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Case Report

A Case of Burnt-Out Langerhans Cell Histiocytosis Presenting as Postpartum Hypopituitarism

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ABSTRACT

Objective: To evaluate the case of a woman who presented with central hypogonadism and diabetes insipidus and further developed a persistent cough leading to an unexpected diagnosis of burnt-out Langerhans cell histiocytosis (LCH).
Methods: Clinical and laboratory endocrine evaluation, magnetic resonance imaging, high-resolution computed tomography, and open-lung biopsy results are discussed.
Results: A 28-year-old woman presented at 10 months postpartum with polydipsia, polyuria, and amenorrhea for 3 months. Her results showed a prolactin level of 25 μg/L (reference,<23.5 μg/L), estrogen level of 91 pmol/L (reference, 110-180 pmol/L), follicle-stimulating hormone level of 6 IU/L (reference, 2-20 IU/L), and luteinizing hormone level of 6 IU/L (reference, 2-70 IU/L). A water-deprivation test found a sodium concentration of 148 mmol/L (reference, 135-145 mmol/L), serum osmolality of 310 mmol/kg (reference, 275-295 mmol/kg), and urine osmolality of 107 mmol/kg (reference, 50-1450 mmol/kg) that improved to 142 mEq/L, 295 mmol/kg, and 535 mmol/kg, respectively, after desmopressin administration. Gadolinium-enhanced pituitary magnetic resonance imaging demonstrated a markedly thickened stalk with uniform enhancement. Chest high-resolution computed tomography confirmed bilateral upper-zone cystic lung disease suggestive of either pulmonary lymphangioleiomyomatosis or LCH. Eventual histology showed CD1a-positive burnt-out LCH. This differentiation was crucial as pulmonary lymphangioleiomyomatosis exacerbates with estrogen therapy and pregnancy, which the patient was able to successfully pursue without disease exacerbation.
Conclusion: The patient's initial presentation was considered as lymphocytic hypophysitis, but subsequent cystic changes on high-resolution computed tomography led to a unifying definitive diagnosis of burnt-out LCH. This case highlights the importance of investigating for uncommon secondary causes of hypophysitis.

Introduction

Pituitary stalk lesions often present with central diabetes insipidus (DI) and varying forms of hypopituitarism termed as infundibulohypophysitis.[1] This poses a diagnostic challenge as multiple pathologies involving the infundibulum can cause a similar clinical picture.[2] Lymphocytic (ie, autoimmune) hypophysitis (LH) is a common cause of infundibulohypophysitis in younger women but is usually a presumptive diagnosis after the exclusion of systemic pathology.[2-4] Langerhans cell histiocytosis (LCH) is a rare clonal infiltrative disorder of specific dendritic-origin cells with a characteristic predilection for the posterior pituitary in adults.[4,5] We present an unusual case of infundibulohypophysitis with atypical pulmonary involvement from burnt-out LCH.

Case Report

A 28-year-old nurse was referred with 3 months of excessive thirst and polyuria of almost 12 liters a day, accompanied by mild

Abbreviations: LH, lymphocytic hypophysitis; LCH, Langerhans' cell histiocytosis; PLAM, pulmonary lymphangioleimyomatosis; DI, diabetes insipidus.

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headache and fatigue. She was 10-months postpartum, following an uncomplicated pregnancy. She breastfed for 4 months and had 2 regular menstrual cycles after weaning. She became amenorrheic after the onset of polyuria. The examination was unremarkable for findings of hypopituitarism or visual field defects. A static pituitary function panel (Table 1) revealed mild hyperprolactinemia and hypogonadotropic hypogonadism with remaining anterior pituitary axes intact. A water-deprivation test found a serum osmolality of 310 mmol/kg, sodium concentration of 148 mmol/L, and urine osmolality of 107 mmol/kg, which normalized completely with desmopressin (Table 1), confirming the diagnosis of DI. Magnetic resonance imaging of the pituitary revealed an enlarged gland and thickened pituitary stalk measuring 5.2 mm, with uniform gadolinium enhancement (Fig. 1). Screening investigations for systemic pathologies were all negative (Table 2), supporting a likely diagnosis of LH. The patient was treated with desmopressin and declined high-dose glucocorticosteroid therapy after extensive discussion, preferring an expectant approach. She was keen to extend her family and understood that assisted fertility may be required if the pituitary function did not recover.

Two months later, she returned with a persistent cough. She was an occasional smoker. Chest radiography and subsequent high-resolution computed tomography demonstrated bilateral upper-zone thin-walled cystic lung disease (Fig. 2 *A*). Respiratory opinion favored pulmonary lymphangioleiomyomatosis (PLAM) based on the clinical-radiological correlation. However, the rarity of coincident hypophysitis and PLAM prompted the consideration of an alternative unifying diagnosis, such as LCH or sarcoidosis. An extensive survey for stigmata of systemic pathologies, including a skeletal survey and calcium metabolism, bronchoscopic lavage, and transbronchial biopsy failed to provide a conclusive diagnosis.

Table 1
Initial Anterior Pituitary Function and Water-Deprivation Test Results

Test	Result			Reference range
Prolactin	25-35			<23.5 μg/L
	526-750			<500 mIU/L
Insulin-like growth factor-1	26			13-44 nmol/L
	198			99-336 ng/mL
Growth hormone	0.66			<10 μg/L
	2			<66 mIU/L
Thyroid-stimulating hormone	1.1			0.3-3.5 mU/L
	1.1			0.3-3.5 μIU/mL
Free thyroxine	13.3			9-19 pmol/L
	1			0.7-1.5 ng/dL
Cortisol	408			160-650 nmol/L
	14.8			6-24 μg/dL
Adrenocorticotropic hormone	3.3			2-11 pmol/L
	15			9-51 pg/mL
Follicle-stimulating hormone	6			2-20 IU/L
	6			2-20 mIU/L
Luteinizing hormone	6			2-70 IU/L
	6			2-7 mIU/mL
Estradiol	91			110-180 pmol/L
	24.8			30-49 pg/mL
Corrected calcium	2.39			2.1-2.6 mmol/L
	9.6			8.4-10.4 mg/dL
Random glucose	4.8			3.6-7.7 mmol/L
	86.5			65-140 mg/dL
	Initial	2-h fast	Desmopressin acetate given	
Serum sodium	145	148	142	135-145 mmol/L
	145	148	142	135-145 mEq/L
Serum osmolality	304	310	295	275-295 mmol/kg
	304	310	295	275-295 mOsm/kg
Urine osmolality	…	107	535	50-1450 mmol/kg
		107	535	50-1450 mOsm/kg

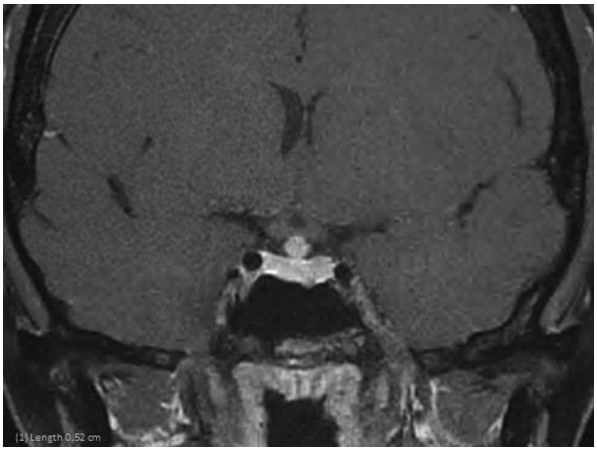

Fig. 1. MRI pituitary: T1W coronal with contrast - thickened pituitary stalk and enhancement. *MRI* = magnetic resonance imaging.

Since a hyper-estrogenic state is known to aggravate PLAM but not LCH, a definitive diagnosis was vital to our patient's fertility plans and sex hormone replacement; hence, our patient underwent an open-lung biopsy. After initial equivocal results for LCH versus PLAM, specialist pulmonary pathologists were able to finally identify CD1a-positive histiocytes from a middle lobe biopsy specimen (Fig. 2 *B*), favoring a working diagnosis of burnt-out LCH.

Our patient was started on sex hormone replacement and desmopressin and advised to cease smoking. Chemotherapy and pituitary irradiation were deemed to pose more harm. There was a gradual radiological improvement of the pituitary stalk without any further change in pituitary function. She later underwent successful ovulation induction resulting in frozen embryos. Over 3 years, her pulmonary LCH appeared stable on serial imaging and pulmonary function tests without any new lesions or systemic involvement.

Discussion

The causes of pituitary stalk lesions presenting with infundibulohypophysitis are diverse, including congenital, inflammatory, infective, and neoplastic diseases.[2,3] The true prevalence of those pathologies remains underreported as many patients are not biopsied due to concerns with significant procedural risk or simply the lack of local expertise.[2] LH and LCH are common in young adults, whereas neoplastic diseases predominate in older adults.[2-4] LH is a

Table 2
Screening for the Causes of Secondary Hypophysitis

Test	Result	Reference range
α-fetoprotein	2	<12 μg/L
	2	<12 ng/mL
β-human chorionic gonadotropin	<2	<2 IU/L
	<2	<2 mIU/mL
Angiotensin-converting enzyme	1.17	0.34-1.19 μKat/L
	69	20-70 U/L
1,25-vitamin D	122	60-208 pmol/L
	46.9	23-80 pg/mL
Ionized calcium	1.29	1.15-1.30 mmol/L
	5.2	4.6-5.2 mg/dL
Immunoglobulin 4	0.69	0.030-2.010 g/L
	69	3-201 mg/dL
Free α-glycoprotein subunit	0.13	<0.6 IU/L
	0.13	<0.6 mIU/mL
perinuclear anti-neutrophil cytoplasmic antibody , cytoplasmic anti-neutrophil cytoplasmic antibody	<40	<40

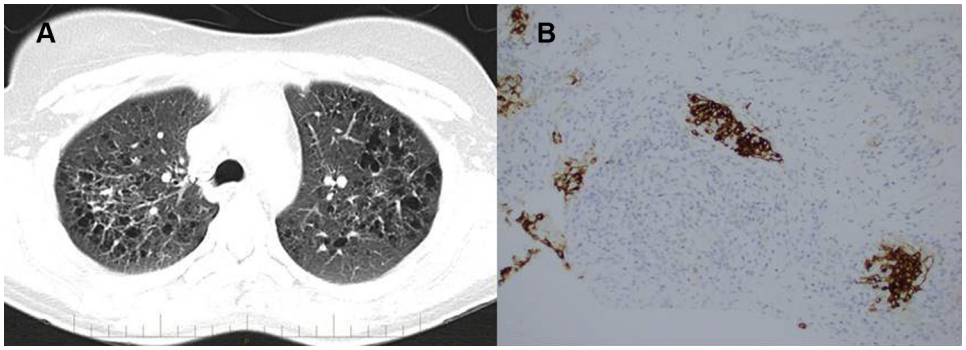

Fig. 2. High resolution chest CT showing thin walled cystic changes (*A*) and CD1a histiocytes on open lung biopsy, ×400 magnification (*B*). *CT* = computed tomography.

common cause of infundibulohypophysitis in young women with a peripartum association.[4] LH typically involves adenohypophysis, preferentially affecting corticotrophs in 75% of cases, followed by thyrotrophs (58.33% of cases), gonadotrophs (50% of cases) and lactotrophs (41.67% of cases), while DI has been observed less frequently (16.7% of cases).[3] Headache is a common complaint; rarely, mass effect may cause optic apparatus compromise.[3] Although pituitary biopsy is the gold standard, in practice, this is often a presumptive diagnosis of exclusion particularly in postpartum women.[2] Systemic diseases such as sarcoidosis, granulomatous vasculitis, tuberculosis, and LCH can present similarly and extrapituitary manifestations usually provide clues to the diagnosis, although it can still prove challenging, as in our case.[1-3,6]

LCH is a poorly understood disorder with a debated pathogenesis characterized by the proliferation and infiltration of bone marrow-derived Langerhans cells.[5,6] Prevalent BRAF and MAP2K1 mutations in LCH cells supports a myeloid neoplasm origin over an inflammatory origin.[7,8] LCH, an orphan disease, typically affects children and much rarely adults (1 to 2 cases per million population).[6,9] All organs can be invaded, but the lungs, bone, skin, and pituitary are those most commonly affected in adults.[6,9] Clinical presentation is heterogeneous, ranging from an indolent single-site disease or stable multisystem disease to disseminated aggressive disease with hematopoietic tissue involvement and high risk of mortality.[1,6,9,10] Infiltration of the pituitary stalk with central DI is among the most common endocrine manifestation, affecting 30% of adults with LCH and 40% of those with multisystem disease.[9] Anterior pituitary deficiencies are reported in 20% of patients with LCH, growth hormone deficiency being the most common, followed by gonadotropins, TSH, and ACTH.[5,11] Our patient had multisystem LCH, involving the lungs and pituitary apparatus, manifesting as central DI and gonadotrophic deficiency with corticotroph sparing. Growth hormone was not assessed formally at the presentation as she had normal insulin-like growth factor-1 levels with hypogonadism but subsequently confirmed intact on glucagon stimulation performed during a fertility workup.

Skeletal involvement in LCH usually comprises asymptomatic, well-defined osteolytic lesions, with or without periosteal reaction on plain x-ray. A few cases may present with painful bony swellings or pathologic fractures.[9] Hence, a full-body skeletal survey with x-ray is recommended.[9] LCH can present on the skin in any region as a maculopapular rash or even as ulcerative lesions.[9] Our patient, thus far, has not developed bone or skin involvement.

Pulmonary disease is the predominant manifestation in adults and occurs almost exclusively in smokers.[10,12] High-resolution computed tomography is almost always diagnostic and classically shows thick-walled, nodular, centrilobular cysts, predominantly distributed in upper lobes.[10-13] Despite significant radiological changes, patients are often asymptomatic or experience mild respiratory symptoms; however, up to 20% develop spontaneous pneumothorax.[10,12,13] Pulmonary LCH is strongly associated with smoking[10] and the resolution of disease following smoking cessation is well documented, making smoking cessation an essential part of treatment.[12]

PLAM was considered a differential to pulmonary LCH, as both diseases cause pulmonary cystic destruction and affect young women.[14] Unlike LCH, it is characterized by pathologic smooth-muscle hyperplasia and invasion within pulmonary lymphatics and airways, causing the destruction of the normal parenchyma.[14] Disease onset is rare outside of reproductive years, with accelerated progression during pregnancy, implicating estrogen in disease exacerbation.[14] Characteristic high-resolution computed tomography features include the diffuse distribution of thin-walled, round, well-defined cysts.[14] It can be exceptionally difficult to distinguish between PLAM and end-stage pulmonary LCH, as shown in our case. Radiologically, late-stage LCH can evolve into a similar appearance, with large thin-walled cysts appearing as the disease wanes.[12,13] Histologically, Langerhans cells may no longer be abundantly identified among tissue scarring, reaching a state described as “burnt-out” LCH, posing a challenge for pathologists.[13]

Ascertaining the correct diagnosis in our patient had profound implications on the prognosis, follow-up, and assisted-fertility options. While there are a few conflicting case reports on LCH and pregnancy, with some reporting improvement and others showing deterioration to no change, there seems to be no adverse impact of LCH on pregnancy.[10,12,16] However, pre-existing DI may worsen during pregnancy and require increased monitoring.[10,12] Assisted fertility and monitoring for the progression of pituitary insufficiency and lung disease in pregnancy will be central in our patient’s care.

Therapeutic approaches for adult LCH patients are largely based on expert consensus and extrapolated from the pediatric population, which may not be appropriate, as adults appear less responsive to chemotherapy and beget higher toxicity.[10,15] The hormonal sequelae in LCH appear permanent irrespective of radiological improvement and chemotherapy.[10,11,16,17] However, focal radiotherapy may help to reduce mass effects.[10,17] Pulmonary LCH in our patient was likely burnt-out, and her respiratory symptoms settled on smoking cessation. As she desired to pursue fertility induction, proactive surveillance was deemed to be the best option in her case. DI predicts multisystem disease, with 50% of patients developing new complications within 1 year of onset, highlighting the importance of long-term follow-up.[18,19]

Conclusion

DI associated with partial hypopituitarism, particularly if it is corticotroph sparing, should raise concerns for a systemic cause

rather than LH. The histology of a peripheral lesion played a vital role in our case, but where that is not possible, the biopsy of the pituitary stalk should be considered, depending on local expertise and individual risk-benefit for each patient. LCH should be a differential in young adults with central DI necessitating a skeletal survey and chest imaging at the least. Ongoing surveillance and follow-up are essential in both LCH and infundibulohypophysitis.

Disclosure

The authors have no multiplicity of interest to disclose.

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