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Primary pituitary lymphoma in immunocompetent patient: diagnostic problems and prolonged follow-up

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Abstract Primary pituitary lymphoma in immunocompetent patients is a rare disease and has been described in less than 20 cases. Moreover, low-grade lymphomas constitute only 3% of all primary central nervous system lymphoma. The objective of this report is to report a low-grade primary pituitary lymphoma, diagnostic problems and to give more evidence about the evolution of this rare disease. A 49 y.o. woman was referred to our clinic with symptoms of hypopituitarism. A diagnostic work-up showed mild anemia, an erythrocyte sedimentation rate of 122 mm/h and a negative Elisa test for HIV. Panhypopituitarism was confirmed and the MRI showed a 20 mm sellar and suprasellar enhancing mass with a thickening of the pituitary stalk, chiasmal compression and bitemporal hemianopsia. She underwent transsphenoidal resection only 10 months later for non medical reasons. During this period she was clinically asymptomatic on hormonal replacement therapy. A new MRI showed regression of the suprasellar extension and invasion to the left cavernous sinus. A firm and infiltrative mass was found during transsphenoidal surgery, and only partial resection was performed. Biopsy showed a low-grade lymphoplasmacytic lymphoma. Staging was negative for other localizations. She was given chemotherapy and localized radiotherapy. Four years after surgery, the sellar MRI showed a 10 mm residual sellar mass with the persistence of a cavernous sinus invasion and she is considered to be in remission. The neurosurgeon and clinician should consider primary pituitary lymphoma as a potential cause of a sellar mass, especially in the presence of diabetes insipidus and an enhancing invasive mass. Neurosurgical biopsy is crucial for a correct diagnosis and prognosis could be better than classic CNS primary lymphomas.

Keywords Insipidus diabetes · Primary pituitary lymphoma · Pituitary tumor · Pituitary adenoma

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Introduction

The Primary Central Nervous System Lymphoma (PCNSL) accounts for 2.7% of all malignant diseases of the CNS, most of them in immunodepressed patients [1]. Furthermore, low-grade lymphomas are extremely rare and constitute only 3% of all primary central nervous system lymphoma. Nevertheless, primary pituitary lymphoma (PPL) in immunocompetent patients is an exceptional diagnostic and to our knowledge, no more than 20 cases have been published [2–8].

The aim of this report is to describe a new case of PPL with an extended follow-up to provide more evidence about the presentation and evolution of this rare disease.

Case report

A 49-year old woman with no remarkable medical history was referred to our clinic with symptoms of

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Table 1 Hormonal evaluation

Hormonal test	Results	Reference range
TSH	0.6	0.4–4.5 uUI/ml
Free thyroxin	0.16	1.0–1.8 ng/dl
Cortisol	5.0	6.4–15 μg/dl
FSH	4.0	23–116 mUI/ml
Estradiol	27	<30 pg/ml
PRL	33.2	<25 ng/ml
Sodium	150	135–145 mEq/l
Plasmatic osmolality	320	285–295 mOsm/kg H_2O
IGF-1	157	55–212 ng/ml

hypopituitarism. A year before she had started with increasing weakness, headache, asthenia and a 10 kg weight lost. There was no fever or sweating. Laboratory tests, including serum glucose, calcium and phosphorus, hepatic and renal tests, chest radiography, thorax, abdominal and pelvis CT and upper gastrointestinal endoscopy were normal. Only a mild anemia and an ESR (erythrocyte sedimentation rate) of 122 mm/h were found. During the last three months she noticed an increase in thirst, polyuria, cold intolerance, abdominal pain, nauseas, and dizziness. Her menopause was at 48-years-old. Physical examination revealed periorbital edema with hypothyroid facies, paleness, and normal blood pressure. Her weight was 53 kg with a BMI of 22 k/m^2. There was no galactorrhea. No palpable lymph node was discovered and there was no hepatosplenomegaly. Hypopituitarism and diabetes insipidus were suspected and the patient was referred to our clinic where laboratory findings confirmed panhypopituitarism (Table 1).

A pituitary MRI showed a 20 mm sellar and suprasellar enhancing mass with thickening of the pituitary stalk and chiasmal compression (Fig 1a, b). A neurophthalmologic study revealed bitemporal hemianopsia. A new thorax CT showed the absence of lymph node enlargement or nodules, a cerebral CT did not reveal bone lesions, a skin evaluation ruled out rash, nodule or erythema nodosum and an ophthalmologic evaluation did not display uveitis. Moreover, serum protein electrophoresis and the count of immunoglobulins were normal, as well as the calcemia (9.7 mg/dl) and an angiotensin converting enzyme serum level of 43.8U/l (NV < 50U7 l), so histiocytosis and sarcoidosis were ruled out. Elisa's test for HIV was negative. The thorax, abdominal and pelvic CT scan displayed no abnormal focal lesions. β-chorionic gonadotropin and alpha-fetoprotein in the CSF were negative and ADA was within normal range. The CSF chemistry and cell analysis showed proteins 0.39 g/l, glucose 0.56 g/l, leukocytes 7.6/mm^3 with 89% lymphocytes and 11% neutrophils.

The patient started treatment with cortisol 30 mg PO. divided bid, DDAVP 1 nasal puff bid (20 μg) and levothyroxine 100 μg PO qd. Transsphenoidal surgery was indicated. It was performed only 10 months later for non medical reasons, when she developed diplopia and a new MRI revealed infiltration of the left cavernous sinus (Fig 1c). A neurophthalmologic study showed normal Goldman campimetry, but left diplopia was confirmed.

The patient underwent tumoral resection through transsphenoidal approach, but the pituitary mass was firm and infiltrative and only a biopsy was performed. A light microscopy showed that the mass contained acidophilic cell nests with a preserved architecture of adenohypophysis, and a small lymphocytes infiltration. The tumoral cells were immunoreactive for B-cell markers CD20, and negative for the T-cell marker CD3 and bcl. Immunoreactivity for the lambda chain was positive in the tumor, whereas the kappa chain was negative (Fig. 2). These pathologic findings were consistent with a lymphoplasmacytic lymphoma (low grade).

CT of the chest, abdomen, and pelvis was negatives for dissemination, as well as bone marrow biopsy. She was treated with methotrexate iv (2 cycles of 1.62 g associated to dexamethasone) and intrathecal (6 cycles) and cytarabine 3 g/m2 (2 cycles). Fractionated conformational radiotherapy to the sphenoid sinus and pituitary region was administrated with a total dose of 30 Gy.

Four years after surgery, the patient remained asymptomatic, and panhypopituitarism was well controlled with cortisol 30 mg PO bid, levothyroxine 100 ug PO qd and DDAVP 1 puff (10 μg) at bedtime. The neurophthalmologic study was normal and the sellar MRI showed a stable

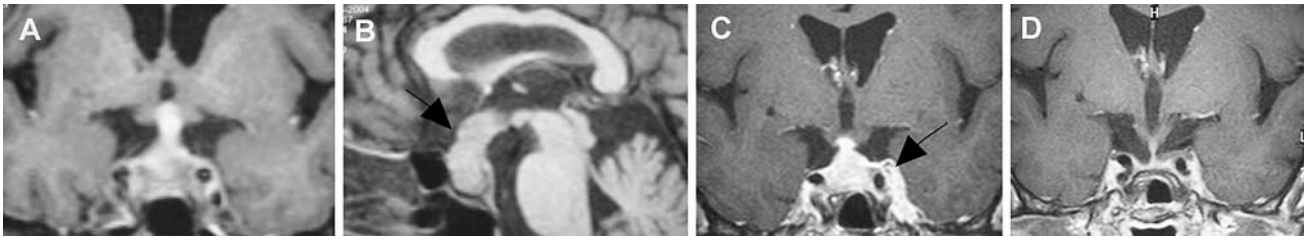

Fig. 1 **a** Gadolinium-enhanced T1 MRI image showing a sellar mass with diffuse homogenous enhancement. **b** Pituitary stalk was diffusely thickened (*arrow*). **c** Ten months later, and without specific therapy, the tumoral mass shows extension to left cavernous sinus (*arrow*). **d** Four years after therapy, only a residual sellar mass was observed, with the persistence of sinus involvement

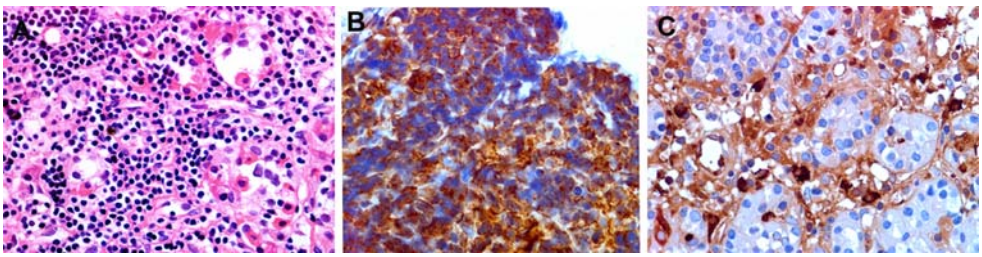

Fig. 2 Histology and immunohistochemestry findings. **a** Adenohypophysis was infiltrated by small lymphocytes (hematoxylin-eosin). Immunohistochemestry shows that the lymphocytes expressed B-cell markers CD20 (**b**) and lambda chain (**c**)

intrasellar 10 mm mass, thinning of the pituitary stalk and persistence of the sinus cavernous invasion (Fig. 1d). She is considered to be in remission.

Discussion

We described the clinical and radiological follow-up of a new case of PPL in an immunocompetent patient, a rare clinical entity that has been reported in less than 1% of a series of 1,120 patients undergoing transphenoidal surgery [9].

The main findings in our patient were a sellar and suprasellar mass involving thickening of the pituitary stalk, associated with diabetes insipidus and hypopituitarism. Differential diagnosis of the sellar mass involving the pituitary stalk includes cystic lesions (craniopharyngioma, Rathke's cleft cyst), primary tumors (pituitary adenoma, meningioma, germ cell tumor) and infectious or autoimmune inflammatory processes (lymphocytic hypophysitis, sarcoidosis and hystiocytosis). In addition, metastatic or hematologic malignancies may also infiltrate the hypothalamic-pituitary system. The presence of a thick pituitary stalk and diabetes insipidus was an argument against pituitary adenoma [9] and the absence of a cystic lesion discarded the possibility of a craniopharyngioma or Rathke's cleft cyst. The radiological image was not suggestive of meningioma or germinoma. Concerning granulomatous diseases, the absence of a systemic involvement, osseous lytic lesions and a normal angiotensin-converting enzyme activity made tuberculosis, Langerhans's cell histiocytosis or sarcoidosis improbable.

A presumptive diagnosis of autoimmune pan-hypophysitis or PPL was made, but only a biopsy can confirm the diagnosis. Unfortunately, a complete description of the radiological aspect was not always available in the published PPL cases, but intense and homogenous enhancement is typically described in primary CNS lymphoma of immunocompetent patients [10]. Cranial nerve involvements resulting from extension to the cavernous sinus have been described in 40% of the PPL and only occasionally in primary hypophysitis [2, 11]. Clinically, the presence of hypopituitarism associated with diabetes insipidus has been reported in 27% of the PPL cases [2] and 83% of the autoimmune pan-hypophysitis cases [12]. Neurological findings with a headache or visual field defects have been described in 55% of patients with PPL [2–8] and 41% of pan-hypophysitis cases [12]. Moreover, association with pregnancy was only present in 18% of pan-hypophysitis cases [12]. Therefore, the clinical and radiological presentation in our case could not discriminate between these two diagnoses and the role of the neurosurgeon is double, total or partial resection of the tumor to improve the clinical mass effect, and to allow the histopathological diagnosis. As seen here, an evolution does not necessarily allow for a correct diagnosis as our patient showed a benign evolution without a systemic widespread of lymphoma, despite other therapeutic interventions during 10 months. We can speculate that the use of corticoids in replacement therapy doses (hydrocortisone 20 mg daily) could explain the slow progression of the disease, reflecting an extreme sensitivity of the tumor to corticoids, but we can not confirm this hypothesis.

Concerning PPL, when the histologic examination was available, 63% had diffuse B-cell-large lymphoma, and when adequate follow-up was available, approximately 60% of the patients had survived >6 months, but only 13% between 12 and 24 months [2, 4–8]. Our patient is the first low grade PPL published, an extremely rare variant that constitutes 3% of all PCNSL [1]. Low grade PCNSL showed an indolent behavior compared with high grade PCNSL and supports the hypothesis that the intrinsic characteristics of the lesion are predictive of the outcome, as suggested in previous reports [2].

Finally, the pathogenic mechanism in PPL is not known; AIDS, pituitary adenoma or lymphocytic hypophysitis have been postulated as risk factors [2, 4, 8, 13, 14]. Because of the prolonged evolution of the disease before surgery, we can not exclude that the lymphoma might have developed in the setting of an unrecognized lymphocytic hypophysitis in our patient.

It has been hypothesized that a polyclonal inflammation can evolve to a monoclonal expansion of lymphocytes, which then suffers a malignant transformation triggered by

an infectious agent [2, 15]. In immunocompromised patients, the Herpes virus and the Epstein Barr genome have been identified [16], but the pathogenic pathway in immunocompetent patient is not known.

In summary, we present the first low grade PPL in immunocompetent patients. PPL is a rare diagnosis, but the clinician and neurosurgeon should have this entity in mind in a patient with a not well-circumscribed and invasive sellar mass, with endocrine and neuroophthalmic symptoms. Our case shows the clinical and radiological limitations to reach a correct diagnostic, highlights the importance of a neurosurgical biopsy and illustrates the variable course of PPL in immunocompetent patient.

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