An intrasellar germinoma with normal tumor marker concentrations mimicking primary lymphocytic hypophysitis

SUMMARY

Intracranial germinomas (GE) are malignant neoplasms most commonly found in the suprasellar region, which may cause anterior and particularly posterior pituitary hormone deficits with central diabetes insipidus (DI). Differential diagnosis of pituitary stalk thickening includes granulomatous, inflammatory, infectious, and neoplastic lesions. Although careful analysis of clinical, laboratory, and imaging findings may facilitate the diagnosis, transsphenoidal biopsy is indicated to confirm the disease, as the correct diagnosis directs the appropriate treatment.

INTRODUCTION

Intracranial germinomas (GE) are malignant neoplasms that most likely arise from primitive germ cells that failed to migrate to the genital crest during embryonic development (1). They represent about 3.4% of all primary intracranial tumors, predominantly affect pre-pubertal children, and are more often localized in the pineal gland or suprasellar region, although bifocal lesions have also been described (1,2). Most commonly, they cause anterior (mainly GH deficiency) and particularly posterior pituitary hormone deficits with central diabetes insipidus (DI) (1).

Other diseases of neoplastic, granulomatous, infectious and inflammatory origin could be difficult to differentiate from GE, because of the similar clinical, imaging and pathological features. In order to elucidate the etiopathogenesis in patients with difficult differential diagnosis, a transsphenoidal biopsy is indicated (1).

Regarding the proper approach, corticosteroids for lymphocytic hypophysitis (LH) and radiotherapy (RaT) plus chemotherapy (ChT) for GE (2), a case of GE mimicking LH is presented.

CASE REPORT

History and clinical examination

After one year of an uneventful delivery, a 24 year-old patient presented amenorrhea (even after breastfeeding...
was stopped, polyuria, polydipsia, fatigue, galactorrhea, dry skin, and hair loss. She described a pulsatile headache since adolescence. Weight and body mass index (BMI) were 63.2 kg and 24.5 kg/m², respectively. Her medical and family history was unremarkable. Physical and neurological examination revealed no abnormality. Biochemical evaluation was normal. Regarding basal hormonal evaluation, she presented hyperprolactinemia (prolactin: 50 ng/mL – normal range (NR): 2.0-15.0 ng/mL), hypogonadotropic hypogonadism, secondary hypothyroidism (fT4: 0.56 µU/mL – NR: 0.70 – 1.50 ng/mL; TSH: 2.3 µU/mL – NR: 0.40-4.5 µU/mL), and low basal serum cortisol (cortisol 8 am: 7.5 µg/dL – NR: 5-25 µg/dL). Central DI was diagnosed based on clinical presentation and response to desmopressin (DDAVP) on the water deprivation test, leading to oral DDAVP treatment. She was also replaced with L-T4 and hydrocortisone acetate. Serum and spinal cerebral fluid (CSF) tumor markers (alpha-fetoprotein and β-HCG) were negative. Physical examination, chest x-ray, blood angiotensin-converting enzyme (ACE) was measured, and a PPD test (Tuberculin Purified Protein Derivative Test) excluded sarcoidosis and tuberculosis, respectively. Other diagnostic work-up included a skeletal survey to rule out histiocytosis. Several serum autoimmune antibodies were positive: anti-thyroid, antinuclear and anti-pituitary (APA) antibodies were positive. The detection of anti-pituitary antibodies was performed by indirect immunofluorescence in tissue sections of human cadaveric pituitary glands based on a research protocol of the University of Sao Paulo Medical School.

Sellar magnetic resonance imaging (sellar MRI) depicted a suprasellar mass extending to the posterior pituitary with normal sellar space, leading to a diffuse thickening of the pituitary stalk (Figure 1A and 1B). Optic chiasm was normal. Invasion of the cavernous sinus was not evident.

Despite the clinical evidence pointing to lymphocytic hypophysitis, a pituitary biopsy through transsphenoidal route was performed in order to rule-out other causes and, therefore, to choose the appropriate therapy. Pathological examination showed a biphasic population of mature small lymphocytes and large neoplastic cells with abundant clear cytoplasm, round central nuclei and prominent nucleoli (Figure 2A). Immunohistochemistry (IHC) was positive for placental alkaline phosphatase (PLAP) (Figure 2B) and c-kit protein (CD 117) in the neoplastic large cells (not shown) confirmed the diagnosis of an intrasellar GE. Immune markers also revealed a population of B-lymphocytes (CD 20 positive – Figure 2C) and T-lymphocytes (CD 3 positive – Figure 2D). The patient was referred to treatment with ChT and RaT with clinical improvement.

Figure 1. Suprasellar mass lesion reaching the posterior pituitary, leading to stalk thickening with normal sella (white arrow); T1- weighted images in coronal (A) and sagittal (B) planes after paramagnetic contrast media administration are shown.
**DISCUSSION**

This study deals with the difficulties in diagnosing pituitary stalk thickening lesions, reporting a patient with a typical clinical and laboratorial picture of LH in which the final histopathological diagnosis was GE.

The differential diagnosis of masses affecting the pituitary stalk is broad and includes inflammatory and infectious diseases, germ cell tumors, gliomas, meningioma, metastatic tumors, and vascular lesions (3).

LH is a rare entity with estimated incidence of one case in nine million persons-year characterized by pituitary and/or stalk autoimmune inflammation. The average age at diagnosis is 34.5 years in females and 44.7 years in males. Lymphocytic adenohypophysitis (LAH) is strongly associated with pregnancy, 57% of cases occurring during gestation or in the postpartum period. This could be related to a pituitary antigens presentation to the immune system, probably due to lactotroph hyperplasia and increase in pituitary blood flow (4).

Clinical presentation of LAH is variable and includes symptoms related to mass compression of sellar neighboring regions (optic chiasm, cavernous sinus), hypopituitarism, and hyperprolactinemia. Its clinical suspicion should be raised if the degree of hypopituitarism conflicts with the appearance of pituitary gland in imaging exams, and rapidly installation of hormonal deficiencies, mainly in the corticotrophic axis, in women in the puerperal period. Central DI can occur if posterior pituitary or pituitary stalk are involved. Sellar MRI routinely shows homogeneous enhancement of the entire gland. The association with other autoimmune diseases happens in 20% of the cases, mostly with Hashimoto’s thyroiditis (5).

The current methods used for APA evaluation are not commercially available and their specificity and sensitivity must be improved in order to permit an accurate diagnosis in LH. Lupi and cols. described about 50% of sensibility of APA in histologically-proven LH. However, APA were also found in other pituitary diseases, such as pituitary adenoma and primary empty sella, and other autoimmune endocrine conditions, such as Hashimoto’s thyroiditis, Grave’s disease, and post-partum thyroiditis (6).
Table 1. Ten cases of germinoma mimicking clinically lymphocytic hypophysitis described in the literature

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical picture</th>
<th>Hormonal evaluation</th>
<th>Thickening of pituitary stalk in sellar MRI</th>
<th>APA</th>
<th>Mononuclear and lymphocytic infiltrate</th>
<th>Serum Tumoral markers</th>
<th>IHC</th>
<th>Initial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozbey and cols., 2006 (1)</td>
<td>24</td>
<td>Female</td>
<td>Headache</td>
<td>Panhyp</td>
<td>Yes + intrasellar mass</td>
<td>ND</td>
<td>ND</td>
<td>β-HCG</td>
<td>PLAP</td>
<td>GCE</td>
</tr>
<tr>
<td>Gutenberg and cols., 2011 (2)</td>
<td>11</td>
<td>Female</td>
<td>Blurred vision, fatigue, polyuria, polydipsia and low stature</td>
<td>Panhyp + DI</td>
<td>No and intra suprasellar mass with posterior extension</td>
<td>Negative</td>
<td>Yes</td>
<td>Negative</td>
<td>CD79 CD3</td>
<td>GCE</td>
</tr>
<tr>
<td>Saborowski and cols., 2007 (12)</td>
<td>12</td>
<td>Female</td>
<td>Low stature</td>
<td>Panhyp + DI</td>
<td>yes</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>Nd</td>
<td>GCE</td>
</tr>
<tr>
<td>Houdouin and cols., 2003 (13)</td>
<td>13</td>
<td>Male</td>
<td>Visual field defects</td>
<td>Panhyp + DI</td>
<td>yes</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>PLAP CD117</td>
<td>Surgery</td>
</tr>
<tr>
<td>Houdouin and cols., 2003 (13)</td>
<td>21</td>
<td>Male</td>
<td>Visual fields defects, polyuria</td>
<td>Panhyp + DI</td>
<td>yes</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>PLAP CD117</td>
<td>Surgery</td>
</tr>
<tr>
<td>Fehn and cols., 1999 (14)</td>
<td>12</td>
<td>Female</td>
<td>Polyuria</td>
<td>Panhyp + DI</td>
<td>Yes + intrasellar mass</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>Nd</td>
<td>GCE</td>
</tr>
<tr>
<td>Terasaka and cols., 2012 (9)</td>
<td>40</td>
<td>Female</td>
<td>Headache, diplopia, amenorrhea</td>
<td>Panhyp + DI</td>
<td>Yes + intra suprasellar mass</td>
<td>ND</td>
<td>Yes and marked fibrous tissue</td>
<td>PLAP CD43; CD45RO; CD20</td>
<td>GCE</td>
<td></td>
</tr>
<tr>
<td>Mikami-Terao and cols., 2006 (10)</td>
<td>13</td>
<td>Female</td>
<td>Headache and pubertal arrest</td>
<td>Panhyp + DI</td>
<td>Yes + intra and suprasellar mass</td>
<td>Positive</td>
<td>Yes</td>
<td>PLAP CD20; CD45RO; CD3; CD5; CD45RO</td>
<td>GCE</td>
<td></td>
</tr>
<tr>
<td>Torremocha and cols., 2002 (15)</td>
<td>45</td>
<td>Male</td>
<td>headache and extraocular muscle palsy</td>
<td>FSH and LH deficiencies</td>
<td>Intrasellar mass extending into right cavernous sinus</td>
<td>ND</td>
<td>Yes</td>
<td>β-HCG in CSF</td>
<td>PLAP Vimentin</td>
<td>GCE</td>
</tr>
<tr>
<td>Endo and cols., 2002 (16)</td>
<td>12</td>
<td>Male</td>
<td>Low stature, fatig, bitemporal hemianopsia</td>
<td>Panhyp + DI</td>
<td>Intra and suprasellar mass extension to right cavernous sinus</td>
<td>ND</td>
<td>Yes with multinucleated giant cells</td>
<td>Negative</td>
<td>PLAP</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

CSF: cerebral spinal fluid; DI: diabetes insipidus; Panhyp: panhypopituitarism; APA: antipituitary antibodies; ND: not done; Nd: not described; PLAP: placental alkaline phosphatase; IHC: immunohistochemistry; GCE: glucocorticoid.

The definitive diagnosis of LH depends on histopathological evaluation. Nevertheless, a presumptive diagnosis could be done in a typical case, and a therapeutic approach should be based on the grade of suspicious and clinical manifestations of LH (7). In the present case, we would like to emphasize the importance of histopathological confirmation since pitfalls in diagnosis may occur.

GE are rare lesions, affecting predominantly pre-pubertal children and are more often localized in the pineal gland and/or in suprasellar region. Clinically, they are present as a triad of central DI, hypopituitarism, and visual disturbances, which could mask other lesions that affect sellar region. This form of brain neoplasm is a highly curable with RaT and ChT (8).

To date, about ten cases (Table 1) of LH clinically mimicking GE have been reported. In most of them, the initial diagnosis was LH, and treatment with corticosteroids was prescribed. The unfavorable clinical follow-up followed by pituitary biopsy was critical for diagnosis. In most cases, the histological diagnosis of GE is not difficult due to its typical pathological finding, the “two-cell pattern” (9).

GE are highly immunogenic tumors and frequently have infiltrating lymphocytes into the tumor (10), but
the finding of APA is rare. Besides, APA positivity in the reported patient harbored others autoimmune disorders, such as Hashimoto’s thyroiditis and positive antinuclear antibody (7,11).

In conclusion, diffuse lymphocytic infiltration in sellar masses and pituitary antibodies do not always indicate a diagnosis of LH, even with its typical clinical and radiological features. However, the precise diagnosis can only be obtained with histological assessment in order to rule out others diseases, such as GE.

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES