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Case Report

Diabetes Insipidus Revealing Langerhans Histiocytosis

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Abstract

Langerhans cell histiocytosis (LCH) is a rare disease characterized by the abnormal proliferation of Langerhans cells, a type of specialized macrophage. It presents a wide range of clinical manifestations, from isolated bone lesions to severe multisystem involvement. We report the case of a 3-year-old child with symptoms of central diabetes insipidus (DIC) revealing, associated with chronic otorrhea, exophthalmos, and splenomegaly. Investigations, including CT scan and bone biopsy, confirmed the diagnosis of HL. Management included administration of desmopressin for DIC, as well as antibiotic treatment for recurrent ENT infections. This case highlights the importance of suspecting HL in the differential diagnosis of pediatric DIC, allowing early identification and management of potential multisystem involvement.

Keywords: *Langerhans Cell Histiocytosis; Desmopressin; Central Diabetes Insipidus; Histology*

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease caused by the abnormal accumulation of Langerhans cells, a specialized type of macrophage involved in immune response regulation. This condition exhibits a wide range of clinical manifestations, from isolated lesions to severe multisystem involvement. Historically, LCH has been described under various clinical entities, including eosinophilic granuloma, Hand-Schüller-Christian disease, Letterer-Siwe syndrome, and Hashimoto-Pritzker syndrome. These entities were later unified under the term "histiocytosis X" due to their shared histological hallmark: significant proliferation of Langerhans cells, identifiable by specific markers such as CD1a, langerin, and Birbeck granules [1-3].

Observation

This is the case of a 3-year-old child with a history of head trauma involving a temporo-frontal impact one year prior and recurrent otorrhea, with no history of consanguinity. The child presented with a polyuria-polydipsia syndrome lasting two months, characterized by a diuresis of 25 cc/kg/h, along with bilateral otorrhea, anorexia, weight loss, and apyrexia. The condition was complicated by dehydration, necessitating hospitalization.

Clinical examination revealed a pale child with mild right exophthalmos and right periorbital swelling without inflammatory signs (Figure 1 and 2), crusted lesions were observed on the scalp (Figure 3), and splenomegaly was noted. The child weighed 10 kg (-3 SD) and measured 90 cm in height (-1 SD). Otoscopic examination showed acute purulent otitis media on the right side with a bulging eardrum and bleeding stigmata on the left side.

Figure 1: *Image showing slight right exophthalmos.*

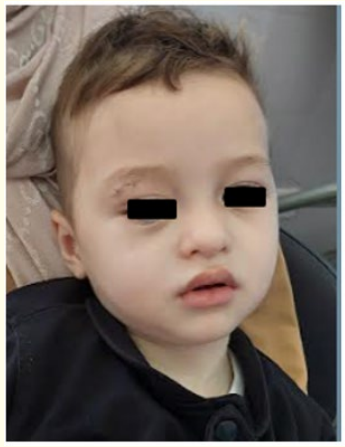

Figure 2: *Image showing right periorbital swelling.*

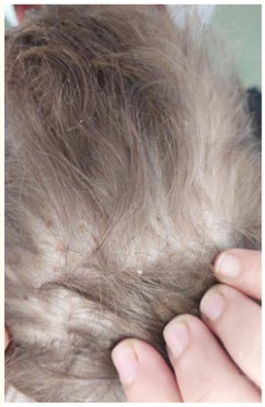

Figure 3: *Image showing crusted lesions on the scalp.*

A brain CT scan (Figure 4) revealed bilateral lacunar lesions at the base of the skull, some punched-out, particularly affecting the orbital process of the right frontal bone, the greater wing of the sphenoid, the squamous part of the right temporal bone, and the occipital bone bilaterally. Additional findings included filling of the Prussak space of the hypotympanic membrane and mastoid cells on the right, consistent with right otomastoiditis.

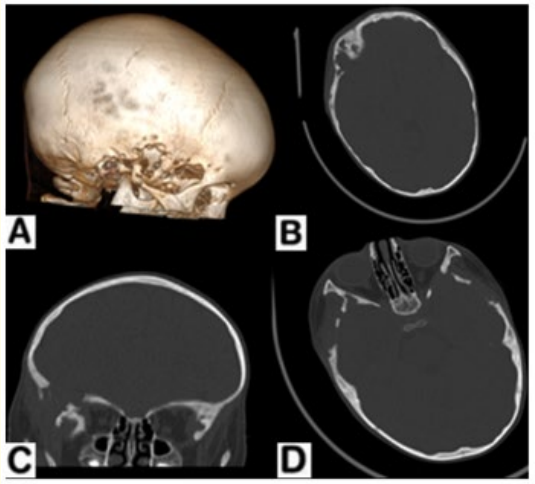

Figure 4: *A brain CT scan shows bilateral lacunar lesions of the base of the skull, some of which are punched out ¨B¨, particularly involving the orbital process of the right frontal bone ¨D¨, the greater wing of the sphenoid bone ¨C¨, the squamous part of the right temporal bone ¨A¨ and the squamous shell bilaterally.*

Laboratory investigations showed hypochromic microcytic anemia with hemoglobin at 10 g/dL, leukocytes at 10,200/mm^3, platelets at 341,000/mm^3 and C-reactive protein (CRP) at 38.20 mg/L. Renal and hepatic function tests were normal. Plasma osmolarity was 284.04 mOsm/L, urine osmolarity was 65 mOsm/L, and antidiuretic hormone levels were < 0.5 pmol/L, confirming the diagnosis of diabetes insipidus. The patient was treated with Minirin (120 µg/day) for diabetes insipidus and with ofloxacin and amoxicillin for otitis, resulting in good clinical progress. An 8-hour cortisol level and thyroid-stimulating hormone (TSH) were within normal ranges.

Follow-up ENT examination showed a polyp in the right external auditory canal with thickening of the eardrum, and on the left, a polyp completely filling the external auditory canal.

The etiological investigation, including a myelogram and osteomedullary biopsy, showed no evidence of tumor infiltration. Skeletal radiographs were unremarkable, and thoraco-abdomino-pelvic CT scan revealed homogeneous splenomegaly (10 cm) without other abnormalities. Echocardiography was normal, and hypothalamic-pituitary MRI showed no abnormalities.

An orbital bone biopsy revealed connective-osseous tissue remodeled by fibrosis and containing a histiocytic-like infiltrate. The infiltrate consisted of clusters of histiocytes with granular, occasionally foamy, eosinophilic cytoplasm, mixed with numerous eosinophilic polymorphonuclear cells and a few multinucleated giant cells, confirming the diagnosis of Langerhans cell histiocytosis.

Discussion

Langerhans cell histiocytosis (previously called histiocytosis X) is a disease characterized by the abnormal proliferation of Langerhans cells with formation of granulomas. These cells, derived from the dendritic lineage, are mononuclear and contain the characteristic racket-shaped Birbeck granules, affecting approximately 5.8 children per million. The central diabetes insipidus (CDI) is often one of the first signs of this disease [4-6].

It is a complex disease that can affect many organs with specific symptoms and complications:

- **Bone involvement:** The bones are most often affected (80% of cases). Symptoms include pain, swelling and sometimes pathological fractures. X-rays show lytic lesions, often in the skull, long bones, and vertebrae.
- **Skin involvement:** Common in infants, this involvement appears as papular, scaly, sometimes nodular lesions on the scalp, trunk and skin folds (armpits and inguinal folds).
- **Hypothalamic-pituitary axis impairment:** Present in approximately 20-25% of patients, this impairment manifests as central diabetes insipidus (CDI) due to a deficiency in antidiuretic hormone (ADH). DIC is often permanent and may be associated with deficiencies of other hormones (such as GH).
- **Hematologic involvement:** This involvement is serious and may include anemia, thrombocytopenia and sometimes bone marrow invasion. Severe forms are manifested by hemoglobin < 7 g/dL and platelets < 20,000/mm^3, indicating a risk of severe complications and a more reserved prognosis.
- **Pulmonary involvement:** This takes the form of peribronchiolar granulomas and causes cystic lesions with a risk of pneumothorax.
- **Liver involvement:** Two forms are described. Acute involvement includes hepatomegaly with cytolysis and cholestasis. It can progress to sclerosing cholangitis, a serious chronic complication that can lead to cirrhosis and progressive liver failure.
- **Splenic involvement:** This manifests as splenomegaly, often associated with hepatic or hematological involvement.
- **Lymph node involvement:** Lymph nodes may be enlarged in any nodal area, although involvement is often asymptomatic. However, mediastinal involvement can lead to a compression syndrome, such as superior vena cava syndrome.
- **ENT and hearing impairment:** Chronic otorrhea is a common symptom, often due to a secondary infection of the ear canal. Damage may include the bony structures of the ear (temporal bone) and result in deafness or balance problems. Chronic sinusitis or pharyngitis may also be present.
- **Gastrointestinal involvement:** Rare, it generally manifests in infants in the form of chronic or exudative diarrhea, associated with hypoalbuminemia. Diagnostic confirmation is based on endoscopy [1,7].

Our case presents several of these features, including diabetes insipidus, orbital bone lesions, splenomegaly, and ENT involvement. Diagnostic confirmation is based on biopsy of the lesions, showing abnormal proliferation of Langerhans cells.

The diagnosis of central diabetes insipidus (DIC) secondary to Langerhans cell histiocytosis is based on several tests. A 14-hour water restriction test is first performed to assess urine concentrating ability. In the case of DIC, the urine remains dilute despite water restriction, whereas a healthy subject should be able to concentrate their urine, indicating a deficiency in antidiuretic hormone (ADH). Then, a desmopressin test (DDAVP) is performed to confirm the central origin of the DIC: the elevation of urinary osmolality post-DDAVP clearly shows that the kidneys respond to ADH, confirming the occurrence of DIC. Finally, an MRI of the hypothalamic-pituitary region is indicated to look for possible abnormalities. In the context of Langerhans cell histiocytosis, MRI may reveal thickening of the pituitary stalk or the absence of hyperintensity of the posterior pituitary gland in T1 sequence and bone lesions. Biopsy of these bone lesions is the only test that can confirm the link with Langerhans cell histiocytosis [5,8].

After confirmation of the diagnosis by biopsy, an extension assessment is essential to adapt the therapeutic management. This assessment begins with a thorough clinical examination, including an ENT and stomatological assessment, aimed at collecting a detailed history of symptoms (pain, swelling, fever, growth disorders, etc.). A minimal biological assessment is required, including blood count, albumin dosage, as well as a liver and inflammatory assessment. X-rays of the chest and skeleton complete this first step. In cases of multi-organ involvement, more in-depth examinations such as chest CT scan or brain MRI may be indicated to refine the assessment. PET scanning, although promising for multiple localizations, still requires validation. According to the classification established by the Histiocyte Society (Table 1), our patient is classified as group 2 [2,7,9-11].

Group 1	Patients with localized, unifocal involvement, limited to a single organ.
Group 2	Patients with multisystem involvement without involvement of critical organs (liver, spleen, bone marrow, lung).
Group 3	Patients with multisystem involvement including at least one major organ at risk among the liver, spleen, bone marrow or lungs.

Table 1: *Classification established by the histiocyte society [2,10,11].*

Treatment of central diabetes insipidus (CDI) is based on general measures and the use of desmopressin (Minirin®), a powerful antidiuretic administered mainly by nasal route. This form, rapid and effective, is preferred for its long duration of action without vasopressin effects. An oral alternative, in the form of 0.1 and 0.2 mg tablets, provides a convenient and well-tolerated option, particularly in cases of respiratory tract infections that may hamper nasal administration. The daily dose required varies widely in children, ranging from 100 to 1000 µg/day, depending on individual needs. Initial treatment of Langerhans cell histiocytosis combines vinblastine and corticosteroids. However, this approach is often insufficient in severe forms, requiring second-line treatments such as cladribine or targeted therapies (BRAF inhibitors or of MEK) for refractory cases [8,12-14].

Conclusion

This case underscores the association between diabetes insipidus and Langerhans cell histiocytosis (LCH), where diabetes insipidus can serve as an early indicator of multisystem involvement. Biopsy confirmation enabled an accurate diagnosis and the initiation of appropriate treatment. Recognizing this link emphasizes the importance of including LCH in the differential diagnosis of diabetes insipidus in children to ensure timely and effective management.

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