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RESEARCH ARTICLE

HYPOTHALAMIC-PITUITARY HISTIOCYTOSIS SEEMS LIKE A REAL TUMOR REVEALED BY DIABETES INSIPIDUS: A CASE REPORT

M. Smouni[1], F. Aziouaz[1], S.Al Guellouj[2], S. Alaoui Rachidi[3], M. Bourkia[4] and M. Benkacem[1]

1. Department of Endocrinology, Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Essaadi University Tangier. Morocco.
2. Department of Dermatology, Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Essaadi University Tangier. Morocco.
3. Department of Radiology, Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Essaadi University Tangier, Morocco.
4. Department of Internal Medicine, Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Essaadi University, Tangier, Morocco.

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Abstract

Introduction: The etiological diagnosis of central diabetes insipidus (DI) is difficult when initial imaging by (MRI) is inconclusive, the association with multisystem lesions should suggest a granulomatous origin.We report a case of Langerhansian histiocytosis revealed by diabetes insipidus.

Observation:A 52-year-old woman was referred to our department for the management of a polyuria-polydipsia syndrome, presenting with sub mammary intertrigo, papilo-squamous lesions on the scalp, inflammatory and ulcerated perianal and vaginal lesions and oral ulcerations. The biological work-up showed hypernatremia, central hypothyroidism, hypogonadotropic hypogonadism and an inflammatory syndrome.The morphological work-up showed a hypothalamic process, a cystic and micronodular pulmonary lesion, a significant peri-renal infiltration with a hairy appearance suggestive of histiocytosis.The skin biopsy concluded a Langerhans cell histiocytosis CD1a+, PS100+, CD163-

The patient was treated with vinblastine and corticotherapy in association with desmopressin and levothyroxine with a good clinical evolution without recovery of the endocrine involvement.

Discussion/Conclusion: Langerhansian histiocytosis is a rare systemic disease of adults. Characterized by infiltration of various organs by CD1a+ histiocytes. Diabetes insipidus, secondary to an infiltration of the post pituitary gland, is the most frequent endocrine disorder that generally precedes the other manifestations of the disease, its diagnosis requires a very meticulous etiological investigation and a regular re-evaluation in order not to miss this pathology.

Corresponding Author:-M. Smouni
Address:-Department of Endocrinology, Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Essaadi University Tangier. Morocco.

Introduction:

Langerhans cell histiocytosis (LCH), previously known as histiocytosis X, is a rare hematological disease of unknown etiology [1] that can occur at any age. However, it preferentially affects children and young adults [2]. It is related to the accumulation within tissues of dendritic cells. These cells have immunological characteristics of Langerhans cells, in particular CD1a and CD207 [3].

For a long time, LCH was considered as a reactive proliferation of Langerhans cells due to inflammatory stress. However, the recent discovery of recurrent oncogenic BRAF mutations in LCH, as well as rare KRAS and TP53 mutations, supports the classification of this disease as a hematologic malignancy [1].

Histiocytic localization in the hypothalamic-pituitary axis represents the most frequent intracranial lesion and classically results in diabetes insipidus, which may be indicative of the disease. This condition has been studied mainly in children, but rarely in adults.

Case report:

We received a 52-year-old patient in the endocrinology department with a history of primary infertility.

The patient has had a polyuria-polydipsia syndrome (PP) for 6 years with fluid intake and output quantified at 6 liters each. The clinical examination objectified papilo-squamous lesions at the level of the scalp, ulcerated perianal and vaginal lesions as well as oral ulcerations evolving, according to the patient, by flare-ups and remissions (Figure 1).

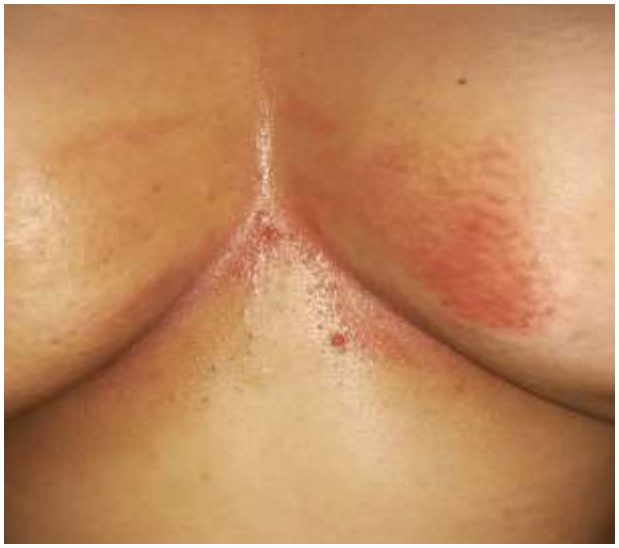

Figure 1: Erythematous papular lesions of the submammary folds.

An obvious cause of the PP syndrome was easily ruled out by a standard work-up, which showed normal blood glucose, calcium, and potassium levels. The high level of sodium confirmed the diagnosis of diabetes insipidus. Furthermore, the hypothalamic and pituitary stem lesion process was in favor of the central origin of diabetes insipidus.

The morphological appearance of the MRI findings and the presence of dermatological lesions with a pattern of flare-ups and remissions led to a suspicion of granulomatous disease. Additionally, a skin biopsy was performed, which indicated an atypical infiltrate with a histiocytic appearance in the papillary and peripapillary dermis, along with epidermotropism. Therefore, the immunohistochemical study confirmed the disease of Langerhans cell histiocytosis with histiocytes positive to CD1a and PS100 marking.

Endocrine evaluation showed thyroid and gonadotropic insufficiency. The extension work-up revealed a cystic lesion in the left lower lobe (LLL) and branching micronodules grouped in small nodular foci in the upper right lobe (URL) and bilaterally in the thoracic region. Additionally, there was significant perirenal infiltration with a 'hairy'

appearance, proximal periureteral fat involvement with slight pyelocaliceal dilatation, and a simple left cortical mid-renal cyst (Figure 2).

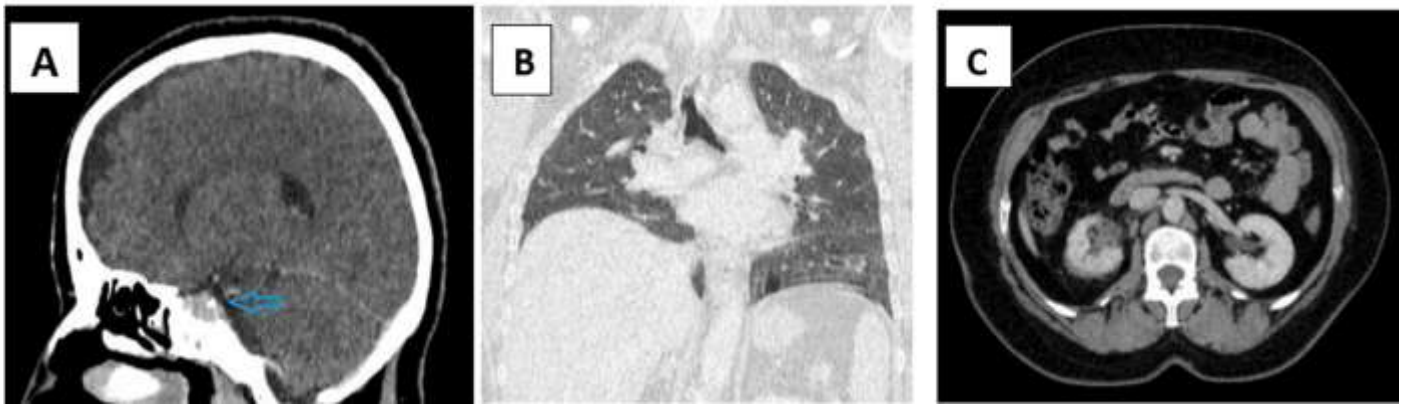

Figure 2: A :Cerebral sagittal section CT image showing a roughly rounded lesion infiltrating the hypothalamus (blue arrow) B: CT image in the coronal section through the thorax, in the parenchymal window, showing a cystic lesion of the LIG. C : Axial section, abdominal CT image showing extensive infiltration of right perirenal, fat and proximal peri ureteral fat

We retained the diagnosis of multifocal histiocytosis and after the opinion of the internists the patient was treated with vinblastine in combination with corticosteroids, Additionally, we administered desmopressin and levothyroxine.

Discussion:

We report a case of a 52-year-old woman with chronic disseminated Langerhans cell histiocytosis (LCH), which was first identified due to involvement of the hypothalamic-pituitary region. This unusual presentation of LCH in adults merits detailed discussion.

Adult Langerhans cell histiocytosis, first described by Lichtenstein in 1953, is a rare and polymorphic condition that progresses through cycles of relapse and remission. It can occur in both sexes at any age and is characterized by the clonal proliferation of Langerhans cells and their accumulation in multiple organs [4].

Although Langerhans cell histiocytosis (LCH) is a rare disease, its incidence is higher in children, occurring in 1 in 200,000 cases, compared to 1 to 2 per million in adults. The actual incidence of LCH in adults may be underestimated, as the clinical signs can be non-specific, leading to a greater number of undiagnosed or misdiagnosed cases [5].

The clinical presentation and prognosis of Langerhans cell histiocytosis (LCH) depend on the patient's age, the number and location of lesions, and the types of organs involved at the time of diagnosis [1]. There are three variants of this unique disease:
1: The acute disseminated form, characterized by widespread systemic involvement, primarily occurs in infants (Letterer-Siwe disease).
2: the chronic disseminated form with often multiple bone lesions and extra-skeletal lesions (Hand-Schuller-Christian disease).
3: The chronic localized form, which may present with solitary or multiple skeletal lesions and sometimes extra-skeletal involvement, is primarily seen in adults (eosinophilic granuloma) [4].

In 50% of cases, Lesions may be skeletal, predominantly cephalic and axial [6]. Cutaneous in 33% of cases with a characteristic topography, and may involve the scalp, retroauricular folds, large flexion creases (as erosive intertrigo with a crusty border), perineum and trunk. Lesions of the palmoplantar region, nails and subcutaneous nodules are also described. Genital lesions are also present and often ulcerating [6].

In the oral cavity, lesions may precede the signs of LCH , usually, they are not specific to the disease. They may include pain, mucosal ulcers, tooth mobility and impaired healing [5].

In our patient, she reported recurrent oral ulceration with tooth mobility and spontaneous loss of 3 teeth, pruritic erythematous lesions in the inter-mammary and submammary areas, scaly lesions on the scalp, as well as inflammatory and ulcerated perianal and vaginal lesions.

Lung lesions are radiologically manifested by a reticulonodular infiltrate, and in more advanced forms, by cysts.

There is a female predominance, and the condition is very common in smokers (>90% of cases). Lymphoreticular involvement, particularly in the lymphatic system, liver, spleen, or bone marrow, is rare but serious and primarily affects children. Neurological and ophthalmological disorders are also described in the literature [6].

Hypothalamic-pituitary axis involvement is seen in 5-50% of patients with LCH [4].

Diabetes insipidus (DI) is the most common endocrine disorder found in 30% of patients [5], It manifests itself by a polyuro-polydipsic syndrome suspected on questioning associated with blood hyperosmolarity and urinary hypo osmolarity. Ideally measured on the morning urine on waking, the dosage of ADH or preferably copeptin, which is abnormally low, confirms the diagnosis of central diabetes insipidus, confirmed by the water restriction test if necessary [4].

Diabetes insipidus can be a revelation of the disease as in our patient's case or occur later in the course of the disease.

The positive diagnosis of pituitary langerhansian histiocytosis is confirmed by the presence of CD1a immunostaining positive histiocytes and PS100 on pituitary biopsy, which should be discussed on a case-by-case basis, if the tumour is larger than 7 mm and no other affected organ is more easily accessible [4].

Brain MRI often reveals a thickening of the pituitary stalk that becomes enhanced after gadolinium or even a true pituitary tumour that can threaten neighbouring structures (notably the optic chiasma) [5].

The search for BRAF-V600E mutation is systematic and facilitates diagnosis and treatment [7].
In our patient's case, careful clinical examination revealed the presence of skin lesions, of which biopsy was the best, easy and accessible way to label the etiological diagnosis of central diabetes insipidus and confirm Langerhans cell histiocytosis.

Involvement of the anterior pituitary gland is also possible. However, it is rare and can lead to pan hypopituitarism, justifying regular evaluation of the various endocrine axes [8]. GH deficiency should be sought in adults, as in this case replacement therapy can improve the patient's psychological and metabolic state. Hypogonadism (gonadotropin (FSH and LH) deficiency) is also possible, with a few cases of amenorrhea described in adult patients. ACTH deficiency is mostly seen in pan hypopituitarism. Thyroid involvement may be of high origin due to TSH deficiency, but also of low origin, following infiltration of the thyroid gland by Langerhans cells [9].

In our patient, the endocrine consequences, in addition to diabetes insipidus, include gonadotropic and thyrotropic insufficiency. The evaluation of the somatotropic axis was not performed.

Numerous studies have observed a high incidence and prevalence of additional malignancies in patients with LCH. These include myeloid leukemias (such as acute myeloid leukemia, myeloproliferative disorders, and chronic myeloid leukemia), lymphomas, and solid organ cancers, particularly affecting the lungs and thyroid.

LCH of the thyroid gland may coincide with papillary thyroid cancer with BRAF-V600E mutations [7].

An assessment of the extent of the disease is imperative and allows for the evaluation of its progression. This includes a blood count, coagulation tests, serum protein electrophoresis, sedimentation rate, CRP levels, and a chest X-ray, skeletal assessment (complete bone X-rays or CT scan), liver, spleen and kidney tests and thyroid (T4, TSH) and pituitary assessment to identify any associated disorders.

Other complementary examinations will be carried out according to the signs of call (cerebral MRI, functional respiratory exploration, dental panoramic, functional respiratory exploration, ENT examination, digestive endoscopy [6-7]

In our clinical case, the work-up showed a cystic lesion in the left lower lobe (LIG) and branching micronodules grouped in small nodular foci in the right upper lobe (LSD) and lower lobe (LI) bilaterally. In the abdominal area, there was significant peri-renal infiltration with a hairy appearance and proximal peri-ureteral fat, with slight pyelocalic dilatation, and a simple cortical left medial-renal cyst

In patients whose diagnosis is not histologically confirmed, close clinical, biological and morphological monitoring should be considered to reassess the need for and justification of a biopsy and to rule out malignancy [10].

Therapeutically, localised forms will benefit from local or moderate systemic treatments. Whereas, multifocal or systemic mono-tissue forms require treatment with chemotherapy. Classically, in the first line the therapeutic protocol is based on the combination of vinblastine and corticoids. In the most severe cases, intensive multidrug therapy is indicated.

Refractory or relapsed cases have been successfully treated with clofarabine, cytarabine, cladribine;

Vemurafenib may be considered in relapsed or refractory cases with BRAF V600E mutations [11].

For the most resistant forms, haematopoietic stem cell transplantation may be discussed [6-11].

For our patient, she was treated with vinblastine 10mg/ml weekly intravenous bolus in combination with prednisone 80mg/dr for 6 weeks with lifelong hormone replacement therapy with good clinical progression.

After 6 weeks of treatment, the response to treatment should be assessed and classified as 'best' if there is complete resolution or regression of disease, 'worst' if there is progression of disease, and 'intermediate' if there is a stable or mixed response with new lesions at one site, and regression at another site [10].

The concurrent occurrence of two distinct histiocytosis in the same patient is exceptional.

Some patients have overlapping forms most often associating Erdheim-Chester disease and HL, but also sometimes Rosai-Dorfman disease, or other rare non-Langerhansian histiocytosis with mostly a better prognosis [12].

In our patient, the initial clinical presentation and histology were highly suggestive of HL. however, imaging was more consistent with Erdheim-Chester disease.

Conclusion:

Langerhans cell histiocytosis is a rare disease in adults, with very diverse clinical aspects ranging from discrete, localized asymptomatic forms to aggressive, widespread multisystem involvement.

Only the anatomopathological study allows to establish its certainty diagnosis. Therapeutic management depends on the site and the number of localizations and its evolution remains capricious.

The disease is often first identified through the occurrence of diabetes insipidus, which may remain isolated for several years. This underscores the need for extended monitoring to detect any systemic involvement during the follow-up of idiopathic central diabetes insipidus. Consequently, endocrinologists play a crucial role in the diagnosis, management, and ongoing care of this rare condition.

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