

CASE REPORT

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Pituitary mass in pregnancy - unlikely to be an adenoma?

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ABSTRACT

Introduction: Lymphocytic hypophysitis (LH) is a rare disease with an annual incidence of approximately one in ten million population. A subsequent pregnancy after pituitary surgery is even rarer. **Case Report:** A 21-year-old primigravida who developed a sudden onset of headache and blurred vision at 35 weeks gestation. Formal examination at the local eye hospital revealed a bitemporal hemianopia and subsequent MRI indicated a pituitary mass with suprasellar extension and chiasmal compression. Transphenoidal endoscopic resection was undertaken and histopathological assessment confirmed a diffusely inflamed pituitary gland with dense chronic inflammatory cell infiltrates overall, consistent with a diagnosis of LH. Rather unexpectedly, the patient retained a regular menstrual cycle post-partum and conceived spontaneously one year later. **Conclusion:** LH must be included in the differential diagnosis of any pituitary mass in pregnancy and/or the

puerperium. Despite its rarity a high index of suspicion is required.

Keywords: Lymphocyte hypophysitis, Pregnancy, pituitary, Transphenoidal surgery

How to cite this article

Thornton EJ, Bonner S, Gnanalingham K, Pal P, Davis J, Byrd L. Pituitary mass in pregnancy - unlikely to be an adenoma? J Case Rep Images Obstet Gynecol 2018;4: 100034Z08ET2018.

Article ID: 100034Z08ET2018

doi: 10.5348/100034Z08ET2018CR

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Received: 26 September 2017

Accepted: 27 December 2017

Published: 22 February 2018

INTRODUCTION

A functional hypothalamic pituitary adrenal (HPA) axis is fundamental in reproduction [1]. The HPA axis is key from conception and throughout pregnancy. It remains an essential component after parturition by playing a central role in breastfeeding.

The pituitary, also known as the hypophysis, is an endocrine gland found at the base of the brain. It is composed of both an anterior and posterior lobe. The anterior lobe is responsible for secreting gonadotrophins (Lutenising hormone, Follicle Stimulating Hormone), growth hormone (GH), thyrotropin (TSH), corticotropin (ACTH) and prolactin [2]. The posterior lobe secretes oxytocin and antidiuretic hormone.

During pregnancy marked physiological and anatomical changes occur within the pituitary gland. There is a remarkable increase in the level of binding proteins and many hormones from the pituitary and the

placenta [3]. Hyperplasia and hypertrophy of lactotroph cells can cause the anterior lobe of the pituitary to double in size [4]. As a consequence the anterior pituitary becomes highly vascular and more vulnerable to infarction. Both ACTH and prolactin levels rise during pregnancy under the influence of hypothalamic and placental factors [5]. Conversely gonadotrophins, GH and TSH levels fall as a result of these influences.

Pituitary enlargement during pregnancy may lead to the release of pituitary antibodies [6]. The pituitary undergoes significant hemodynamic change. During pregnancy the pituitary derives more of its blood supply from the systemic circulation as opposed to the hypothalamic pituitary portal system and thus the pituitary is more accessible to the immune system [7, 8]. It therefore follows that any pituitary disease which affects the HPA axis can interfere with essential reproductive processes.

Autoimmune hypophysitis is a rare inflammatory disease of the pituitary gland with an annual incidence of 1 in 7-9 million. Inflammation may predominantly target the anterior pituitary (lymphocytic adenohypophysitis) or the posterior pituitary (infundibuloneurohypophysitis) [4]. Whilst lymphocytic hypophysitis (LH) can rarely be seen in men and children, it most commonly manifests during the later stages of pregnancy and/or the puerperium.

The clinical presentation of LH may be confused with that of a pituitary adenoma. Both pathologies can present with headache, nausea and vomiting and hormonal imbalances including hypopituitarism and diabetes insipidus [9]. Visual impairment may arise in either condition if there is compression at the optic chiasm due to mass effect which typically presents with a bitemporal hemianopia. Whilst there can be diagnostic uncertainty between these two conditions, LH should be suspected if:

- Symptoms occur during pregnancy or in the postnatal period
- MRI imaging demonstrates diffuse contrast enhancement with gadolinium
- TSH and/or ACTH deficiency is present with normal GH and gonadotrophin profile.

The radiological findings may further help differentiate between the two diagnoses as outlined in the Table 1 [4].

Here, we present a case that proved to be a challenge both from a diagnostic and management perspective and we highlight features, both clinical and radiological, that might help in distinguishing a pituitary adenoma from the rarer LH. Despite undergoing extensive pituitary surgery the patient achieved a further pregnancy after the index case.

CASE REPORT

A 21-year-old primigravida presented at 35 weeks gestation with a sudden onset of headache and blurred

vision. She was normotensive with no proteinuria. Formal examination at the local eye hospital revealed a bitemporal hemianopia and subsequent MRI indicated a pituitary mass with suprasellar extension and chiasmal compression (Figure 1A). The lesion was heterogeneous in signal characteristics with areas of cystic change posteriorly. No contrast enhanced MR sequences were undertaken.

Initial endocrine assessment confirmed an elevated prolactin level (3876 mU/L; range 29-452), which was thought to be due to a combination of pregnancy, prolactin production by a pituitary adenoma and/or due to compression of the pituitary stalk.

The working diagnosis by the obstetricians was that of pituitary macroadenoma and, given the raised prolactin, she was commenced on Bromocriptine. Although her vision improved a little the Bromocriptine was poorly tolerated and therefore abandoned a few weeks later. After multidisciplinary discussions between the anaesthetist, endocrinologist and obstetrician, labour induction was agreed. Pain relief was provided by an epidural and labour was covered with hydrocortisone in case she had pituitary ACTH deficiency. She gave birth to a healthy female infant of normal birth weight, by spontaneous vaginal delivery.

Seven weeks post-partum, her visual field defects persisted and a repeat MRI scan confirmed that the suprasellar lesion was unchanged in size or nature. Repeat endocrine assessment now revealed a normal serum prolactin (290 mU/L) but confirmed partial ACTH deficiency. Given the ongoing visual deficits, following joint consultation between the endocrinologists and neurosurgeons, surgical decompression was deemed appropriate.

An endoscopic transsphenoidal resection of a relatively firm pituitary lesion with central areas of cystic change was undertaken. Post-operative recovery was uneventful other than for transient diabetes insipidus. Her visual field deficits resolved and post-operative MR confirmed satisfactory decompression of the optic chiasm (Figure 1B).

Histopathological assessment confirmed a diffusely inflamed pituitary gland with dense chronic inflammatory cell infiltrates, notably histiocytes (CD68 immunopositive) and lymphoid follicles with germinal centres (immunopositivity for CD3, marker for T lymphocytes and CD20, marker for B lymphocytes) (Figure 2). Overall, these findings were consistent with a diagnosis of LH.

Following surgery, the patient retained a regular menstrual cycle and conceived spontaneously one year later. She continued on the hydrocortisone throughout the subsequent pregnancy, which progressed to a spontaneous vaginal delivery (labour supported with additional corticosteroid cover) of a male infant. She remains well and plans to have a Progesterone Secreting Intrauterine System (Mirena Coil) inserted soon. There was no recurrence of her previous LH.

Table 1: Comparison of radiological findings seen in Lymphocytic Hypophysitis and Pituitary Adenoma as seen on MRI

Typical Radiological Findings	Pituitary Adenoma	Lymphocytic Hypophysitis
Gland Enlargement	Asymmetrical	Symmetrical
Pituitary Stalk Thickening	Absent	Usually present
Pituitary Stalk Position	Deviation	Usually central
Sellar Floor Involvement	Can be seen occasionally	Rarely seen
Post gadolinium enhancement	Enhancement usually heterogenous	Diffuse and homogenous enhancement seen
Posterior Pituitary Signal	Usually present	Usually absent

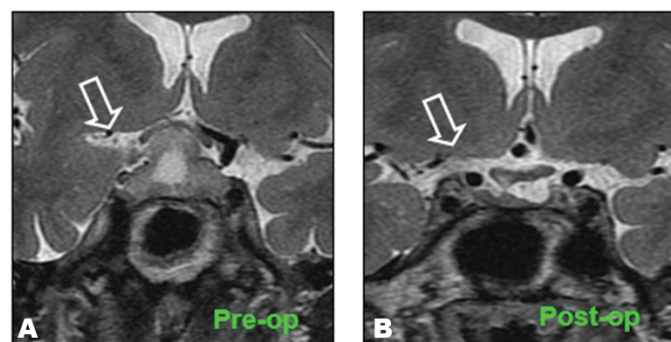


Figure 1: (A) Pre-operative coronal T2 weighted MRI, shows a heterogeneous pituitary lesion (arrow) with chiasmal compression. (B) Post-operative coronal T2 weighted image confirms macroscopic clearance of the lesion with no chiasmal compression.

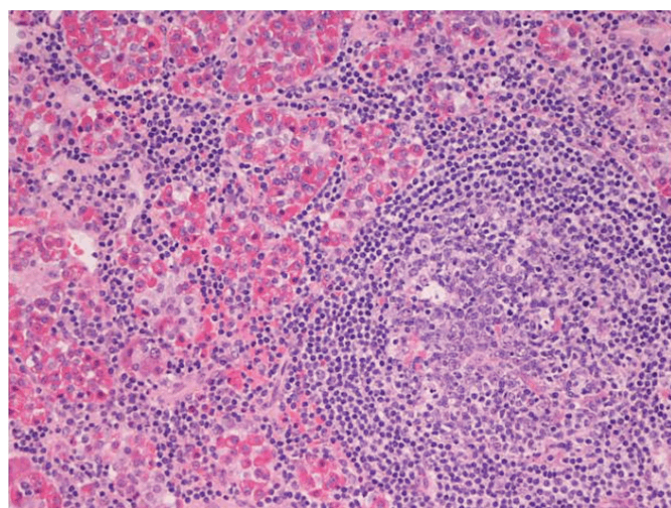


Figure 2: Photomicrograph of H and E staining shows infiltration of the pituitary gland acinar structures by an inflammatory infiltrate composed predominantly of lymphocytes and histiocytes with prominent germinal centres (magnification x20).

DISCUSSION

LH is a rare inflammatory disease with an annual incidence of only 1 in 7–9 million with predilection in females and pregnancy, in particularly, in the late third trimester and/or the puerperium as discussed in this case [4]. Moreover, subsequent pregnancy after such extensive pituitary surgery is rare and, has not been reported in literature [10]. Clinical presentation and radiological findings may mimic a pituitary adenoma.

Three different subtypes of autoimmune hypophysitis are described in the literature; lymphocytic, granulomatous, and/or xanthomatous [11]. The former is strongly associated with the post-partum period and often presents with features of a mass lesion, variable loss of anterior pituitary function and, more rarely posterior pituitary involvement [12]. The most common radiological features of LH are a diffusely enlarged pituitary mass, characterized by symmetrical, homogenous enhancement after gadolinium injection and a thickened pituitary stalk on MRI (Table 1). [12,13] Although, no contrast studies were performed in the present case, the heterogeneous appearance of the mass would be atypical for LH. Thus, although MR features can help differentiate between a pituitary adenoma and LH, as in the present case the radiological features of LH can be atypical [4].

There are no definite biochemical or serological markers for LH, and the diagnosis therefore depends on an initial clinical suspicion and the presentation in pregnancy. Diagnosis is often then confirmed by biopsy and histological examination which shows the infiltration of pituitary tissue by lymphocytes and occasionally plasma cells and macrophages [14]. Although the aetiology remains unknown, considerable evidence exists to support an autoimmune pathogenesis [13, 15].

The treatment for LH is controversial, and partly complicated by reports of spontaneous shrinkage of the lesion over time [4]. Consequently in patients clinically and radiologically suspected to have LH, an initial period of supportive treatment alongside hormone replacement and a trial of high dose steroids may be appropriate [12, 13]. Similarly treatment with agents directed at immune modulation, including azathioprine have been described and would be acceptable in late pregnancy [16]. Success has been reported in some cases [17]. Although treatment with dopamine agonists (e.g. Bromocriptine) can lower the high prolactin level, the beneficial impact of this drug on the course of the disease is unproven, and did not prove useful in this case in shrinking the pituitary mass [13].

In patients where the diagnosis is in doubt and/or where there is visual impairment as noted in in this case, transsphenoidal surgery to obtain a histological diagnosis and to decompress the optic chiasm would be appropriate. With respect to endocrine function, although spontaneous recovery of pituitary gland function have been reported, in most patients the hypopituitarism

does not recover. [12, 13; 18] Subsequent pregnancy is dependent on a relatively normal hormone profile and may require hormonal assistance.

In a recent multi-centre observational study 22 patients were included and studied over a mean follow-up period of 8.6 years (range 4–26 years) [18]. In two-thirds of the patients (N = 14) LH was diagnosed based on their clinical, biochemical and radiological findings. The surgical cohort (N = 8) were statistically more likely to have presented with larger lesions, with suprasellar extension and greater visual field defects.

Despite its rarity a high index of suspicion is required. Factors which increase suspicion of LH include context (e.g. pregnancy or puerperium), atypical pattern of hormone deficiency (e.g. ACTH deficiency occurring with normal LH/FSH and GH reserve) and/ a clinical presentation inconsistent with the size of the pituitary mass on imaging. Radiological features can be difficult to interpret with absolute certainty. Experienced endocrinologists should be familiar reviewing these images and be skeptical when findings are not typical of those seen in a pituitary adenoma [19].

CONCLUSION

LH must be included in the differential diagnosis of any pituitary mass in pregnancy and/or the puerperium. A presumptive diagnosis of LH can often be made on balance of clinical features and without biopsy. All treatment options should be considered (to include expectant whilst awaiting natural shrinkage) during comprehensive, multidisciplinary discussions – thereby ensuring optimal management. In the modern era, the majority of patients with LH are diagnosed by non-surgical means and undergo medical management.

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Author Contributions

Emma Jayne Thornton – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

S. Bonner – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

K. Gnanalingham – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

P. Pal – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

J. Davis – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

L. M. Byrd – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None

Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

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