CASE REPORT

Granulomatous hypophysitis: a case of severe headache

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SUMMARY

Idiopathic granulomatous hypophysitis (GH) is an uncommon inflammatory disease of the pituitary with impairment of pituitary gland function due to infiltration by lymphocytes, plasma cells and macrophages. We report the case of a 39-year-old woman who presented with worsening of headaches for 1 month and blurring of vision over 5 days. An MRI revealed a homogeneous supra-sellar mass evoking a pituitary tumour with bulky pituitary stalk extending into the left and right cavernous sinuses. Hormonal investigations showed anterior pituitary hormone deficiencies; meanwhile histopathological examination revealed an aspect of hypophysitis. Clinical and radiological remission occurred immediately postglucocorticoid therapy with the addition of a steroid-sparing agent later in view of recurrence of symptoms on glucocorticoid dose reduction. GH has important diagnostic and therapeutic implications, as clinical and radiological features ameliorate via medical treatment. With further understanding and recognition of the disease, we hope to highlight a case of GH, in which signs and symptoms improved after initiation of corticosteroids.

BACKGROUND

After decades of its discovery, idiopathic granulomatous hypophysitis (GH) is still a rare and under-reported inflammatory disease of the pituitary gland. A systemic review of 82 cases in 2014 represents the biggest data set thus far with concluding statements on female predilection and surgery offering a better clinical outcome compared to corticosteroid therapy.¹ This case report highlights the diagnostic difficulty of GH which subsequently demonstrated very good response to glucocorticoid therapy.

CASE PRESENTATION

A 39-year-old woman presented to the emergency department with 1-week history of blurring of vision, nausea, vomiting and extreme fatigue associated with worsening of left frontotemporal headache for a month. There was no history of fever or altered level of consciousness. Significant medical history started in 2005 when she presented to another medical centre with 6 months' history of galactorrhoea accompanied by transient episodes of severe headache relieved by simple analgesia. Investigations then showed a prolactin level of 1470 μ IU/mL ($n < 500 \mu$ IU/mL). Other pituitary hormones were normal. MRI of the brain revealed an enlarged pituitary gland with a poorly

enhancing lesion measuring 1.2×1.2 cm extending into an enlarged stalk. The optic chiasm was normal. A diagnosis of macroprolactinoma was made and she was started on oral bromocriptine. MRI of the pituitary repeated 3 months later revealed a normal pituitary gland and stalk with absence of any lesion. She continued bromocriptine for 1 year and subsequently stopped due to resolution of the symptoms and normalisation of the serum prolactin level. In 2007 she delivered her third child, a healthy baby girl with uneventful antenatal and postnatal courses. However, her headache recurred 4 months after delivery associated with failure of lactation and amenorrhoea. She was diagnosed to have migraine and was started on oral antimigraine treatment. She remained amenorrhoeic but did not seek further medical advice for this condition. The headache persisted over the years with increasing frequency and severity. One week prior to admission to our medical centre, she noted blurring of vision, nausea, vomiting and extreme fatigue. There was no history of galactorrhoea, weight loss or visual field loss. There was no significant family history and she was a non-smoker.

On examination, her blood pressure was 90/60 mm Hg, pulse rate was 60 bpm and afebrile. She did not appear cachexic, and there were no obvious signs of hypothyroidism. Cranial nerve examination revealed left lateral rectus palsy with no evidence of nystagmus. Other neurological examinations were unremarkable.

INVESTIGATIONS

Blood examinations revealed anterior pituitary hormone deficiencies including adrenocorticotrophic hormone (ACTH) < 1 pmol/L (N: < 11), cortisol 63 nmol/L (N: > 550), thyroid stimulating hormone (TSH) 0.014 mIU/L (N: 0.5–4.67), free thyroxine (FT4) 10.4 pmol/L (9.14–23.81), luteinizing hormone (LH) 0.04 mIU/mL (N: 1.3–12.9), follicle stimulating hormone (FSH) 0.37 mIU/mL (N: 0.95–11.95), oestradiol 49 pmol/L (N: 77–921) and prolactin 190 mIU/L (N: 59–169). An MRI of the pituitary showed a homogeneous supra-sellar mass measuring 2×2.6×1.6 cm with bulky pituitary stalk (figure 1A). Repeat MRI pituitary images after initiation of treatment demonstrated normal pituitary and normal pituitary stalk (figure 1B).

The mass had extended into the left and right cavernous sinuses, encasing the left internal carotid artery. The left optic nerve, tract and chiasm could not be visualised. She was started on oral

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Figure 1 Contrast-enhanced T1-weighted MRI of the sellar region on coronal view comparing the initial image (A) and post-treatment image (B). Heterogeneously enhancing sellar mass displaces the optic tract superiorly with involvement of both cavernous sinus in (A) and complete resolution of the sellar mass in (B). 3V, third ventricle; LLV, left lateral ventricle; RCS, right cavernous sinus; ROT, right optic tract; SM, sellar mass; SS, sphenoid sinus.

hydrocortisone and levothyroxine replacements. She subsequently underwent a transsphenoidal approach pituitary biopsy, which was complicated by transient cranial diabetes insipidus. Repeated MRI showed unchanged size of the pituitary tumour. Her symptoms worsened with complete loss of vision in the left eye associated with severe headache requiring daily analgesia and she was scheduled for a repeat debulking surgery. Histopathological examination of the pituitary tissues subsequently revealed the presence of non-caseating granulomas composed of macrophages and multinucleated giant cells with lymphocytes rimming the periphery (figure 2) consistent with granulomatous inflammation. Tests for sarcoidosis, tuberculosis (TB), histiocytosis X and syphilis were proven negative. A diagnosis of GH was made and she was initiated on oral prednisolone 40 mg daily. The following day, she experienced complete relief of her headache and regained full vision of her left eye. The prednisolone was gradually reduced to 10 mg daily over a period of 4 months. Repeated MRI pituitary images 3 months later demonstrated reduction of the sellar mass with normal pituitary stalk. Prednisolone was further reduced with the

Figure 2 Presence of non-caseating granulomas composed of macrophages and multinucleated giant cells with lymphocytes rimming the periphery consistent with granulomatous inflammation.

introduction of azathioprine for steroid-sparing immunosuppressant therapy. An MRI of the pituitary performed 8 months after the initiation of steroid showed a normal pituitary gland (figure 1B). She continued to be symptom free with low-dose prednisolone and azathioprine.

DIFFERENTIAL DIAGNOSIS

1. GH
2. Lymphocytic hypophysitis (LYH)
3. Non-functioning pituitary macroadenoma

TREATMENT

She initially underwent a transsphenoidal approach pituitary biopsy, which was complicated by transient cranial diabetes insipidus. Repeated MRI showed unchanged size of the pituitary tumour. Her symptoms worsened with complete loss of vision in the left eye associated with severe headache requiring daily analgesia and she was scheduled for a debulking surgery.

After reviewing the histology slides containing pituitary tissue obtained from her initial transsphenoidal approach pituitary biopsy, a diagnosis of GH was made and she was started on oral prednisolone 40 mg daily. The following day, she experienced complete relief of her headache and regained full vision of her left eye. The prednisolone was gradually reduced to 10 mg daily over a period of 4 months. Repeated MRI pituitary images 3 months later demonstrated reduction of the sellar mass with normal pituitary stalk.

OUTCOME AND FOLLOW-UP

Prednisolone was further reduced with the introduction of azathioprine for steroid-sparing immunosuppressant therapy. MRI of the pituitary performed 8 months after initiation of steroid showed a normal pituitary gland. She continued to be symptom free with low-dose prednisolone and azathioprine.

DISCUSSION

Autoimmune hypophysitis (AH) is the most common presentation of a chronic inflammatory pituitary disorder.² It constitutes a spectrum of pituitary abnormalities differentiated by varying levels of lymphocyte and granulocyte manifestations in histopathological

examinations.² Histologically, LYH is better described; meanwhile, the description of GH is limited to few case reports and case series.³ LYH occurring during pregnancy and peripartum periods are well documented. No such relation to pregnancy has been described with GH. This case report, thus, highlights the rarity of GH occurring within the postnatal period, which started 4 months after the delivery of her third child in 2007. The delay in diagnosis emphasises the importance of having the suspicion towards AH in women with postnatal headaches.

GH which occurs 1 in 10 million cases and accounts for <1% of all pituitary tumours,¹ was described by Brissaud, Gougerot and Gy in 1908 and further defined by Simmonds in 1917.^{1 4} It can occur as idiopathic primary GH (IGH) or secondary to other diseases including TB, sarcoidosis, syphilis, Wegener's GH, Langerhans histiocytosis, pituitary adenoma and Rathke's cleft cyst rupture.¹ Hunn *et al*¹ recently described the biggest case series of 82 reports and identified a female predilection. Our patient manifested many features consistent with the report including a mean age of presentation at 43 years with other common presenting symptoms including headaches (61%), vision changes (41.5%) and suppressed hypothalamic–pituitary–adrenal axis (73.1%).¹ Unlike LYH, autoimmunity was not a prominent feature in IGH.

In addition, 10 years prior to presentation to our medical centre, she was diagnosed as macroprolactinoma in view of her symptoms, biochemical results and MRI which improved with bromocriptine. Unfortunately as it has been a decade since her presentation, her old films were not able to be retrieved. Nevertheless, the resolution of symptoms, biochemical results and MRI findings with bromocriptine could be a coincidence as it could also represent a cyclical clinical course of IGH.

Biochemically, ACTH deficiency was frequently observed as reported by in a large case series of AH,^{5 6} which could either occur as part of the panhypopituitarism or it may occur in isolation.^{1 5 7} Suppressed gonadal axis, a prominent feature in our patient, was reported in 66.1% of cases.¹ Hyperprolactinaemia is a less common presentation affecting between 15% and 30% of patients, manifesting as abnormal menstruation, galactorrhoea and failure to lactate.^{3 8} It is believed to be multifactorial, attributed to pituitary stalk compression or due to the inflammatory process, which may directly alter the inhibitory dopamine receptors.⁷ However, during her subsequent presentation in 2015, her prolactin level was not elevated, which may be explained by the specific destruction of the lactotrophic cells by inflammation.⁹

Radiologically GH presents as an intrasellar mass with supra-sellar extension which has similar features to other conditions including pituitary adenoma, pituitary haemorrhage, aneurysm, granulomatous diseases, parasellar tumours and cysts. Furthermore, the lesion is commonly isointense on T1-weighted images and heterointense in T2-weighted images. Loss of posterior pituitary bright spot and thickening of the pituitary stalk has been reported to be the most common findings in radiological studies in patients with GH.^{10 11}

Histological features of GH include collection of histiocytes, multinucleated giant cells and variable number of lymphocytes and plasma cells.¹² As it is a diagnosis of exclusion, absence of acid-fast bacilli and fungus on special stains, negative immunostaining for Langerhans cells favours the diagnosis of GH. Apart from that, where resources allow, other diagnostic measures to exclude systemic diseases should also be conducted including Mantoux testing, chest radiography, TB PCR of cerebrospinal fluid and pituitary tissue serum syphilis testing and measurement of serum ACE.

Antipituitary autoantibodies may play a role in the pathogenesis of autoimmune pituitary disorders. Nevertheless, it is non-specific as it can also be elevated in empty sella syndrome, isolated pituitary hormone deficiencies, panhypopituitarism and individuals with isolated hyperprolactinaemia.¹³ Hence, due to this reason, and also due to lack of resources, we did not proceed in sending an antipituitary autoantibody test for our patient.

The main treatment goal for AH is symptomatic relief of the mass effect and replacement of hormonal deficiencies. Surgery was previously a common treatment option until the more current literature demonstrates favour towards glucocorticoids. Hashimoto *et al*⁵ observed 158 cases of LYH and found that a higher percentage of patients (62.5%) who received supraphysiological doses of glucocorticoid (prednisone-equivalent dose ≥ 10 mg/day) demonstrated significant reduction of pituitary mass. Hunn *et al*¹ reported a trend towards better outcome with surgical excision alone compared to surgery and corticosteroid treatment although the latter may have been added in severe cases only thus influencing the outcome. This case report thus presents a challenge to that conclusion, demonstrating a remarkable immediate response to high-dose corticosteroid in a histologically confirmed GH, completely avoiding surgical intervention. Other forms of steroid-sparing immunosuppressive therapy including azathioprine are potentially effective but yet to be confirmed.¹⁴

AH has important diagnostic and therapeutic implications as the clinical, hormonal and radiological presentations mimic many pituitary disorders. GH is a rare cause of AH in which histopathological diagnosis is still the confirmatory test and surgery the mainstay of treatment. This case report clearly supports the above statement whereby initiation of glucocorticoid therapy proved to be very effective resulting in immediate and sustained tumour remission.

Learning points

- ▶ Autoimmune hypophysitis consisting of lymphocytic hypophysitis and granulomatous hypophysitis is the most common presentation of a chronic inflammatory pituitary disorder.
- ▶ The most common presenting symptoms are headache, vision change and suppressed hypothalamic–pituitary–adrenal axis.
- ▶ It is important to have a high clinical suspicion in patients presenting with the above symptoms as remission is attainable with medical therapy that is, glucocorticoids $\pm$ steroids sparing agents.

Contributors SFWMH was involved in writing and editing. MFH was involved in writing, interpretation of radiological scans. SAMA contributed to writing and interpretation of histological slides. RAG was involved in writing and editing.

Competing interests None declared.

Patient consent Obtained.

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