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Arginine Vasopressin Deficiency Associated With Langerhans Cell Histiocytosis: A Case Report of Late Disease Reactivation After 33 Years

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Abstract

Arginine vasopressin deficiency (AVP-D) is a frequent complication of Langerhans cell histiocytosis (LCH) due to infiltration of the pituitary gland and destruction of AVP-producing neurons.

We present the case of a 68-year-old male with a history of pulmonary LCH in complete remission who presented with new-onset polyuria and polydipsia. Due to self-imposed fluid restriction to limit polyuria, the patient presented with severe dehydration and hypovolemic hypernatremia. After stabilization, AVP-D was diagnosed based on a water deprivation test and the administration of desmopressin. Brain magnetic resonance imaging (MRI) showed thickening of the pituitary stalk and slight loss of the posterior bright spot, corroborating the diagnosis of LCH-associated AVP-D with a latency of 33 years. The patient was started on oral desmopressin, with resolution of symptoms, and was referred to a tertiary care hospital for follow-up and treatment of LCH reactivation.

This case highlights the chronic nature of LCH and the potential for reactivation many years after the initial diagnosis. Routine clinical follow-up is essential to ensure the timely detection of reactivation and initiation of treatment.

Categories: Oncology, Internal Medicine, Endocrinology/Diabetes/Metabolism
Keywords: arginine-vasopressin deficiency, hypovolemic hypernatremia, langerhans cell histiocytosis, pituitary stalk, water deprivation test

Introduction

Arginine vasopressin deficiency (AVP-D), previously called central diabetes insipidus [1], is caused by a decrease in the production of arginine vasopressin (AVP), also known as antidiuretic hormone. AVP is secreted by magnocellular neurons in response to plasma osmolality. The cell bodies of these neurons reside in the supraoptic and paraventricular nuclei of the hypothalamus, and their axons terminate in the posterior hypophysis. AVP is responsible for urine concentration in the renal distal tubule and medullary collecting ducts through increased expression of aquaporin-2 and reabsorption of free water, ultimately regulating plasma osmolality [2].

The etiologies of AVP-D include any type of damage to the neurohypophysis resulting in the destruction of 80% of neurons [3], such as trauma; infection (encephalitis and chronic meningitis); neoplastic infiltration or compression (suprasellar germ cell tumors and metastases); vascular damage (Sheehan's syndrome and hypoxic encephalopathy); inflammatory conditions (lymphocytic infundibuloneurohypophysitis, vasculitis, and lupus erythematosus); or granulomatous infiltration (sarcoidosis and histiocytosis), as well as various genetic or congenital causes [4].

Langerhans cell histiocytosis (LCH) is a rare inflammatory myeloid neoplasm characterized by the clonal proliferation of pathogenic, bone marrow-derived Langerhans cells, which accumulate alongside an intense inflammatory infiltrate [5]. The disease can manifest at any age, although it is most common in children, and exhibits an extremely heterogeneous clinical course, ranging from localized, self-healing lesions to chronic, life-threatening multisystemic disease [6]. It can affect many organ systems, and its clinical manifestations are variable, most often involving the skin, bones, and lungs [7].

Patients with LCH are at a substantially higher risk of developing AVP-D due to infiltration of the neurohypophysis by malignant myeloid dendritic cells, which is considered an irreversible complication of the disease [8]. This risk is even higher in patients with multisystemic disease, disease reactivation, prolonged disease, or craniofacial bone involvement [9].

Case Presentation

A 68-year-old male patient presented to our emergency department (ED) complaining of a one-month

history of sudden-onset, severe polydipsia, polyuria, and xerostomia.

The patient reported that his symptoms commenced abruptly, prompting a daily water intake of 4-5 L. He was suffering from significant polyuria, voiding five to six times during the day and awakening every three hours overnight with abundant micturition. He denied other symptoms, changes in medication, recent illnesses, infections, and trauma.

His medical history was notable for pulmonary fibrosis secondary to LCH, which had been diagnosed 33 years prior. The patient recalled no chemotherapeutic treatment and was routinely followed up by a pulmonologist at a tertiary care hospital; however, the corresponding medical records were unavailable.

Additional comorbidities included non-insulin-treated type 2 diabetes mellitus, essential hypertension, and benign prostatic hyperplasia. He had an implantable loop recorder for a previous study of syncope (with no dysrhythmic findings). He had a smoking history of 45 pack-years (currently abstinent), a daily consumption of 27 g of alcohol, and denied any use of illicit drugs. His home medications consisted of losartan 50 mg daily, a fixed-dose combination of metformin 1,000 mg and dapagliflozin 5 mg twice daily, *Serenoa repens*, and a fluticasone/salmeterol inhaler, with no active prescriptions for anticholinergic agents.

Initial evaluation in the ED revealed normal renal function, normal serum electrolytes, and a controlled glycemic profile (Table *1*).

Parameter	ED visit	Outpatient re-evaluation	Inpatient	At discharge	One-month follow-up	Reference range	Unit
Serum sodium	141	156	125 (nadir)	134	140	132-145	mEq/L
Serum osmolality	-	328	-	-	292	280-300	mOsm/kg
Serum creatinine	0.81	0.9	0.9	0.93	1	0.7-1.3	mg/dL
Fasting plasma glucose	-	170	-	-	-	70-100	mg/dL
HbA1c	6.4	7.7	-	-	7.1	<5.7	%
C-reactive protein	-	0.46	-	-	-	<0.5	mg/dL
Erythrocyte sedimentation rate	-	17	-	-	-	<20	mm/h
Spot urine osmolality	-	560	-	-	-	50-1200	mOsm/kg
24-hour urine volume	-	-	4.5*	-	-	0.8-2.0	L/24 h
24-hour urine osmolality	-	-	200*	-	-	300-900	mOsm/kg
24-hour urine protein	-	-	35*	-	-	<150	mg/24 h

TABLE 1: Evolution of laboratory parameters.

Dashes (-) indicate parameters not measured at that time point.

*Collected after withdrawal of the sodium-glucose cotransporter 2 inhibitor and before the water deprivation test.

ED, emergency department; HbA1c, hemoglobin A1c

Brain computed tomography (CT, Figure *1*) showed potential thickening of the pituitary stalk and decreased permeability of the suprasellar cistern.

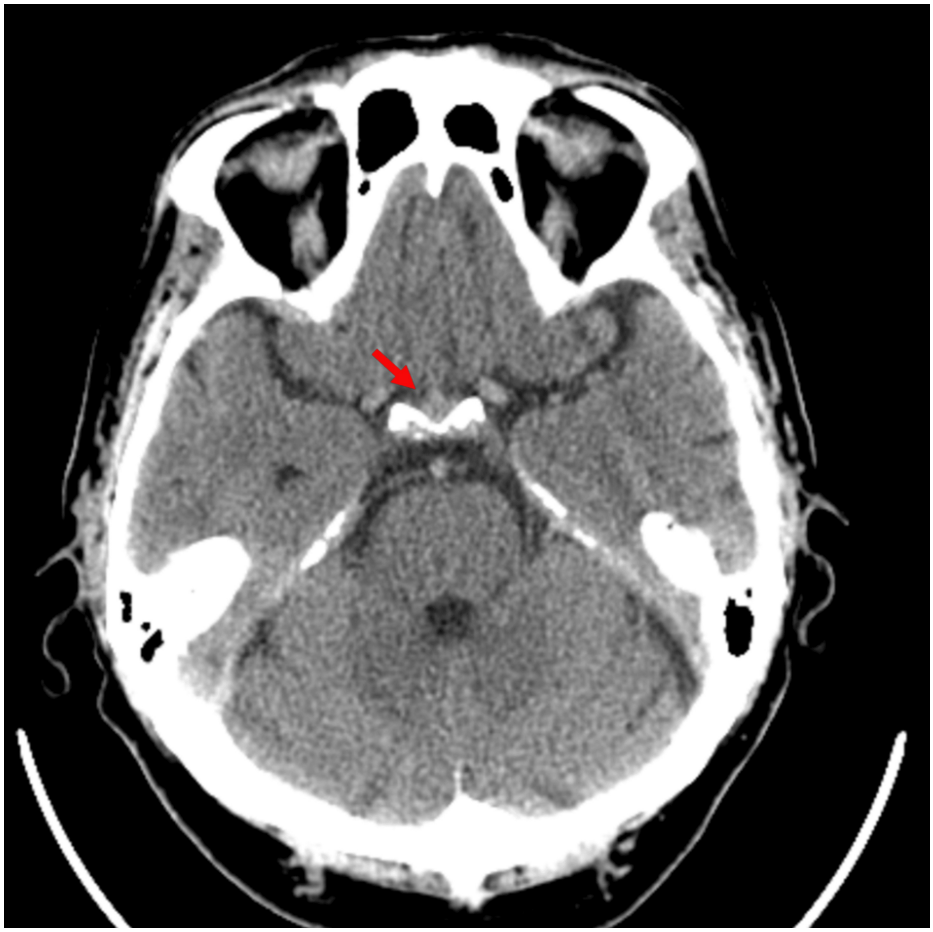


FIGURE 1: Axial computed tomography image showing potential thickening of the pituitary stalk, indicated by the red arrow.

The patient was discharged from the ED with close outpatient follow-up within 2 weeks to resume the investigation.

On re-evaluation, he remained equally symptomatic, and severe xerostomia restricted his ability to consume solid foods - his diet was limited to soup and fruit - contributing to a self-reported weight loss of 14 kg over the course of the past month. The patient had been resorting to fluid restriction (approximately 3 L daily) to reduce urinary frequency, with little success. In fact, physical examination revealed deeply dehydrated mucous membranes.

Laboratory investigations obtained at this time demonstrated hypernatremia with a serum sodium of 156 mEq/L and an elevated serum osmolality of 328 mOsm/kg. A simultaneous urine sample yielded an osmolality of 560 mOsm/kg, without leukocyturia or proteinuria. Glycemic control had concurrently deteriorated, as evidenced by a fasting glucose of 170 mg/dL and an HbA1c increase to 7.7%, presumed secondary to his carbohydrate-heavy and fluid-restricted diet. Inflammatory markers were within the normal range, and serum protein electrophoresis showed no monoclonal component (Table *1*).

Given the clinical triad of severe dehydration, hypernatremia (with hyperosmolality), and polyuria, in the context of suggestive CT findings and known LCH, a working diagnosis of AVP-D was strongly suspected. Therefore, he was electively admitted to the Internal Medicine Department for further investigation and treatment.

Hospital course and diagnostic workup

Upon admission, the patient was initially managed with intravenous fluids to safely correct the severe hypernatremia and clinical dehydration. His baseline sodium-glucose cotransporter-2 inhibitor ((SGLT2i) therapy was suspended to prevent confounding osmotic diuresis during the diagnostic evaluation. Baseline 24-h urine testing revealed polyuria (4.5 L) with low osmolality (200 mOsm/kg) and insignificant proteinuria (35 mg).

Once serum sodium levels were trending toward normal and euvolemia was restored, a formal water deprivation test followed by a desmopressin challenge was performed (Figure 2).

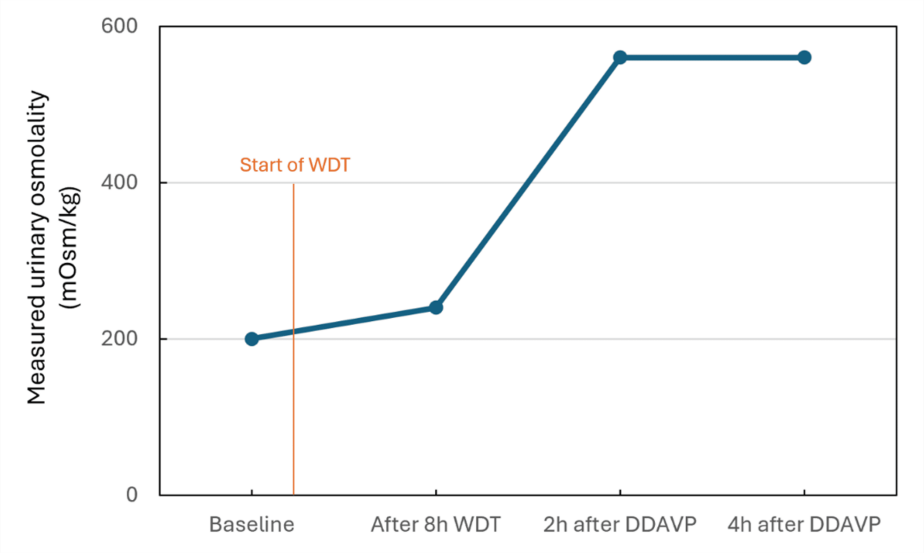


FIGURE 2: Measured urinary osmolality at baseline, eight hours after water deprivation testing (WDT), and two and four hours after intravenous administration of 1 µg 1-deamino-8-D-arginine vasopressin (DDAVP).

Following an eight-hour period of strict fluid restriction and clinical monitoring, the patient's urine osmolality was measured at 240 mOsm/kg. Subsequent administration of exogenous desmopressin resulted in a urinary osmolality increase to 560 mOsm/kg, representing a rise of greater than 100%. This robust response was consistent with complete central AVP-D.

Proceeding with the workup, a contrast-enhanced magnetic resonance imaging (MRI) scan of the sella turcica was performed, which revealed an attenuation of the normal physiological discrimination of the neurohypophysis, with only a discrete spontaneous T1 hyperintensity in the posterior pituitary, compatible with ongoing loss of the bright spot (Figure 3). The pituitary stalk exhibited atypical characteristics, with an inferior glandular insertion ⩾2 mm in transverse diameter (Figure 4). These findings raised a strong diagnostic suspicion of a chronic inflammatory or infiltrative process, consistent with the working diagnosis.

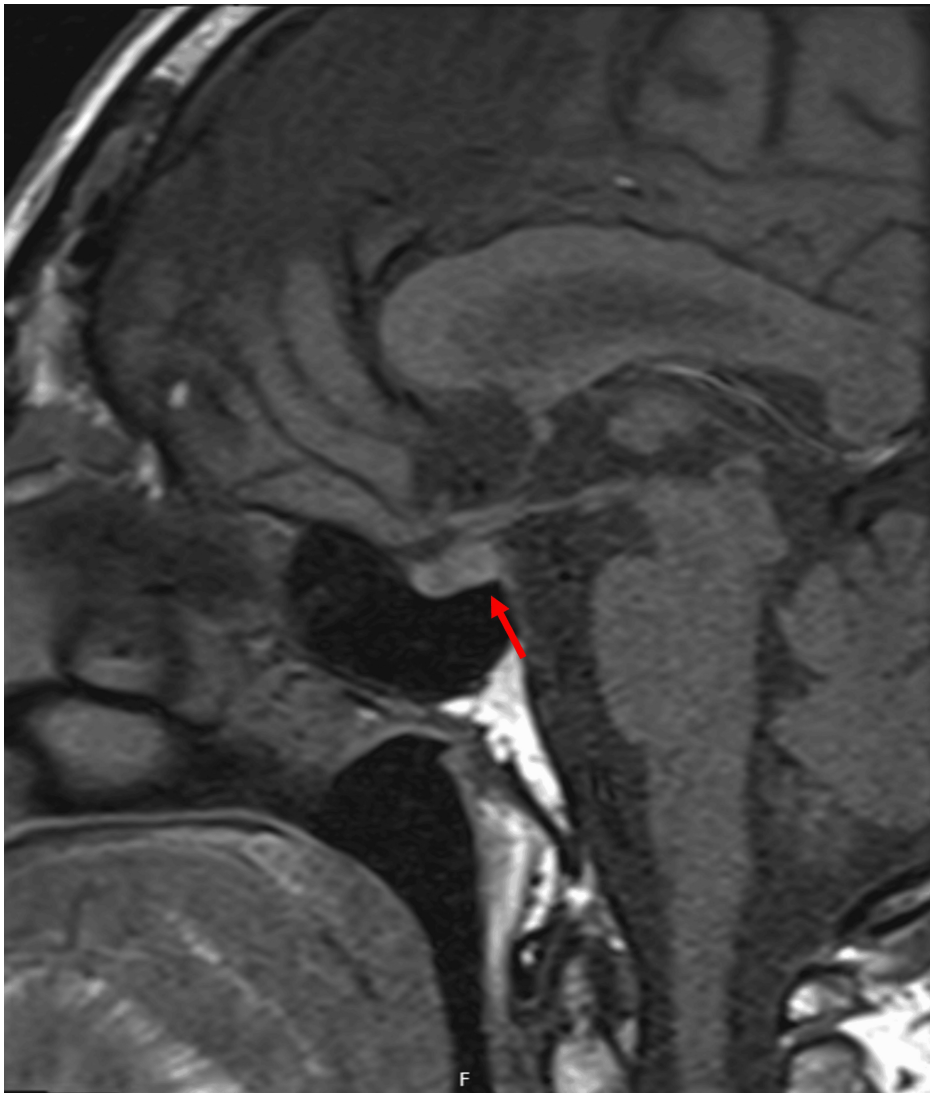


FIGURE 3: Sagittal T1-weighted magnetic resonance imaging showing loss of the posterior pituitary bright spot, highlighted by the red arrow.

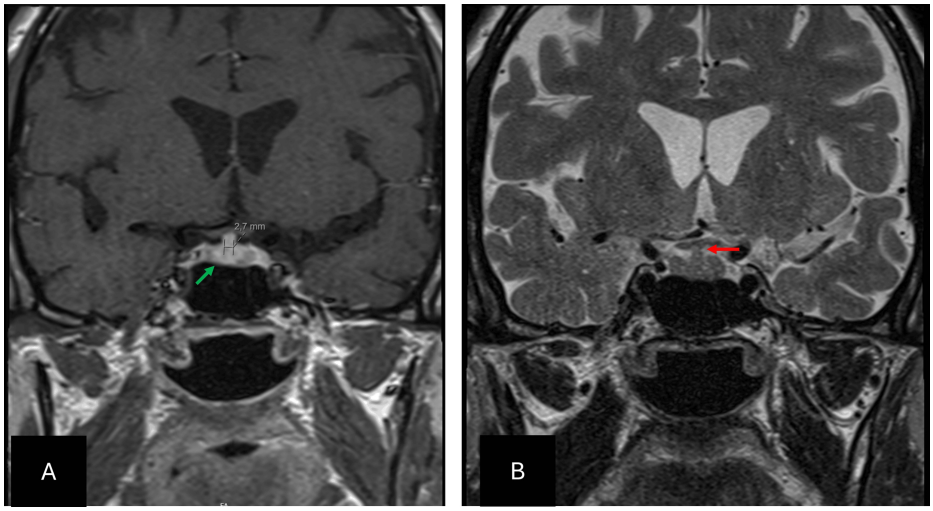


FIGURE 4: Coronal T1 (panel A) and T2-weighted (panel B) magnetic resonance imaging showing pituitary stalk thickening, highlighted by green and red arrows.

To evaluate for concurrent anterior pituitary dysfunction, hormone testing was performed (Table 2), which was unremarkable.

Hormone	Value	Reference range	Unit
Free T3	2.3	2.3-4.2	pg/mL
Free T4	1.05	0.80-1.80	ng/dL
TSH	1.5	0.55-4.78	mIU/L
FSH	15.2	1.4-18.1	mIU/mL
LH	10.1	3.1-34.6	mIU/mL
Estradiol	30.5	<39.8	pg/mL
Total testosterone	325.1	187.7-684.2	ng/dL
Morning cortisol	7.26	3.44-22.45	µg/dL
ACTH	12.7	7.2-63.3	pg/mL
Prolactin	13.4	2.1-17.7	ng/mL

TABLE 2: Measured serum hormone levels to exclude concomitant endocrinopathies.

Of note, insulin-like growth factor 1 testing was not available at our hospital at the time.

T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ACTH, adrenocorticotropic hormone

The patient was initially started on a fixed evening dose of 1 µg intravenous desmopressin (since oral desmopressin was not immediately available), coupled with a daily fluid restriction of 1.5 to 2 L, and serum sodium was measured daily. This initial regimen precipitated an episode of iatrogenic hyponatremia, with serum sodium reaching a nadir of 125 mEq/L. After transition to 50 µg oral lyophilized desmopressin, there was improvement in hyponatremia (Figure 5), alongside excellent symptomatic control of both polyuria and polydipsia. The patient was discharged in a clinically improved and euvolemic state, with instructions to maintain his oral desmopressin regimen and closely monitor his fluid intake.

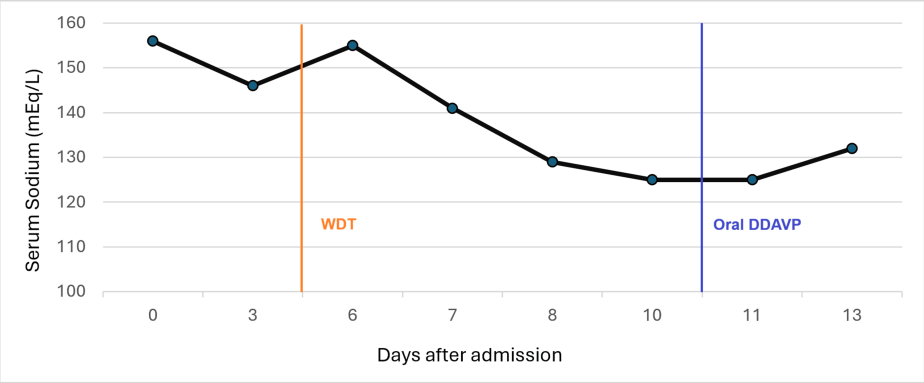


FIGURE 5: Measured serum sodium concentration in mEq/L after admission.

Water deprivation testing (WDT) was performed overnight between days 5 and 6. Between days 10 and 11, the patient was transitioned from 1 µg IV desmopressin to 50 µg oral desmopressin.

On outpatient follow-up after one month, the patient was asymptomatic and maintaining a varied diet, with a serum sodium of 140 mEq/L, a serum osmolality of 292 mOsm/kg, and a reduction in HbA1c from 7.7% to 7.1%.

After discharge, the patient was referred to a tertiary hospital for further follow-up and treatment, where he was already being seen by a pulmonologist for his pulmonary fibrosis.

Discussion

We report a case of new-onset AVP-D, 33 years after the initial diagnosis of pulmonary LCH in a 68-year-old patient. We present the diagnostic process and initiation of treatment.

Our patient exhibited polyuria and polydipsia, a classical presentation for AVP-D. Initial evaluation in the ED was notable for the absence of hypernatremia and clinical dehydration - in fact, patients rarely present with these findings in the absence of an impaired thirst response [10]. However, the patient later resorted to self-imposed fluid restriction, which, in conjunction with an inability to concentrate urine, led to significant dehydration and hypernatremia, precipitating inpatient admission, where a diagnosis of AVP-D was made with a water deprivation test and concurrent imaging.

Of note, an initial urine osmolality of 560 mOsm/kg is not typical of AVP-D. However, the patient was being treated with an SGLT2i, which may confound the diagnosis by increasing urinary osmolality due to osmotic diuresis, as previously reported [11], highlighting the importance of withholding this medication before testing.

The prevalence of AVP-D in patients with LCH is variable - in pediatric studies, it has been reported to be between 16% and 29.6% [12,13] - and, in a retrospective study of four trials, it was present in 12% of 1,741 patients with LCH [14]. The onset of AVP-D is highly variable - it can be present at the diagnosis of LCH in 6% of cases or manifest later, with a median interval to onset of 19 months and a cumulative risk rising to an estimated 20% after 15 years [14].

Most studies on LCH are done in children (as they represent most new diagnoses), and adult data are lacking [13,15]. In adults, most cases of LCH present as a single-system disease, with pulmonary LCH (PLCH) in 85% of patients, contrary to pediatric populations, where multisystemic disease is more prevalent [16]. In a prospective cohort of 102 patients with PLCH, 8% presented with pituitary involvement at the time of diagnosis [17].

Reactivation is a common occurrence in LCH, with a cumulative risk of 46% at 5 years, especially in severe multisystem disease, where most reactivations occur within 2 years of treatment cessation [18]. Conversely, most cases of PLCH have a favorable outcome, either spontaneously or after treatment with glucocorticoids [16]. However, as was seen with our patient, the progression from single-system disease to multisystemic disease has been reported [19].

Although definitive diagnosis of LCH typically warrants histopathological confirmation [20], a pituitary biopsy was deferred in this patient. Biopsy is generally indicated for mass lesions, whereas in our patient, neuroimaging demonstrated isolated stalk thickening with attenuation of physiological differentiation and

loss of the posterior bright spot, without a measurable mass. Consequently, given the substantial risk of iatrogenic injury to the hypothalamic-pituitary axis outweighing the diagnostic benefit, the biopsy was deferred and a presumptive diagnosis was made. Other differential diagnoses were considered, especially the possibility of metastatic adenocarcinoma - considering the patient's smoking history, pulmonary adenocarcinoma was a concern. However, the patient had a recent thoracic CT scan (ordered by his pulmonologist), which did not raise this concern. However, other primary neoplasms should have been pursued, and this is an important limitation. Positron emission tomography-CT (PET-CT) scanning is not available in our hospital in a timely manner, and the patient would undergo restaging and further investigation after referral to the tertiary care center.

To our knowledge, this is one of the longest reported latencies to the development of AVP-D in current literature.

An expert panel on behalf of Euro-Histio-Net recommends that new-onset AVP-D should be considered as a reactivation of disease and that, despite the irreversibility of AVP-D in this context, systemic treatment should be initiated to prevent the development of further hormonal deficiencies [15]. Our patient had regular follow-up with a pulmonologist at a tertiary care hospital due to his pulmonary fibrosis secondary to PLCH and, as such, was referred to said tertiary care center for specialized oncological management.

Conclusions

This case report highlights an exceptionally delayed presentation of AVP-D, manifesting 33 years after the initial diagnosis and remission of PLCH. Progression from PLCH to multisystemic disease can occur at any stage, and regular clinical follow-up should take this into account with an adequate history and careful symptom review. The development of polyuria and polydipsia should prompt evaluation for possible AVP-D and, when confirmed, systemic treatment is warranted.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Alexandre Castro Lopes, Sara Bravo, Clara Pinto, Mariana Sousa, Joana Melo

Acquisition, analysis, or interpretation of data: Alexandre Castro Lopes, Clara Pinto, Mariana Sousa

Drafting of the manuscript: Alexandre Castro Lopes, Clara Pinto, Mariana Sousa

Critical review of the manuscript for important intellectual content: Alexandre Castro Lopes, Sara Bravo, Clara Pinto, Mariana Sousa, Joana Melo

Supervision: Alexandre Castro Lopes, Mariana Sousa

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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