mucosa on the intine of the bilateral sphenoid sinus, enlarging pituitary stalk, and tongue-shaped extending upwards the basal hypothalamus (Fig.1). In follow-up, recurrence of inflammatory tissue had not been observed in the two cases, so steroid treatment was gradually stopped.

DISCUSSION

GRH is a rare chronic inflammatory disorder of the pituitary. In view of its insidious clinical course mimicking pituitary adenoma (Bhansali *et al*., 2004; Jastania *et al*., 2004; Thiryayi *et al*., 2007) and acute progress time mimicking acute meningitis (Cooper *et al*., 1999; Yoshioka *et al*., 1992), GRH was difficult to be diagnosed and treated correctly in primary admission time. Transphenoidal biopsy or surgery was usually required to establish diagnosis. Clinically, the most common symptoms and signs of GRH were attributable to impairment of vision and varying headache (Table 1). Until a complete examination, their pituitary hypofunction was likely ignored (Jastania *et al*., 2004; Thiryayi *et al*., 2007). Some studies reported that GRH patients could be successfully treated by corticosteroid alone (Bhardwaj *et al*., 2005; Bhaya, 1999), however, we hold that an early surgical exploration is necessary, for it is believed to benefit patients for their visual recovery (Arsava *et al*., 2001; Honegger *et al*., 1999).

Commonly, GRH presents with a diffusive enlargement of the pituitary mass with hypointense or isointense on T1-weighted imaging, but hyperintense on T2-weighted imaging. Usually the gland shows a diffusive heterogeneous enhancement. Typically, the lesion appears to be an enlarged and enhanced sellar mass with pituitary stalk enlargement on expanding pituitary fossa, extending into the suprasellar area with a tongue shape and compressing optic chiasm, sometimes invading into the bilateral cavernous sinus

Table 1 Summary of the definite cases reported with primary and secondary granulomatous hypophysitis

Literature	Age	Sex	Chief complaint	Etiology	Treatments
Albini *et al*., 1988	19	F	Pituitary insufficiency	Rathke's cleft cyst	TS
Arsava *et al*., 2001	53	F	Hypopituitarism and ophthalmoplegia	Idiopathic	Steroid treatment
Bhardwaj *et al*., 2005	42	F	Diplopia, headache	Tuberculosis	TS, antitubercular therapy
Bhaya, 1999	24	M	Headache	Intrasellar tuberculoma	TS, antituberculous drugs, thyroid hormones and steroids
Brisman *et al*., 1996	65	F	Headaches, hypopituitarism, and visual disturbances	Idiopathic	Surgery
Cooper *et al*., 1999	32	F	Headache, worsening vision	Idiopathic	TS, hormone replacement therapy
de Bruin *et al*., 1991	33	F	Deterioration of visual acuity	Pregnancy, Crohn's disease	TS
Fernandez *et al*., 1990	69	F	Gastrointestinal hemorrhage	Idiopathic	Autopsy
Hassoun *et al*., 1985	65	F	Hypopituitarism	Idiopathic	Hypophysectomy
Honegger *et al*., 1997	16	F	Meningitis	Idiopathic	Surgery
	48	F	Headache	Idiopathic	Surgery
Illueca *et al*., 2002	55	F	Headache, panhypopituitarism	Idiopathic	TS
Inoue *et al*., 1997	62	F	Subacute unilateral ophthalmoplegia	None-mention	TS
Goyal *et al*., 2000	48	F	Progressive visual loss	Wegener's granulomatosis	Steroid management
Nagi *et al*., 2002	23	F	Polyuria, polydipsia	Idiopathic	Pituitary biopsy
Roncaroli *et al*., 1998	37	F	Headache, amenorrhea	Ruptured intrasellar Rathke's cleft cyst	TS
Shimizu *et al*., 1998	49	M	Panhypopituitarism and diabetes insipidus	Idiopathic	Transsphenoidal pituitary biopsy
Simmonds *et al*., 1917*	45	F	Headache	Idiopathic	Autopsies
Thiryayi *et al*., 2007	21	F	Headaches	Wegener's granulomatosis	Steroid treatment
Wilson *et al*., 2000	54	F	Acute onset diabetes insipidus	Idiopathic	Biopsy, high-dose steroids and local low-dose radiation
Yoshioka *et al*., 1992	76	F	Meningitis, hypopituitarism visual impairment	Idiopathic	Steroid administration

*Roncaroli *et al*., 1998; M: male; F: female; TS: transsphenoidal surgery

or vicinal dura and revealing 'enhanced dural tail' (Unlu *et al*., 2006; Vasile *et al*., 1997). Some authors also noted the appearance of mucosal thickening in the bilateral sphenoid sinus (Goyal *et al*., 2000) in GRH cases, but marked and homogeneous contrast enhancement of the pituitary gland was treated as a characteristic of LYH (Yamagami *et al*., 2003). The boundary was not very smooth and clear. Untypically, presenting as non-functioning pituitary adenoma, GRH localizes in enlarged sella and pituitary roundly suffused with isointense on T1- or T2-weighted imaging, but enhanced evidently (Hassoun *et al*., 1985; Madsen and Karluk, 2000).

The etiology of primary hypophysitis is still not fully clarified. Histologically, compared with other three primary hypophysitis subtypes, GRH, XH and NEH, LYH seems to be related to autoimmune. LYH is a rare but well-reported entity that mimics pituitary adenoma and occurs mostly in female in the peripartum period. We also found clinical and laboratory suggestions to illuminate an autoimmune basis of primary GRH. A controversy about the composition of the inflammatory infiltrate and the relevant immunopathogenic effector mechanisms still exists (Gutenberg *et al*., 2005). The common histological findings of GRH include multinucleate giant cells, histiocytes, and infiltration by numerous lymphocytes and deposition of calcium (Higuchi *et al*., 1993; Shimizu *et al*., 1998). Some reported that histopathological examination showed a chronic inflammatory reaction with epithelioid and giant cells bordered by a heavy lymphocytic reaction, resembling tubercles, and immunohistochemistry result was characterized by histiocytes ($CD68^+$) and a heterogeneous inflammatory infiltrate ($CD45RO^+$, $CD20^+$) (Gutenberg *et al*., 2005; Honegger *et al*., 1999). Some histopathology revealed extensive infiltration of lymphocytes, plasma cells, histocytes and other inflammatory cells (Sautner *et al*., 1995). Some pathologic reports clearly revealed Langhans type of giant cells. When macrophages were stimulated, a great number of the large mononuclear cells could be found to be positive with staining for macrophage factor. Immunostaining for white blood cells (WBCs) with the leucocyte common antigen (LCA) revealed that the lymphocytes (especially B lymphocytes) were strongly positive throughout. We noticed that fibrosis tissues were commonly found and presented in varying degrees, explaining the whitish discolorations. Toughness and adherence therefore often were explored by the neurosurgeons upon trans-sphenoidal biopsy and microresection. In contrast, pituitary adenomas mostly arising from the adenohypophysis are usually grayish white, fleshy or with cystic change, and easy to be curetted. The various reported secondary causes of GRH include tuberculosis, sarcoidosis, syphilis, Wegener's granulomatosis, mycotic granuloma and foreign body granuloma due to ruptured Rathke's cleft cyst, systemic immunologic diseases such as Takayasu's disease, Crohn's disease, and so on (Albini *et al*., 1988; de Bruin *et al*., 1991; Toth *et al*., 1996; Caturegli *et al*., 2005). Our cases were idiopathic GRH. If some lesions were considered to be idiopathic giant cell granulomatous hypophysitis, systemic granulomatous diseases should be ruled out.

The evidence of coexisting lymphocytic and granulomatous hypophysitis could be found in some special cases (Miyamoto *et al*., 1988). For this reason some authors reported that they had similar clinical symptoms at different stages of one same disease (Sato *et al*., 1998). It was suggested that the two diseases represented an autoimmune procedure from a predominant pure lymphocytic infiltration of early lesion to a granulomatous form appearing later. We noticed that GRH has individual histopathology with multinuclear giant cells, mostly occurring in adult females far after peripartum period, and mostly presenting ophthalmoplegia or visual defect caused by intrasellar mass instead of headache (Arsava *et al*., 2001; Illueca *et al*., 2002). However, some reported that clinical signs of lymphocytic hypophysitis were characterized by meningitis, hypopituitarism, or diabetes inspidus (Tashiro *et al*., 2002). We argue that GRH should keep its special classification and be distinguished from LYH.

In literature, bilateral abducens or oculomotorius paresis has never been found in GRH patients. Our cases and other reported cases highlight the importance of considering one-side abducens or oculomotorius paresis in the differential diagnosis of sellar lesions. All these cases illustrate that idiopathic GRH should not be ignored in the differential diagnosis when a pituitary mass presented double vision associated with single oculomotorius or abducens nerve neuropathy, hypopituitarism but hyperprolactinaemia, and meningitis-like symptoms. The modestly high

level of prolactin is attributable to pituitary stalk compression. Preoperationally, idiopathic GRH could be mimicked as acute meningitis (Cooper *et al*., 1999). These patients usually have symptoms such as headache, photophobia, fever, nausea, vomiting, worsening vision, and minimal or non-round pituitary mass. In an acute period, lumbar puncture should be regarded as an important preoperative diagnostic method, but it is often ignored. It provides cerebrospinal fluid lymphocytic cell counter, protein level, and evidence to rule out acute meningitis (Shimizu *et al*., 1998).

At the present, histopathology is a golden standard for the diagnosis of GRH, while it is difficult to make preoperative definite diagnosis of GRH. Typical imaging feature and endocrine examination could help to distinguish this rare disease from pituitary adenoma. If preoperative diagnosis is doubtful, transsphenoidal biopsy is a feasible alternative; however, if patients are suffering from hypopituitarism, tentative methylprednisolone therapy could be performed. Yamagami *et al*.(2003) reported a successful treatment for mass reduction of pituitary gland and restoration of pituitary function with high dose methylprednisolone pulse therapy (HDMPT) in LYH patients. Idiopathic GRH rarely responded well to HDMPT (Nagi *et al*., 2002), but it was proved to be effective for mass reduction of pituitary gland and restoration of pituitary function.

It has been proposed that the suspected inflammatory lesions of the pituitary should be managed conservatively to obviate the need of surgery (Beressi *et al*., 1994). In case of progressive compression, which causes optometric deterioration during conservative management, the trans-sphenoidal surgery is both diagnostic and therapeutic treatments and should be performed as soon as possible (Scanarini *et al*., 1989). Postoperative steroid stosstherapy and continued regular dose treatment should be considered as a necessary management. Our two patients both had remission of headache, hypopituitarism, ophthalmoplegia, and visual defect during a 1- or 2-year follow-up.

CONCLUSION

In conclusion, GRH is a rare entity that mimics pituitary adenoma, diabetes insipidus, or acute meningitis both clinically and radiologically. In most cases, the diagnosis was not totally affirmed until a histopathological study. Preoperative steroid therapy has been reported to improve clinical or radiological outcome. We suggest that MRI screening for an important sign of GRH that pyramidally-shaped enhanced sellar mass extends to a tongue-shaped hypothalamus could help with an early diagnosis. Trans-sphenoidal surgery is both diagnostic and therapeutic strategies, which should be performed for patients suffering visual loss. Pathological features of the surgical specimen often reveal a granulomatous area with multinucleated giant cells, plasma cells, and lymphocytes.

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