CLINICAL COURSE OF A PITUITARY MACROADENOMA IN THE FIRST TRIMESTER OF PREGNANCY: PROBABLE LYMPHOCYTIC HYPOPHYSITIS

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SUMMARY Recent findings revealed that the clinical features of lymphocytic hypophysitis are more complicated than previously thought. It is rarely described in the first trimester of pregnancy and signs of meningeal irritation are infrequently reported. In this study, a pregnant woman in her first trimester of pregnancy with clinical and radiological characteristics of a pituitary macroadenoma is described. The patient’s pituitary profile revealed a relatively low prolactin for her stage of pregnancy. Unusual findings were neck stiffness associated with headache, nausea and vomiting. She was treated conservatively. Spontaneous complete resolution of the pituitary mass in the postpartum period led us to conclude that the correct diagnosis should be hypophysitis. Hypophysitis should be considered in the differential diagnosis of a pituitary mass presenting in early stages of pregnancy with symptoms mimicking hyperemesis gravidarum and/or meningeal irritation. (Int J Clin Pract 1999; 53(6): 478-481)

Lymphocytic hypophysitis is now recognised as a cause of hypopituitarism. The disease shows a predominant female predilection of approximately 8:5:1, and young women during late pregnancy or in the postpartum period are commonly affected. Clinical presentation and radiological findings may mimic a pituitary adenoma. Computed tomography (CT) or magnetic resonance imaging (MRI) reveals features of an enlarging pituitary mass with frequent evidence of suprasellar extension in 83-95% of patients. Pituitary enlargement is generally diffuse and symmetric. Asymmetrically enlarged pituitary glands with biopsy-proven lymphocytic hypophysitis have also been described.

In this study, a pregnant woman with clinical and radiological features of a pituitary macroadenoma is described. The patient’s clinical course and postpartum imaging study led us to the diagnosis of hypophysitis.

CASE REPORT

In January 1997, a 31-year-old woman was admitted to our hospital in the second month of pregnancy after five days of severe headache, nausea and vomiting. Her past history revealed she suffered from migraine headaches. On physical examination her blood pressure was 90/60 mmHg with a heart rate of 88 beats/min. Mild neck stiffness was noted. Examination of the gastrointestinal, respiratory and cardiovascular systems were unremarkable. Ocular fundi were normal. Contrast-enhanced MRI of the cranium disclosed a well-defined intrasellar mass measuring 1.5 x 1.8 cm (Figure 1). The mass filled the sella turcica and extended superiorly to affect the central portion of the optic chiasm. The sellar mass was poorly enhanced by contrast medium (gadolinium) and the normal pituitary could be separated from the ‘tumour’. There was a questionable minimal defect of the bitemporal visual field. MR angiography showed no evidence of subarachnoid haemorrhage. Cerebrospinal fluid (CSF) analysis disclosed no evidence of meningitis or subarachnoid haemorrhage. Clinical presentation raised the suspicion of pituitary apoplexy. Basal serum samples were obtained and twice-daily methylprednisolone 20 mg was given parenterally because of suspected hypoadrenalism.

The results of routine urinalysis, a complete blood count with a differential count and measurement of urea nitrogen, glucose and electrolyte levels were all normal except for a high ESR (57 mm/h). The results of hormonal assays were: total T3: 1.8 ng/ml (NR 0.5-1.8 ng/ml for non-pregnant women); total T4: 14.1 μg/dl (NR 4.8-12.8 μg/dl for non-pregnant women); TSH: 1.5 μU/ml (NR 0.4-4.0 μU/ml);
prolactin: 12.6 µg/l (NR 35 µg/l in the first trimester of pregnancy)\textsuperscript{1,9,10} – i.e. a relatively low prolactin level for her stage of pregnancy – and basal 8.00 a.m. cortisol 15.5 µg/dl (NR 5-25 µg/dl). Repeat contrast-enhanced sella MRI disclosed no evidence of intrasellar haemorrhage. Parenteral glucocorticoid treatment was decreased gradually and stopped after three days. The neck stiffness and headache disappeared within 10 days.

The initial presentation was thought to be caused by hyperemesis gravidarum and an attack of migraine headache. The diagnosis was non-functioning pituitary macroadenoma. Because of the absence of pituitary dysfunction (except for the relatively low prolactin level for her stage of pregnancy) and of significant visual field defect, it was decided to manage the patient conservatively. Her follow-up policy consisted of monthly visual field examination. No visual field deterioration was observed during follow-up.

In June 1997, a healthy male infant was born with an uneventful vaginal delivery. Steroid therapy was not necessary during delivery. Lactation started immediately in the postpartum period and continued. Over the next two months regular menstruation resumed. Hormonal evaluation at six months revealed the following findings: free T4: 19 pmol/l (NR 12-25 pmol/l), TSH: 1.2 µU/ml, basal 8.00 a.m. cortisol: 37 µg/dl, and prolactin: 12.8 µg/l (NR <20 µg/l for non-pregnant women). A repeat MRI scan six months after delivery showed complete resolution of the pituitary mass (Figure 2).

**DISCUSSION**

Although a tissue diagnosis was not obtained in this patient, it was felt that the clinical course of a resolving pituitary mass in a pregnant woman was typical of lymphocytic hypophysitis. Pituitary adenoma is unlikely because of shrinkage of the mass without any apoplexy. Lymphocytic hypophysitis presents most often during late pregnancy or in the postpartum period.\textsuperscript{1,2} Several reports of this disorder in men, and in non-pregnant and post-menopausal women, were described recently.\textsuperscript{6,8,11-13} Thodou et al\textsuperscript{6} described 10 of 16 cases with lymphocytic hypophysitis associated with pregnancy: two patients presented during the second trimester, two during the third trimester and six during the postpartum period. As far as we know, this is the first case presented in the first trimester of pregnancy with a clinical picture mimicking hyperemesis gravidarum and meningeval irritation. Unusual findings in our case were the presence of mild neck stiffness associated with headache.

A recent report indicated the presence of a meningitis-like clinical presentation with severe headache and neck stiffness in two out of nine cases with biopsy-proven hypophysitis.\textsuperscript{13} In these cases, the most striking features of biopsy-proven lymphocytic and/or granulomatous hypophysitis were the increased CSF cell count and related meningitis. An increased ESR (52 mm/h and 90 mm/h) was observed in two of the nine cases. CSF was found to be sterile. Lymphocytic hypophysitis was not associated with pregnancy in any of these patients. In one of two patients with clinical signs of meningitis, CSF cell count rapidly declined without specific antimicrobial therapy, and fever and episodes of meningitis ceased once the inflammatory lesion had been removed.\textsuperscript{13}

An increased CSF white cell count with or without associated meningitis has been documented in some cases of lymphocytic hypophysitis.\textsuperscript{6,8,11,13,14} Although an increase in CSF cell count was not demonstrable in our case, headache and neck stiffness indicated the possible involvement of the subarachnoid space during the inflammatory process. An increased ESR in our patient should be considered as an additional finding to support the suspicion of hypophysitis.

The natural history of lymphocytic hypophysitis is variable. In most cases, progressive severe and permanent hypopituitarism reflects the degree of destruction of hypophyseal cells.\textsuperscript{14} A fluctuating clinical course and recurrent symptoms have been reported\textsuperscript{6,8,11,14} and symptoms of panhypopituitarism eight years after pregnancy-related lymphocytic hypophysitis have been demonstrated.\textsuperscript{15} Spontaneous partial or total pituitary functional recovery and/or resolution of the mass have been described in some patients.\textsuperscript{6,15}

Bitton et al\textsuperscript{10} reported the clinical course of a 27-year-old woman in her seventh month of pregnancy with a diagnosis of biopsy-proven lymphocytic hypophysitis. Clinical presentation suggested a pituitary macroadenoma with partial hypopituitarism. The patient was treated with steroids and replacement doses of thyroid hormone. Full recovery of both size and hormonal function of the pituitary was demonstrable after delivery. In our case the prominent abnormality was the relatively low prolactin level for her stage of pregnancy. Reusch et al\textsuperscript{12} described a similar patient with a pituitary mass and visual field defect in whom the pituitary hormone profile revealed an abnormal thyroid axis and a relatively low prolactin level for her stage of pregnancy. Spontaneous and continuous lactation after delivery in our case indicated that lactotrophs gained normal function in the postpartum period. In addition, no other pituitary functional abnormalities were noted.

Pituitary failure disproportionate to the relatively small intrasellar mass is a suspicious finding for hypophysitis.\textsuperscript{4,11} With a relatively small inflammatory lesion there may be
dramatic hypopituitarism, which is not often seen with small adenomas. But selective deficits of anterior pituitary hormones have also been reported. 1,3,9,20 In our patient a relatively large pituitary lesion without apparent functional defect was found. This lesion was asymmetrically enlarged and the normal pituitary was distinct from the 'tumour'. Our patient's well-preserved pituitary function relative to the pituitary mass might be explained by the absence of diffuse inflammatory infiltration throughout the pituitary which could interfere with pituitary function. A relatively localised collection of lymphocytes and adjacent normal anterior pituitary tissue was described in one previous case of lymphocytic hypophysitis. 3 In our patient the absence of irreversible pituitary cell destruction may have been responsible for the well-preserved pituitary function during follow-up.

Radiological features suggestive of lymphocytic hypophysitis are diffuse enlargement of the pituitary and homogeneous signal enhancement after gadolinium injection. 1,2,3,5,6,8 Marked contrast enhancement in MRI or CT is typical of inflammatory lesions of the pituitary. 1,4 Ring-like enhancement has also been reported. 4 Our patient did not show homogeneous contrast enhancement after gadolinium and the pituitary gland was asymmetrically enlarged. These are unusual findings for lymphocytic hypophysitis. Similar unusual biopsy-proven cases of lymphocytic hypophysitis with asymmetrically enlarged pituitary and/or poorly enhanced intrasellar mass lesion have been described. 2,5,6,9

Beneficial effects of corticosteroids have been described in lymphocytic hypophysitis. 1 Corticosteroids rapidly improved the effects of the mass, and pituitary function returned after glucocorticoid treatment in some patients. 1,4,6,9,12 However, for most patients, symptoms recurred during therapy or after reduction and withdrawal of corticosteroids. 1,4,6,10,12 Cases that did not respond to steroids have also been described. 1,10,12 In our patient, a small course of methylprednisolone may have contributed to the regression of the pituitary mass and the relatively benign clinical course, but this is unlikely when the dose and duration of this treatment are compared with the corticosteroid regimens reported previously. 1,2,3

Inflammatory lesions of the pituitary have been recognised increasingly in the past decade. Opinion now favours conservative management in patients with suspected hypophysitis unless optic nerve compression and/or progressive compressive symptomatology are present. 1,2,3,4 In these circumstances it is recommended that patients are managed conservatively when the symptoms develop in a classic clinical setting, i.e. a pituitary mass in a female during late pregnancy or in the postpartum period, or in patients with pituitary hormone deficiencies in association with a co-existing autoimmune disorder. Surgery should be performed only if the presence of visual impairment or other potentially irreversible neurological signs make it unavoidable. 1

Clinical suspicion should also be extended to women with

or without pituitary dysfunction presenting during the early stages of pregnancy with a pituitary mass and symptomatology suggesting hypercortisolemia gravidarum and/or meningeal irritation.

REFERENCES