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Germinoma Misdiagnosed as Lymphocytic Hypophysitis

Serdar Şahin[1], Ozan Başkurt[2], Nil Çomunoğlu[3], Pınar Kadıoğlu[1], Nurperi Gazioğlu[2]

[1]Department of Endocrinology and Metabolism, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey
[2]Department of Neurosurgery, İstinye University Faculty of Medicine, İstanbul, Turkey
[3]Department of Pathology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

A 34-year-old male patient with decreased libido, visual disturbance, and intermittent severe headache was referred to our Pituitary Center. Endocrinological evaluation at presentation revealed panhypopituitarism and hyperprolactinemia (Table 1). Despite appropriate hormone replacement therapy, his symptoms persisted. Ophthalmologic examination revealed decreased visual acuity, right temporal hemianopsia, and bilateral pallor of the optic disk. Pituitary magnetic resonance imaging (MRI) showed a thickening in the upper half of the pituitary stalk that extended to the right half of the chiasm (Figure 1a).

Serum levels of alpha-fetoprotein, β-human chorionic gonadotropin and angiotensin-converting enzyme were normal, and scrotal ultrasound findings were normal. Chest computed tomography (CT) and a tuberculin test ruled out sarcoidosis, tuberculosis, and lung cancer. Flow cytometry results of the cerebrospinal fluid were normal, and positron emission tomography-CT showed pathological hypermetabolism only in the right optic chiasm. Other diagnostic studies, including a skeletal examination to exclude histiocytosis, were normal.

An extended endoscopic transsphenoidal biopsy of the pituitary stalk lesion was performed. The lesion appeared as a yellowish, soft mass (Figure 1b). The postoperative course was uneventful. The pathological examination showed infiltration of lymphocytes, plasma cells, and histiocytes; thus, he was diagnosed as having primary lymphocytic hypophysitis (LH). High-dose methylprednisolone was administered immediately intravenously and then orally. There was no clinical response after 6 weeks of treatment and careful reevaluation of the biopsy identified two cell populations: larger tumor cells with atypical nuclei and small reactive lymphoid cells (Figure 1c). By demonstrating that these atypical cells were positive for Sal-like protein 4 (SALL4), a diagnosis of germinoma was made (Figure 1d). The patient received chemotherapy (bleomycin, etoposide and cisplatin). MRI revealed regression of the tumor after three courses.

TABLE 1. Serum Levels of Hormones at Presentation

TSH, µUI/ml	0.5
fT3, ng/dl	1.2
fT4, ng/dl	0.8
PRL, ng/ml	80
FSH, mIU/ml	0.5
LH, mIU/ml	0.3
Total testesteron, ng/dl	120
GH, ng/ml	0.5
IGF-1, ng/ml	90
ACTH, pg/ml	5
Cortisol, µg/dl	2.9

ACTH, adrenocorticotropic hormone; AFP, alpha-fetoprotein; Beta-hCG, beta-human chorionic gonadotropin; FSH, follicle-stimulating hormone; fT4, free thyroxine; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone.

Pituitary germinomas are difficult to distinguish from LH because of their similar clinical, radiological, and histopathologic findings. However, their distinction is important because of the different therapeutic approaches.[1,2] In the case of a double lesion in the suprasellar and pineal regions, MRI may be pathognomonic for germinomas. However, pituitary stalk thickening may be seen radiologically in germinomas and LH.[1,2] In addition, germinomas are highly immunogenic tumors and can cause a strong immune response that can attack the pituitary gland and lead to secondary hypophysitis.[1,2] Therefore, a rich lymphocytic infiltrate is sometimes found in germinomas which is very challenging to identify.[3,4]

Corresponding author: Ozan Başkurt, Clinic of Neurological Surgery, Mardin Kızıltepe Public Hospital, Mardin, Turkey
e-mail: ozanbskrt@gmail.com

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ORCID iDs of the authors: S.Ş. 0000-0002-6233-5418; O.B. 0000-0003-1021-6529; N.Ç. 0000-0002-2319-1757; P.K. 0000-0002-8329-140X; N.G. 0000-0001-7785-8628.

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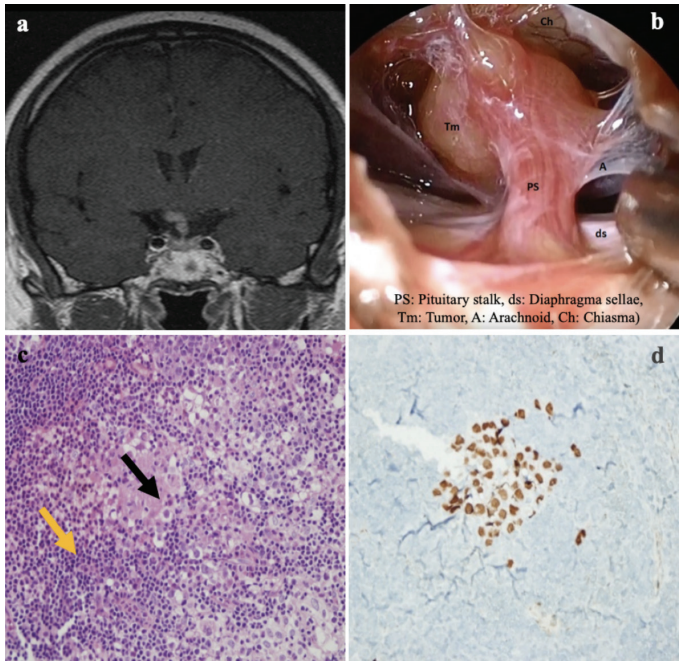

FIG. 1. a) Pituitary magnetic resonance imaging (T1-weighted, coronal); thickening on the upper half of the pituitary stalk extending to the right half of the chiasm, b) Yellowish soft mass in the upper part of the pituitary stalk, c) Larger tumor cells (black arrow) with atypical nuclei and small reactive lymphoid cells (yellow arrow) (hematoxylin and eosin staining *400), d) SALL4(+) large atypical tumor cells (SALL4 *400).

SALL4, a zinc finger transcription factor, is a novel stem cell tumor marker which essentially functions in maintaining pluripotency and self-renewal of embryonal stem cells.[5] Therefore, SALL4 is strongly positive in all gonadal yolk sac tumors, seminomas/dysgerminomas, and embryonal carcinomas.[5]

Endoscopic transsphenoidal biopsy for the diagnosis of pituitary stalk lesions is safe and effective. Germinoma should be considered in LH cases that progress despite treatment, even if the initial pathological examination revealed a lymphocytic infiltrate. SALL4 may play a role in excluding LH.

Informed Consent: Informed consent was obtained from the patient.

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