Submitted: 13.02.2022
Accepted: 23.02.2022
Early publication date: 12.07.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0038
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 5/2022

Insipid diabetes and vaginal ulcers: evidence for the diagnosis of Langerhans cell hypophysitis

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Key words: *Langerhans cell histiocytosis; diabetes insipidus; vaginal ulcers*

The clinical presentation of Langerhans cell histiocytosis (LCH) is highly heterogeneous [1–5]. The pituitary gland is affected in 25% of cases, with insipid diabetes often becoming its introductory manifestation [4]. Involvement of the genital tract is a rare finding; the vulva is the most common site [3, 6]. The concomitant occurrence of these characteristics should lead to the suspicion of such a diagnosis.

We present the case of a 39-year-old female patient, who had been showing polydipsia for 15 months, drinking around 5 to 6 litres of water per day, craving cold beverages, as well as presenting polyuria and nycturia. She had been medicated with fluvoxamine, bisoprolol, zolpidem and alprazolam for about 9 months. Her age at menarche was 11 years; IIIG/IIP with an abortion at the seventh month of pregnancy in the last pregnancy due to pre-eclampsia. Irrelevant family history. She also reported complaints of vaginal itching and dryness. The patient denied having experienced fever and weight loss, as well as other systemic symptoms; she also denied headaches and visual alterations. On objective examination with an uncharacteristic biotype, haemodynamically stable, and with body mass index (BMI) 29.3 kg/m^2. Without hepatosplenomegaly. No skin rashes. Gynaecological examination revealed vesicular and ulcerated lesions in the vulvar region of various sizes and at different stages of healing. Analytically, she showed sodium concentration 152 mmol/L, a low urine density, and a low urinary osmolality. The basal hormonal study revealed no changes (Tab. 1). Water restriction test was not performed. Pituitary magnetic resonance imaging (MRI) revealed the absence of a spontaneous hypersignal in T1-weighted images of the neurohypophysis and a thickened pituitary stalk. The diagnosis of central diabetes insipidus (CDI) of unclear aetiology was established, and the patient started treatment with oral desmopressin 0.06 mg 2 doses/day, showing an improvement of symptoms.

Due to the coexistence of lesions in the genital tract, the patient underwent a punch biopsy of the vulvar lesion, which suggested LCH. Immunostaining of the S-100 and CD1a antigens corroborated this diagnosis.

Complementary investigation ruled out other autoimmune, infectious, or neoplastic diseases. The angiotensin-converting enzyme serum concentration, sedimentation rate, and beta-2 microglobulin serum concentration were normal, and the viral markers [human immunodeficiency virus (HIV), hepatitis C

Table 1. ***Endocrinological assessment of the patient on admission***

	Result	Reference values
Creatinine [mg/dL]	1.00	0.70–1.20
Sodium [mmol/L]	152.00	135.00–145.00
Potassium [mEq/L]	4.90	3.50–5.00
Cortisol (8 h) [μg/dL]	23.00	5.00–25.00
ACTH (8 h) [pg/mL]	46.80	0.00–46.00
PRL [ng/mL]	8.80	4.70–23.30
FSH [mUI/mL]	8.02	1.50–12.40
LH [mUI/mL]	2.90	1.70–8.60
Estradiol [ng/L]	21.70	12.00–233.00
TSH [uUI/mL]	1.58	0.27–4.20
FT4 [ng/dL]	0.94	0.93–1.70
Urine density	1003.00	1005.00–1015.00
Urinary osmolality [mOsm/kg]	108.00	> 300.00

ACTH — adrenocorticotropic hormone; PRL — prolactin; LH — luteinizing hormone; TSH — thyroid stimulating hormone; FT4 — free thyroxine

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virus (HCV), and hepatitis B virus (HBV)] were negative. Abdominal, pelvic, and thoracic computed tomography reported a 4 mm nodule in the posterior aspect of the right lower lobe of the lung, which is still being monitored. A fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET/CT) scan showed a discrete focus of FDG uptake in a right axillary lymph node, after which a lymph node biopsy was performed, with no meaningful changes.

In view of the clinical, laboratory, and imaging findings, the pituitary disease was considered a manifestation of LCH. The involvement of organs such as the spleen, liver, lungs, and bone marrow was excluded. Because this is a multisystemic disease, the patient started chemotherapy with cladribine (6 cycles), having recovered her menstrual cycle. However, treatment with desmopressin is ongoing, given the persistence of CDI. The topical application of antifungals and corticoids resulted in the resolution of the genital lesions.

The endocrine system can be affected, due to the migration of Langerhans cells [7, 8]. In our case, CDI was the first manifestation of the disease. The involvement of thyrotrophic, somatotrophic, or gonadotrophic strains can also occur and appears to result from the thickening of the pituitary stalk [2, 7]. However, LCH presents rarely simultaneous and multiple endocrine disorders at the onset of the disease [4].

Given that a biopsy of the pituitary gland would be a very invasive and risky procedure, and due to the coexistence of vulvar lesions, the patient underwent a biopsy of one such lesion. The anatomopathological examination and CD10 and protein S-100 positivity confirmed the diagnosis of LCH [1, 3, 5]. The mutational analysis was not performed. Thus, a presumptive diagnosis using the clinical, laboratory, and imaging findings, as well as the histology of the vulvar lesions, allowed the diagnosis of LCH to be established and excluded the need for a biopsy of the pituitary.

Treatment with cytarabine for one year is the preferred systemic treatment for adults [2]. In the case of vulvar ulcers, the treatment can vary from resection surgery to topical corticosteroids or chemotherapeutic agents [3, 8]. CDI is usually irreversible in most patients, supporting the need for lifelong replacement with desmopressin [7]. When present at the onset, central diabetes insipidus, other hypothalamic dysfunctions and hormone deficiencies of the anterior pituitary usually have a poor response to treatment, despite the improvement of other non-endocrine organs. The permanent lesions in the hypothalamus and pituitary sustain the continuation of the endocrine assessment and intervention [4].

Conflict of interest

The authors have no conflicts of interest to disclose

Statements of ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Data were collected retrospectively.

Funding

No funding was available.

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