AN UNUSUAL CASE OF LYMPHOCYTIC HYPOPHYSISIS IN A YOUNG MAN PRESENTING WITH ELEVATED SERUM IGF-1

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Abstract
Objective. To describe an unusual case of lymphocytic hypophysitis in a man, presenting with an elevated serum Insulin like growth factor-1 (IGF-1) level.

Case report. We report the case of a 27 year old male presenting with a 2 week history of severe headaches. Magnetic resonance imaging of the head showed an adenoma-like pituitary. The physical examination was normal, laboratory tests revealed secondary hypothyroidism and hypogonadism along with an elevated IGF-1. Complete transsphenoidal resection of the pituitary mass was done. Tissue analysis was diagnostic for lymphocytic hypophysitis. No evidence of a somatotroph adenoma was found. After surgery the patient developed panhypopituitarism and diabetes insipidus.

Discussion. IGF-1 is a sensitive disease related marker in acromegaly and corresponds to disease activity. However, it should not be used as the sole marker for diagnosis of disease. Inflammatory lesions of the pituitary gland, such as lymphocytic hypophysitis, can clinically and radiologically mimic tumors of the sellar region.

Conclusion. We report an index case of a young male who presented with elevated serum IGF-1 level in the setting of lymphocytic hypophysitis. This case illustrates the dilemma associated with reliance on the IGF-1 levels for diagnosis of acromegaly, since an elevated IGF-1 level in the presence of a pituitary mass may not always be a somatotroph tumor. We propose the differential diagnosis should also include autoimmune hypophysitis.

Key words: Lymphocytic hypophysitis, IGF-1, male, histopathology, panhypopituitarism.

INTRODUCTION

Lymphocytic hypophysitis is a rare inflammatory condition of the pituitary gland. The clinical presentation commonly includes headaches, visual field abnormalities, and hypopituitarism caused by inflammatory destruction of the hypophysis and/or the compression of the residual normal gland (1). On MRI,
lymphocytic hypophysitis commonly appears as a symmetric pituitary mass with homogeneous enhancement after gadolinium injection and a thickened infundibulum, making it difficult to distinguish from a pituitary tumor (2). There are no definite biochemical or serological markers for this disorder and the diagnosis can only be clearly established by histological examination. The defining pathological feature is polyclonal lymphoplasmacytic infiltration and focal or diffuse adenohypophysial destruction with associated fibrosis (3).

The disease usually affects young women during late pregnancy or in the postpartum period. About 15% of reported cases occurred in men. Many reports suggest an autoimmune pathogenesis of this condition (4). Supporting data include isolation of antipituitary antibodies, female predominance, and association with other autoimmune disease (5). We describe a case of a young male with no underlying autoimmune disease who presented with a pituitary macroadenoma and an elevated serum IGF-1. He was given a clinical diagnosis of acromegaly pre-operatively but the pathological specimen demonstrated lymphocytic hypophysitis.

CASE REPORT

A 27 year old male presented with a 2 week history of severe frontal headaches. He had no past medical history. His father had recently been diagnosed with vitiligo, but there was no family or personal history of other endocrine or autoimmune diseases. The patient denied cold intolerance, constipation, change in skin or hair, polyuria, polydipsia, any changes in dentition, skin tags, diaphoresis, change in hand or foot size, or coarsening of facial features. The physical examination was normal, including normal visual fields to confrontation. Magnetic resonance imaging of the head showed pituitary enlargement, suggestive of a macroadenoma with no evidence of stalk thickening or encroachment of the optic chiasm (Fig. 1).

Figure 1. Preoperative magnetic resonance imaging scan (T1 weighted coronal and sagittal section). Arrows demonstrate a large pituitary mass with no encroachment of the optic chiasm.
Initial laboratory tests revealed an elevated IGF-1 at 469 ng/mL, using an Immunolite IGF-1 assay with a coefficient of variation of 8.7%. TSH was low at 0.14 mU/L with a normal serum FT4 of 1.05 ng/dL. Total serum testosterone was low at 113 ng/dL with an FSH of 2.6 IU/L and lutropin at 1.8 IU/L. Serum prolactin was normal at 8 ng/dL and serum cortisol at 10:30 am was 7.7 μg/dL (Table 1).

Table 1. Preoperative measurement of serum hormones

<table>
<thead>
<tr>
<th>Test</th>
<th>Level</th>
<th>Normal</th>
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<tbody>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>469</td>
<td>117-329</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>8</td>
<td>2-18</td>
</tr>
<tr>
<td>Lutropin (IU/L)</td>
<td>1.8</td>
<td>1.5-9.3</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>2.6</td>
<td>1.4-18.1</td>
</tr>
<tr>
<td>Total serum testosterone (ng/dL)</td>
<td>113</td>
<td>241-827</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>0.14</td>
<td>0.4-5.0</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>1.05</td>
<td>0.7-1.85</td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>7.7</td>
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Because of the pituitary mass, elevated IGF-1 and headaches the patient was given the diagnosis of acromegaly and underwent complete transsphenoidal resection of the pituitary mass. At surgery, the neurosurgeon found a soft necrotic mass with no evidence of a delineated solid tumor. Tissue analysis was consistent with lymphocytic hypophysitis with foci of subacute to chronic destruction of the adenohypophysis with fibrosis and macrophagic infiltrates. There were a few CD20 positive B cells and numerous CD3 positive T cells in the infiltrate (Figs. 2, 3). The pathology was unusual in that the inflammatory and macrophagic infiltrates extended at least focally into the neurohypophysis. The immunostains for GH, ACTH, β-TSH, and prolactin all labeled cells within intact acini. There were no areas where the acinar profiles were disrupted and no evidence of a somatotroph adenoma.

Figure 2. Hematoxylin and eosin stain showing intact gland and foci of fibrosis within the adenohypophysis.
Post operatively the patient developed panhypopituitarism and diabetes insipidus (Table 2). The patient had significant polyuria (>700 cc/hr), hypernatremia with a serum sodium at 146 mmol/L (normal range 133-144 mmol/L), low urinary sodium at 21 mmol/L and low urine specific gravity at 1.002 (normal range 1.003-1.035), postoperatively on day #2. The symptoms resolved after initiating DDAVP, and the polyuria recurred if the patient missed a dose of DDAVP, confirming the diagnosis of permanent diabetes insipidus. Twelve weeks after surgery, serum IGF-1 fell to 66 ng/mL.

<table>
<thead>
<tr>
<th>Test</th>
<th>Level</th>
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<tbody>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>61</td>
</tr>
<tr>
<td>Total testosterone (ng/dL)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>T3 (ng/dL)</td>
<td>54</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>0.63</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>1.002</td>
</tr>
<tr>
<td>MRI scan</td>
<td>Empty sella</td>
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DISCUSSION

We describe an unusual case of lymphocytic hypophysitis in a young man with a pituitary adenoma and an elevated IGF-1 level. Lymphocytic hypophysitis affects females 8 times more often than males (6), usually during late pregnancy or the early postpartum period. The mean age of diagnosis is 34.5 years for females and
Hypophysitis with elevated IGF-1

44.7 years for males (7). Our case differs from the more typical patient because of his male gender, his younger age and his presentation with an elevated IGF-1 level. While there is a single case report of a female with lymphocytic hypophysitis and an elevated IGF-1 level (8), to our knowledge this is the first reported case in a man.

Lymphocytic hypophysitis is often associated with abnormalities in pituitary function. Patients may present with selective loss of ACTH or TSH that presumably is the result of targeted autoimmune attack (9, 10). About 50% of patients have hyperprolactinemia, perhaps due to the loss of the dopaminergic inhibition from stalk involvement and/or the release of prolactin during lactotroph destruction. An autoimmune mechanism involving the production of lactotroph stimulating antibodies by plasma cells in the setting of lymphocytic hypophysitis has also been described (11). An elevated IGF-1 in the presence of lymphocytic hypophysitis was previously reported in a female patient, but in that case the histology demonstrated somatotroph and lactotroph lysis with extracellular GH and prolactin identified on immunostaining. No such abnormality was found in the male case reported here.

The cause of our patient’s elevated IGF-1 level is unclear. On our literature review we did not come across any studies which describe a direct correlation between the somatotroph tumor size and serum IGF-1 levels. On review of data from our facility, patients who present with pituitary adenomas greater than 1 cm in size routinely have serum IGF-1 levels more than two standard deviations above the normal range. It can be hypothesized in this case that the minimally elevated serum IGF-1 was probably a reflection of GH synthesized and secreted by the inflammatory cells themselves, as has been previously described in vitro (12).

An elevation in serum IGF-1 has been described to be the single best test for the diagnosis of acromegaly because serum IGF-1 concentrations are elevated in virtually all patients with acromegaly and are rarely elevated in normal individuals (13, 14). While a single random plasma IGF-1 level provides an accurate reflection of GH secretion, IGF-1 concentrations are regulated by genetic factors, nutrient intake, growth hormone and other hormones like T4, cortisol, sex steroids and the accuracy of IGF-1 measurement in diagnosing GH deficiency or excess depends on the contributions of these variables. For maximal utility, it is necessary to establish well defined normal ranges because of the age related nature of normal plasma IGF-1 concentrations, which requires adequate numbers of normal individuals. Also, IGF-1 in the plasma exits as part of a high molecular weight complex in which it is bound to carrier proteins, which can interfere with plasma IGF-1 measurements by radioligand assays. Therefore, it is necessary to employ an initial extraction stage in order to eliminate binding protein interference. The immunolite assay used in this case was done utilizing the above mentioned steps and the result was interpreted according to age and sex —adjusted normative data.

Our case demonstrates that reliance on a single test for the diagnosis of acromegaly may not be a wise strategy. We suggest that the diagnosis be verified with an additional test, such as an oral glucose tolerance test, which was not done in our case. If this test was done and the GH was suppressed to below the expected
concentration of 1 μg/L (15) the patient may have been able to avoid surgery and the subsequent surgical complications of panhypopituitarism and diabetes insipidus. In general, lymphocytic hypophysitis can be managed conservatively unless there is evidence of suprasellar extension and optic nerve compression. In some cases, pituitary function may spontaneously recover over time (16-18). This case demonstrates the importance of including lymphocytic hypophysitis in the differential diagnosis of a pituitary tumor with an elevated serum IGF-1 level.

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References


