Lymphocytic hypophysitis

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INTRODUCTION

The first case of lymphocytic hypophysitis was reported in 1962 by Goudie and Pinkerton1 involving a young post-partum woman with Hashimoto’s thyroiditis who subsequently died from progressive hypopituitarism. Post-mortem examination revealed destruction of anterior pituitary acini and lymphocytic infiltration, suggesting an autoimmune aetiology. More than one hundred cases have since been reported. The clinical features of this unusual disease vary remarkably and there is no single characteristic presentation. The radiological features can also be difficult to distinguish from those of other pituitary disorders in which mass lesions occur. Histology, immunohistochemistry and detection of anti-pituitary cytotoxic antibodies are keystones in diagnosis. The clinical, radiological, histopathological and immunological features of three cases of lymphocytic hypophysitis are reported.

CASE REPORTS

Case 1

A 30-year-old woman presented, one month post-partum, with a three month history of progressive visual failure. She was otherwise asymptomatic. Examination revealed reduced visual acuity of 6/9 in the right eye and 6/48 in the left eye and a dense bitemporal hemianopia. CT scan of the brain revealed an enhancing sellar mass with suprasellar extension, measuring 2 cm in supero-inferior dimension. There was an area of hypodensity within the mass and bony erosion of the sellar floor. Magnetic resonance imaging (MRI) showed thickening of the pituitary stalk and three small discrete hypointense lesions up to 5 mm in size on T1-weighted imaging. The left parietal skull defect was also noted.

Plain radiograph of the skull showed an expanded pituitary fossa and an incidental well-defined lytic lesion involving the left parietal bone with sclerotic margins. CT scan showed a slightly enlarged pituitary gland that was heterogeneous in density. In addition, there was a well-defined lytic expansile lesion measuring 4.5 cm in diameter over the left parietal bone. This was interpreted as a benign cranial vault lesion.

Histopathological examination showed destruction of anterior pituitary acini and dense lymphoplasmacytic and histiocytic infiltration with a dense fibroplastic stroma (Figs. 2A and B). Large numbers of CD3+ T lymphocytes were detected with immunohistochemistry (Fig. 2B).

She made an excellent recovery post-operatively. At 3 months follow-up, her visual acuity had improved to 6/5 bilaterally.

Case 2

A 56-year-old woman presented with an acute history of diabetes insipidus, confirmed on a water deprivation test. There were no associated visual disturbances, headache or vomiting. She had a history of hypothyroidism, of presumed autoimmune aetiology, 7 years previously and had been on thyroxine replacement.

Plain radiograph of the skull showed an expanded pituitary fossa and three small discrete hypointense lesions up to 5 mm in size on T1-weighted imaging. The left parietal skull defect was also noted.

Her hormonal profile was essentially normal except for a mildly elevated prolactin of 557 mU/L (60–400 mU/L).

She was commenced on intranasal desmopressin and transphenoidal biopsy was performed to obtain a histopathological diagnosis. The sections showed fragments of amorphous eosinophilic material consistent with cyst contents. Some ciliated cuboidal epithelial cells, consistent with cyst lining cells, were also identified. A fragment of anterior pituitary tissue with preserved acinar architecture was included. Immunohistochemistry identified scattered CD3+ T lymphocytes, both within acinar epithelial cells and between intact acini (Fig. 3). No plasma cells were identified. The features were interpreted as Rathke’s cleft cyst with the T cell infiltration of anterior pituitary acini suggesting lymphocytic hypophysitis.

Summary

Lymphocytic hypophysitis is a rare but important cause of pituitary hypofunction which predominantly affects young women in the peripartum period. It is believed to be an autoimmune disorder with an association with other autoimmune disorders and expression of anti-pituitary cytotoxic and anti-nuclear antibodies. Clinically, it presents most frequently with symptoms and signs attributable to pituitary hypofunction, headache, visual disturbance and amenorrhea. It is difficult to distinguish lymphocytic hypophysitis from a pituitary adenoma on pre-operative imaging and definitive diagnosis rests on histology which classically demonstrates destruction of anterior pituitary acini by an inflammatory infiltrate rich in plasma cells and T lymphocytes. Surgical management therefore plays a crucial role to obtain a histological diagnosis and to relieve pressure effects on the optic apparatus in patients with visual disturbances.
Anti-pituitary cytosolic antibodies were detected in serum, supporting lymphocytic hypophysitis. The patient was well six months after surgery but required intranasal desmopressin.

**Case 3**

A 72-year-old woman with a history of rheumatoid arthritis presented with a two week history of nausea, vomiting, anorexia and lethargy. There was no complaint of headache or visual disturbance. She was dehydrated and hyponatraemic with a serum sodium of 117 mmol/L. Assessment of the hormonal profile showed low free T4 and free T3 and mildly elevated prolactin (819 mIU/L).

MRI revealed a 1 cm diameter enhancing mass expanding the pituitary fossa, extending into the suprasellar cisterns and abutting but not compressing the optic chiasm (Figs. 4A and B). CT scan showed no bony erosion of the pituitary fossa. The patient underwent transphenoidal excision of the pituitary lesion. At surgery, the pituitary gland was noted to be extremely tough and fibrous with yellow discoloration. Frozen section revealed a granulomatous process and a partial resection was performed.

Anti-pituitary cytosolic antibodies were detected in serum, supporting lymphocytic hypophysitis.

The patient was well six months after surgery but required intranasal desmopressin.
Histopathological examination showed extensive destruction of anterior pituitary acini by a dense infiltrate of lymphocytes, plasma cells and histiocytes. In addition, several well-formed non-necrotising granulomas, composed of epithelioid histiocytes and an occasional multi-nucleated giant cell, were identified (Fig. 5). No organisms were seen. The features were interpreted as lymphocytic/granulomatous hypophysitis.

Anti-pituitary cytosolic antibodies were detected in serum.

DISCUSSION

These three cases illustrate the variation in clinical presentation, radiological features and histopathology of lymphocytic hypophysitis.

Clinical features

Lymphocytic hypophysitis is a rare cause of hypopituitarism, occurring predominantly in young women in the peripartum period.

Until the report by Guay et al. in 1987 of an affected male, the condition was thought to occur exclusively in women. Lymphocytic hypophysitis in non-pregnant women is also not uncommon. The most frequent presentation is pituitary dysfunction. This can vary from pan-hypopituitarism to partial hypopituitarism to single hormone deficiency. Interestingly, McDonald et al. reported a case in a woman presenting with hyperprolactinaemia 10 years after her last pregnancy. The disorder involves the adenohypophysis and spares the neurohypophysis. The development of diabetes insipidus is therefore a relatively infrequent occurrence. Symptoms of mass effect are common. Suprasellar extension may lead to compression of the optic chiasm and visual field defects. Visual deterioration may develop or occur in a dramatic fashion. Other symptoms include headaches, nausea and vomiting. Symptoms, attributable to hormonal abnormalities, include amenorrhoea, galactorrhoea, anorexia, fatigue, postural hypotension and emotional disturbances. Presentation with sudden onset of aseptic meningitis have also been reported. (Table 1 summarises the common manifestations.) The natural history of lymphocytic hypophysitis is not fully known. There have been reports of patients with histologically proven lymphocytic hypophysitis which regressed spontaneously without corticosteroid treatment or surgery. Gagneja et al. reported a patient with spontaneous regression of her pituitary mass who subsequently became pregnant with no post-partum recurrence. Disease recurrence has been described. This can occur up to 2 years after the time of original diagnosis. Lymphocytic hypophysitis appears to behave in a fashion similar to other autoimmune diseases which are characterised by remissions and relapses.

Table 1 Incidence of symptoms in lymphocytic hypophysitis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Hypopituitarism</td>
<td>70</td>
</tr>
<tr>
<td>Headaches</td>
<td>62</td>
</tr>
<tr>
<td>Visual field defects</td>
<td>40</td>
</tr>
<tr>
<td>Amenorrhoe</td>
<td>40</td>
</tr>
<tr>
<td>Galactorrhoea</td>
<td>14</td>
</tr>
<tr>
<td>Febrile prodrome</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>9</td>
</tr>
</tbody>
</table>
Pathogenesis

Lymphocytic hypophysitis is believed to be an autoimmune disorder. Anti-pituitary cytosolic antibodies are detectable in serum and the infiltrating inflammatory infiltrate usually has a substantial plasma cell component. There is also a 30% association with other autoimmune conditions, in particular, thyroiditis, adrenalsitis, atrophic gastritis and retroperitoneal fibrosis.\(^1\)\(^{10}\)\(^{11}\) Lymphocytic hypophysitis can be induced experimentally in rats by the injection of isologous and homologous pituitary tissue.\(^12\) Studies in animal models also suggest that the natural history of the condition begins with inflammatory enlargement, progressing to fibrosis, atrophy and acinar destruction.

Anti-nuclear antibodies have been found in patients with lymphocytic hypophysitis.\(^2\)\(^{13}\)\(^{14}\) Guay et al.\(^5\) reported a case with elevated anti-nuclear antibodies which became undetectable three months after surgical resection. Anti-mitochondrial, anti-gastric parietal cell and anti-smooth-muscle antibodies have also been reported.\(^15\)\(^{29}\) This has led to a wider search for anti-pituitary antibodies. Mayfield reported a case with antibodies against all anterior pituitary cell types.\(^8\)\(^9\) Bottazzo and Doniach\(^11\) identified autoantibodies to proline-secreting cells in about 7% of patients with one or more autoimmune disorders. The significance of the presence of autoantibodies is still unclear as they have also been reported in normal individuals. It has been found that 18% of women have anti-pituitary autoantibodies in the first week after delivery. This may explain the higher occurrence of lymphocytic hypophysitis in the post-partum period.\(^22\)

Pathology

The classical histopathological features of lymphocytic hypophysitis are destruction of anterior pituitary acini by an inflammatory infiltrate rich in plasma cells and T lymphocytes, as illustrated in Case 1. Fibroplastic proliferation with collagen deposition is also a common feature and explains the firm consistency characteristic of the tissue. Residual pituitary cells can be identified by immunostaining for pituitary hormones. Oncocytic change may be seen in residual pituitary cells. These features were not as obvious in Case 2 and only the identification, by immunohistochemistry, of T cells within acinar epithelial cells as well as between intact acini, suggested the diagnosis of lymphocytic hypophysitis. This was confirmed by the detection of anti-pituitary cytosolic antibodies in the patient’s serum. Case 3 was noteworthy because of the presence of non-necrotising granulomas. These may be seen occasionally in lymphocytic hypophysitis. The term “granulomatous hypophysitis” has been used in these instances.\(^18\) However, the presence of granulomas requires consideration of sarcoidosis and infection with either acid fast organisms or fungi, in the differential diagnosis. Some tumours also need to be excluded. These include germinoma, particularly because of the prominent lymphocytic component, plasmacytoma and lymphoma.

Radiology

The radiological distinction between lymphocytic hypophysitis and pituitary macroadenoma can present some difficulty. Plain radiographs have little role in diagnosis as the pituitary fossa may be normal in size with little, if any, bone remodelling. They may, however, be useful for pre-operative planning. CT typically shows an enhancing sellar mass which is indistinguishable from a pituitary macroadenoma.

MRI presently offers some hope of distinguishing lymphocytic hypophysitis from macroadenomas. Lymphocytic hypophysitis typically appears as a hypointense or isointense lesion on T1-weighted imaging that is hyperintense on T2-weighted imaging. Recently, there has been interest in identifying pathognomonic MRI features. Honegger et al.\(^23\) reviewed their experience with nine cases of granulomatous and lymphocytic hypophysitis and reported that the most characteristic feature is the tongue-like extension along the basal hypothalamus. Marked contrast enhancement was also reported and a normal-sized or slightly enlarged fossa is typical. Significantly, they found stalk enlargement, a feature not included in other reports. Inflammatory reaction of the sphenoid sinus was another finding in their series. Again, this feature does not appear to have diagnostic specificity.

Dural enhancement is regarded by Ahmad et al.\(^24\) as suggestive of lymphocytic hypophysitis. However, this is not a universally accepted view. Non-specific peripheral enhancement may raise suspicion of pathology other than adenoma but is not specific for lymphocytic hypophysitis. Much more experience with enhanced MRI in inflammatory disorders of the pituitary is required before the diagnostic value of peripheral enhancement can be ascertained.\(^25\)

Using dynamic MRI, Sato et al.\(^26\) showed that the enhancement time was delayed to over 90 s in lymphocytic hypophysitis. They attributed the delay to vascular changes secondary to inflammation and concluded that dynamic MRI can display an abnormality of the hypophyseal vasculature even if the pituitary disease is seen to have regressed on conventional MRI.

It would be reasonable to conclude that current imaging modalities do not allow a definite diagnosis of lymphocytic hypophysitis to be reached in the majority of cases.

Management issues

Apart from the difficulties associated with clinical and radiological diagnosis of lymphocytic hypophysitis, a management dilemma also arises because the natural history of this rare condition is unclear. In the presence of mass effect causing visual deterioration, surgically debulking is clearly indicated. However, when the presentation is less dramatic, the management controversy is essentially twofold: should the patient be treated expectantly or should the patient be treated expectantly based on circumstantial clinicoradiographic evidence or should definitive tissue diagnosis be obtained surgically? There have been reports of spontaneous resolution of lymphocytic hypophysitis without surgery or corticosteroid therapy. Beressi et al.\(^27\) reported a case of lymphocytic hypophysitis which was successfully treated with corticosteroids alone. They advocated a short trial of low-dose steroids in patients without visual impairment as a therapeutic test. Response to steroid therapy by inducing volume reduction and improving hormonal status may serve as confirmatory evidence of lymphocytic hypophysitis. Prasad et al.\(^28\) in their review on the need for open exploration of the sella in lymphocytic hypophysitis, recommended conservative management in patients with highly probable lymphocytic hypophysitis without visual impairment or associated hormonal hyperfunction. Their criteria for diagnosis of highly probable lymphocytic hypophysitis include: (1) gestational or post-partum hypopituitarism; and (2) presence or absence of a contrast enhancing sellar mass. Should conservative measures fail, tissue diagnosis is recommended. They also proposed subtotal decompression when vision is threatened to avoid unnecessary removal of normal pituitary gland.

Honegger et al.\(^23\) reported nine cases of granulomatous and lymphocytic hypophysitis and advocated early surgery to obtain histopathological diagnosis. They recommended removing abnormal tissue and preserving normal-lookinig pituitary tissue to minimise the risk of hypopituitarism. Expectant management is
only justified in the absence of pituitary, hypothalamic and visual dysfunction and with shorter follow-up intervals.

**CONCLUSION**

Lymphocytic hypophysitis still poses a challenge even with the availability of modern imaging modalities. Surgery is currently necessary for debulking and to obtain a histopathological diagnosis. Expectant management should be undertaken with caution in view of the often insidious and protean presentation of this enigmatic condition.

**REFERENCES**