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

Germinoma intrasselar com marcadores tumorais normais mimetizando hipofisite linfocítica primária

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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. Arq Bras Endocrinol Metab. 2013;57(7):566-70

SUMÁRIO

Germinomas intracranianos (GE) são neoplasias malignas comumente na região suprasselar, podendo causar deficiência hormonal da hipófise anterior, em particular da hipófise posterior, com diabetes insípido central (DI). Entre os diagnósticos diferenciais do espessamento de haste hipofisária, incluem-se doenças granulomatosas, inflamatórias, infecciosas e neoplásicas. Embora as avaliações clínica, laboratorial e a ressonância magnética selar sugiram o diagnóstico, a biópsia transesfenoidal está indicada para confirmação, visto que o diagnóstico correto direciona o tratamento. Arq Bras Endocrinol Metab. 2013;57(7):566-70

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/m^2, 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 supraselar 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.

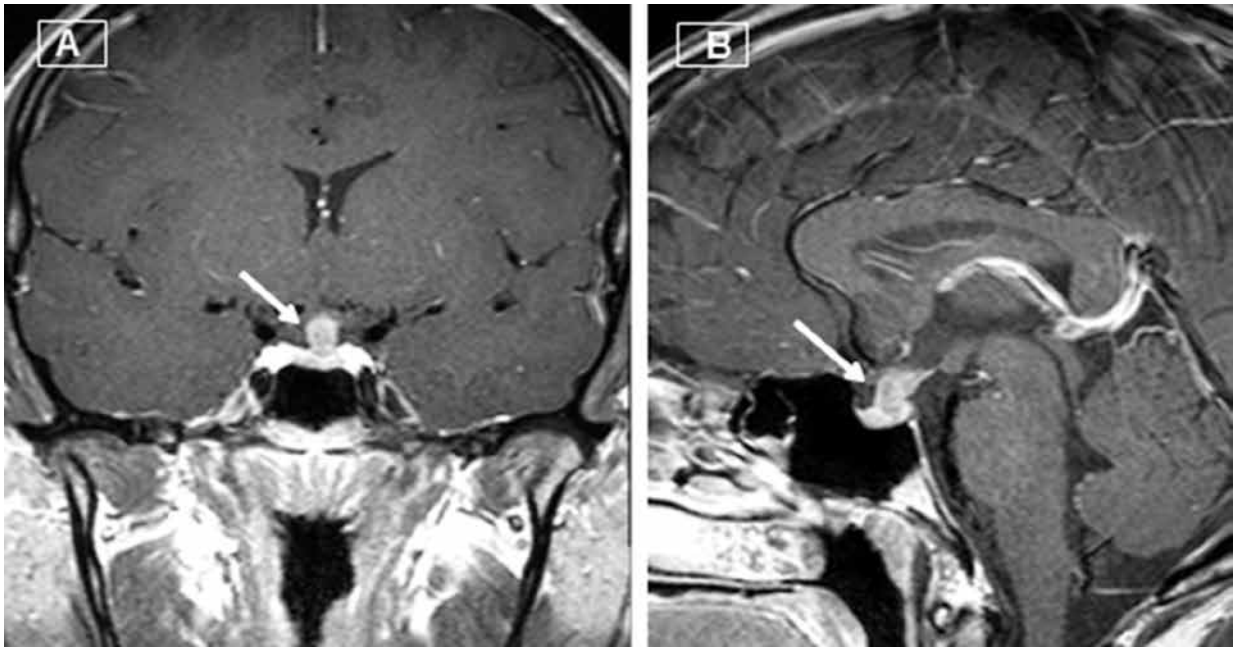

Figure 1. Suprasellar mass lesion reaching the posterior pituitary, leading to stalk thickening with normal sella (white arrow); T1- weighted images in coronal (**A**) and sagittal (**B**) planes after paramagnetic contrast media administration are shown.

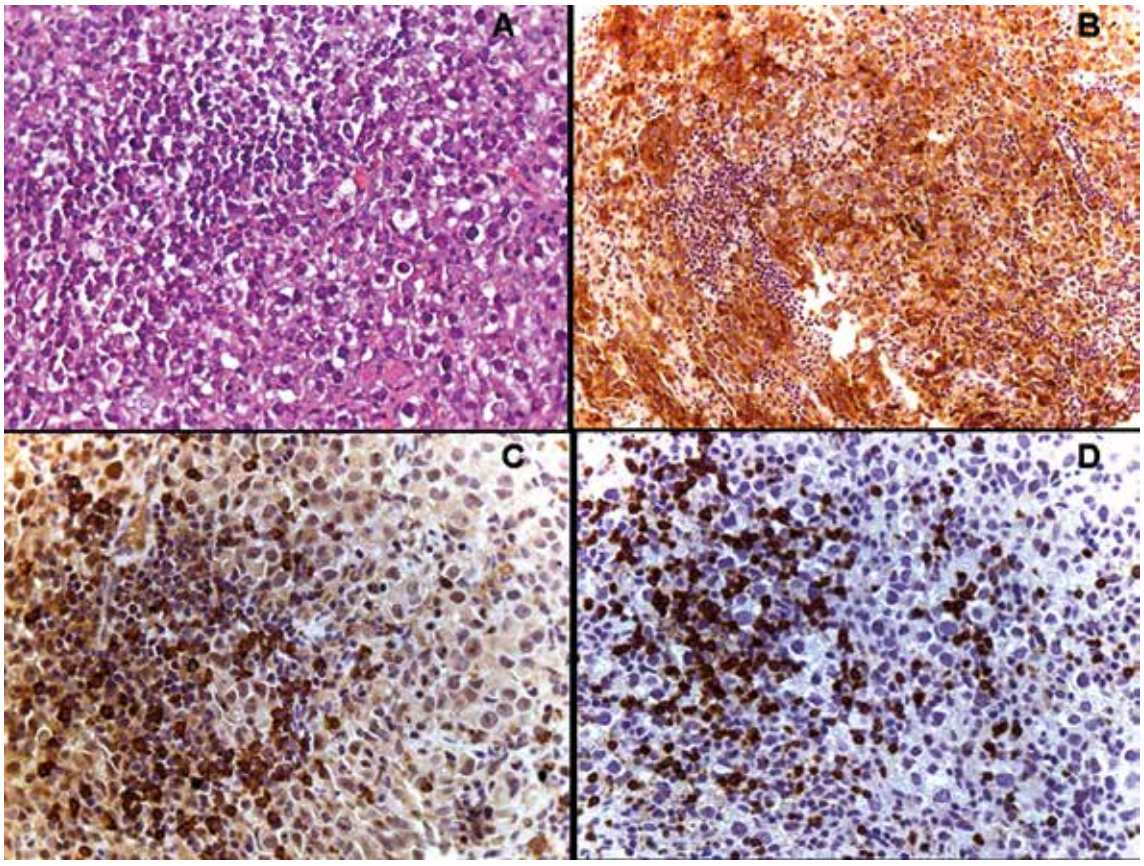

Figure 2. (**A**) Large tumor cells with round nuclei and abundant clear cytoplasm. Presence of moderate lymphocytic infiltrate. (H & E, 200X); (**B**) Tumor cells showing PLAP immunoreactivity; (**C**) Presence of B-lymphocytes (CD 20 positive); (**D**) Presence of T-lymphocytes (CD3 positive).

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 others 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

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

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.

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