Monostotic Langerhans' Cell Histiocytosis in a Child with Central Diabetes *Insipidus*

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Langerhans' cell histiocytosis (LCH) comprises a rare group of reticuloendothelial system disorders that can produce focal or systemic manifestations. Diabetes insipidus is considered to be an important indicator of serious underlying diseases in children, including LCH. We report the case of a young patient with monostotic LCH confined to the mandibular ramus, who was diagnosed with the disease after presenting symptoms of central diabetes insipidus and was satisfactorily treated with multi-agent chemotherapy. Additionally, we discuss the clinical, radiographic, histological and immunohistochemical findings, as well as the multidisciplinary approach of this important disease, which should receive attention by dental practitioners, especially when it occurs in children.

Keywords: *Langerhans cell histiocytosis; mandible; children; central diabetes insipidus; chemotherapy.*
J Clin Pediatr Dent 36(4): 377–382, 2012

INTRODUCTION

Langerhans' cell histiocytosis (LCH), formerly known as histiocytosis X, comprises a group of rare disorders of the reticuloendothelial system. This disease is histologically characterized by an idiopathic proliferation of the Langerhans cells and may produce focal or systemic manifestations.[1] In normal tissue, Langerhans cells are nonadherent and nonproliferative cells of bone marrow origin, which migrate through lymphatic vessels to the epidermis, regional lymph nodes, thymus, and oral-pharyngeal mucosa.[2,3] In the presence of LCH, Langerhans cells acquire the morphology of immature dendritic cells, losing their ability to serve as antigen-presenting cells. Thus, they can no longer migrate from the pathological site for the recruitment of inflammatory cells.[2,4]

The understanding of LCH as a specific entity dates back to 1865, when Thomas Smith published a case of skin infection and skull lesions in a child, now identified as a clonal proliferation of Langerhans cells. In 1868, Paul Langerhans described in the epidermis a cellular pattern constituted by non-pigmented dendritic cells. Twenty-five years later, Alfred Hand reported an alleged case of tuberculosis in a 3-year-old boy expressing exophthalmus, excessive thirst and polyuria, which rapidly led to death. Post-mortem examination revealed the presence of skull lesions. In 1905, Hand reported another case of a young patient whose clinical manifestations included exophthalmos, diabetes insipidus and destructive bone lesions. Schüller (1915) and Christian (1920) reported cases of other children who presented this clinical triad of symptoms. Similar cases presenting these clinical features were then termed "Hand-Schüller-Christian disease." Furthermore, Letterer (1924) and Siwe (1933) described an acute fulminant non-leukemic multiorgan disorder of the reticuloendothelial system, characterized by bone defects associated with splenomegaly, hepatomegaly and lymphadenopathy, posteriorly known as Letterer-Siwe disease. During the same period, Mignon reported the first case of eosinophilic granuloma in a 12-year-old boy, which was first suspected to be a skeletal lipoid granulomatous process, clinically resembling Hand-Schüller-Christian disease. In 1940, the term eosinophilic granuloma of bone was

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designated by Lichtenstein and Jaffe to identify this condition. Despite the aggressive behavior observed in eosinophilic granuloma of bone, these lesions were thought to correspond to viral granulomas. Finally, the term histiocytosis X was introduced by Lichtenstein and Jaffe in 1953 to include Hand-Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma as a single entity.[1,2,4-6]

Since all three diseases are characterized by abnormal proliferation of histiocytic cells with typical Birbeck granules, this microscopic feature cannot be used to differentiate between Hand-Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma. The most currently accepted classification system for histiocytic disorders, established by the Writing Group of the Histiocyte Society and World Health Organization (WHO), determines differential diagnosis based on the predominant cell type inside the infiltrate. Thus, histiocytoses were reclassified into dendritic cell disorders (LCH, secondary dendritic cell process, juvenile xanthogranuloma, and solitary histiocytoma with a dendritic phenotype), macrophage-related disorders (hemophagocytic syndromes, Rosai-Dorfman disease, and solitary histiocytoma with a macrophage phenotype), and malignant histiocytic disorders (monocyte-related leukemia, extramedullary monocytic tumor, and dendritic cell or macrophage-related histiocytic sarcoma).[7]

The presentation of LCH varies from a spontaneously regressing solitary bone lesion to a multisystem life-threatening disorder, especially when it occurs in children.[8] There have been very few published reports on monostotic LCH affecting the posterior mandible in children with central diabetes insipidus (CDI). We report the case of a young boy with monostotic LCH involving the mandibular ramus, who was diagnosed with the disease after presenting clinical symptoms of diabetes insipidus. Due to the grave importance of early diagnosis to establish treatment, we have also discussed the significance of a multidisciplinary approach.

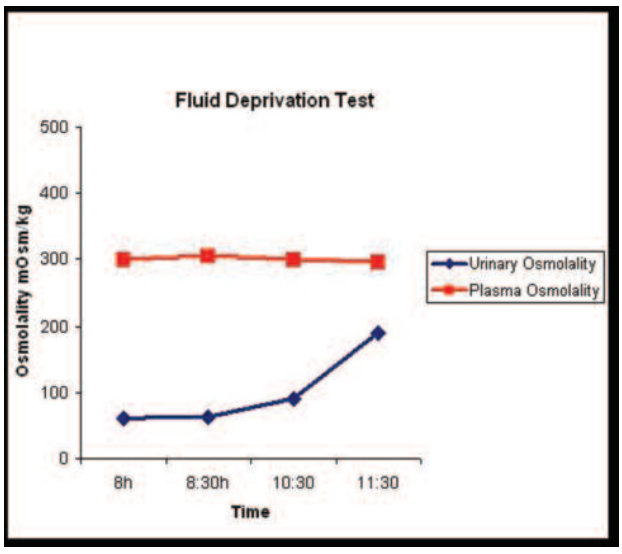

Figure 1. Fluid deprivation test showing a low urinary osmolality.

CASE REPORT

A 5-year-old boy presented for evaluation at the Endocrinology Unit of the University Walter Cantídio Hospital (HUWC) in the state of Ceará (Brazil) with clinical signs and symptoms of polyuria (over 4 liters of urine *per* day) and excessive thirst, associated with rapid weight loss. Examination revealed low urinary density, hypernatremia and increased serum osmolarity. Thus, the hypothesis of central diabetes insipidus was raised. The patient was submitted to a water deprivation test (Figure 1), which confirmed the diagnosis of CDI. Nuclear magnetic resonance imaging of the pituitary was initially performed to investigate the associated etiologic factors, which showed thickening of the pituitary stalk and lack of visualization of the neurohypophysis. Pituitary axis function (thyrotrophic, somatotrophic, corticotrophic and gonadotrophic hormones) was within normal limits. Finally, bone scintigraphy showed an area of radioisotope hyperuptake restricted to the right mandibular ramus but not in the remaining skeleton (Figure 2). Imaging exams (computed tomography and panoramic radiography) were requested for a more detailed visualization of the region. The exams revealed an area of radiolucency in the right mandibular ramus surrounded by a well-defined radiopacity and presence of areas of cortical bone fenestration (Figure 3). LCH was considered the probable diagnosis based on associated pituitary stalk thickening, lack of visualization of the neurohypophysis, presence of CDI and destructive bone lesion.

The patient was referred to the Oral-Maxillofacial Surgery Unit of the HUWC for a biopsy and subsequent anatomopathological analysis. Extraoral clinical examination showed no significant facial asymmetry. This finding was confirmed by intraoral inspection and palpation.

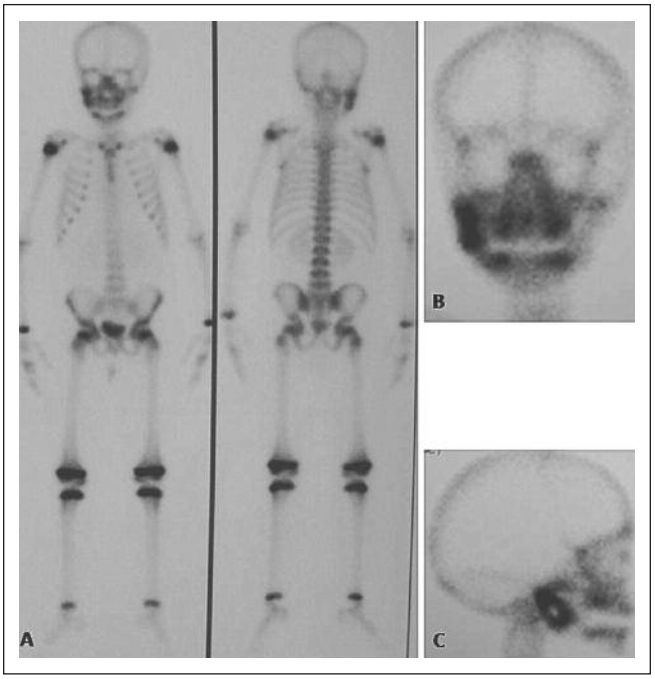

Figure 2. Bone scintigraphy showing an area of radioisotope hyperuptake in the right mandibular ramus in the absence of other skeletal involvement.

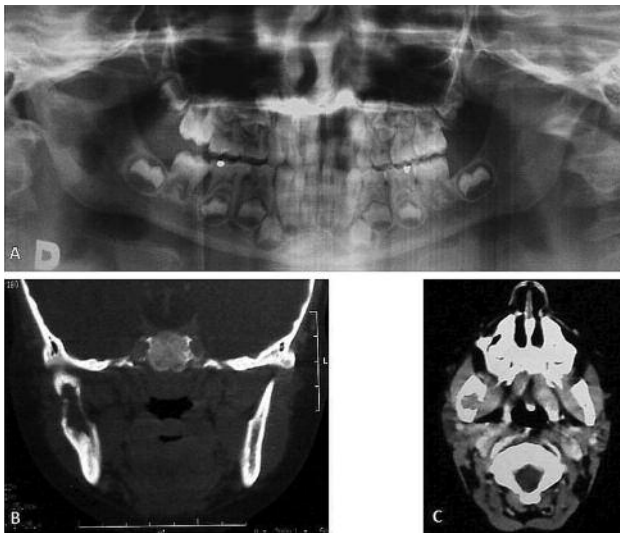

Figure 3. Radiography images showing a radiolucent area in the right mandibular ramus (A) and evidence of cortical fenestration (B, C).

Preoperative hematological tests were requested and an incisional biopsy was performed under general anesthesia. The material was sent for histopathological analysis (Figure 4), confirming LCH as the final diagnosis based on morphological (diffuse infiltrate of Langerhans cells intermingled with diverse eosinophils) and immunohistochemical findings (positive for CD1a, neural S-100 protein and CD68). The patient was then referred to the Ceará Cancer Institute (Brazil), where he underwent 28 chemotherapy sessions with vinblastine (Velban®) combined with prednisone. At the 12 months post-chemotherapy evaluation, control radiography showed lesion involution (Figure 5). Patient is currently undergoing symptomatic treatment of CDI with desmopressin acetate (DDAVP) and continues to be clinically stable despite the persistence of this endocrinopathy.

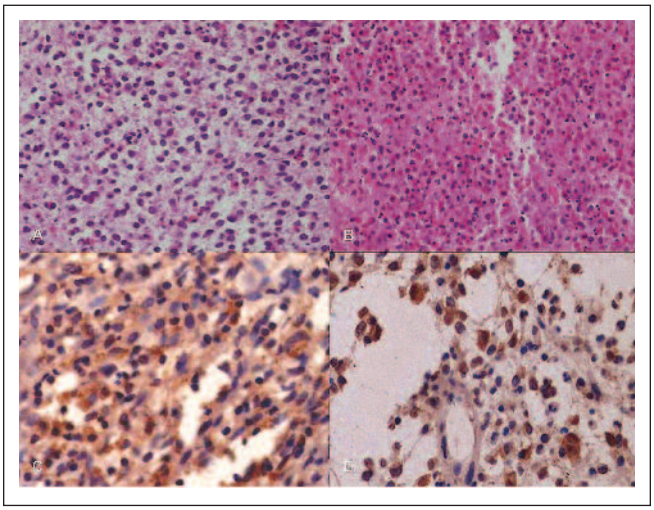

Figure 4. Histological pattern (A, B) of LCH showing a prominent infiltrate of mononuclear cells intermingled with numerous eosinophils (H&E, x200). Immunohistochemical staining (C, D) showing positivity for CD1a and neural S-100 protein (original magnification: x200).

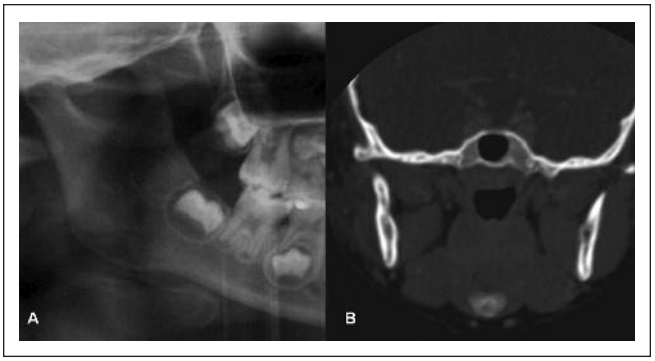

Figure 5. Postoperative panoramic radiography (A) and computed tomography (B) obtained 12 months after chemotherapy.

DISCUSSION

CDI in children and young adults is an uncommon heterogeneous condition of idiopathic etiology, with an estimated prevalence of 30 to 50%, affecting approximately one quarter of LCH-patients and many individuals with multisystem diseases.[9] The presence of Langerhans cell-infiltrate into the hypothalamus, pituitary stalk or posterior pituitary is an usual cause of CDI. This condition is considered an important indicator of serious underlying diseases in children, such as tumors, central nervous system malformations (germinoma, craniopharyngioma), vascular diseases, traumatic injuries to the hypothalamic-pituitary area, surgery or radiation, genetic defects in the synthesis of vasopressin, autoimmune and inflammatory conditions, as well as LCH.[9,10] When LCH is associated with multisystem diseases, DI is frequently observed as an early symptom in young children, preceding the onset of other signs of the disease.[11] Thus, when CDI is diagnosed by clinical and laboratory tests, LCH is a clinical hypothesis that must be considered. Radiological findings such as enhancement and thickening of the pituitary stalk indicate a probable diagnosis of LCH.

In the pediatric population, LCH is an important condition with an estimated annual frequency of 2 to 5 cases per million children, and is slightly more prevalent among boys. The condition is more frequent in infants, followed by young children and adolescents.[8] During childhood, LCH can manifest from the newborn period to 15 years-age, with a peak incidence at 1-4 years of age,[8] as observed in the present study. Clinical features range from a single bone lesion to multiple skeletal lesions, often affecting different visceral sites such as skin, lymph nodes, bone marrow, liver, spleen, and central nervous system.[4]

This report supports the current classification of LCH because the present case does not meet any of the classically described Langerhans cell diseases (eosinophilic granuloma, Letterer-Siwe disease and Hand-Schüller-Christian disease). Although Hand-Schüller-Christian disease is characterized historically by DI, exophthalmos and osteolytic lesions,[12-16] no evidence of exophthalmos was observed in the present case. In addition, computed tomography of the abdominal organs showed no signs of splenomegaly, hepatomegaly or visceral infiltrative disease. Thus, we believe that the present case is an interesting report of LCH at an initial stage, with

central nervous system involvement, without affecting other organs or systems.

According to Kilborn et al.,[8] the radiographic features of bone lesions encompass two main phases. First, bony lesions may show an aggressive pattern of osteolysis and appear permeative, with a wide zone of transition and a laminated periosteal reaction. In this stage, the differential diagnosis includes osteomyelitis, Ewing's sarcoma, and malignant hematological diseases. In the advanced phase, the lesions present a more benign pattern, including well-defined sclerotic margins, a thin zone of transition and a mature or absent periosteal reaction. The differential diagnosis includes central hemangioma, fibrous dysplasia, giant cell lesion, aneurysmal and simple bone cysts, non-ossifying fibroma, and healing metastases. In both phases, computed tomography is a valuable tool for the evaluation of cortical disruption and bone destruction.

Bone scintigraphy is necessary to evaluate multiple involvements and to rule out polyostotic disease. Hence, this type of advanced imaging resource was also presently used to determine bone involvement. On bone scintigraphs, LCH typically appears as a focus of avid tracer uptake or, alternatively, as a circumscribed rim of increased radiotracer activity surrounding a photopenic region.[17] In addition, CDI usually is not related to sellar erosion.[9-11] Liu et al.[11] reported a case of LCH with multisystem involvement in a patient with DI who presented a large pituitary stalk mass, in which no relationship with sellar erosion was observed. Thus, the absence of radioisotope hyperuptake in the sella of the present patient was an expected finding and was probably due to the pathophysiology of CDI.

Appropriate treatment requires the classification of disease severity, including the number of organ systems affected, sites involved, unifocal or multifocal nature, and presence or absence of organ dysfunction.[7] Patients with bone, skin, lymph node or pituitary involvement are considered to be at low risk, whereas those with LCH involving the liver, lung, bone marrow and spleen are considered to be at high risk.[11] In the present case, the disease was classified as low risk with a favorable prognosis.

Different therapeutic modalities are available for LCH but no consensus exists regarding the best management.[18] Surgery, radiotherapy, chemotherapy, combined therapy, hormone replacement therapy, and systemic and intralesional corticosteroids have been used.[19-22] Alternative methods, such as the use of monoclonal antibodies that target CD1a or CD207, specific cytokine inhibitors and, more recently, the use of 2-chlorodeoxyadenosine have gained increased importance as therapeutic agents.[2]

Localized and single mandibular lesions are usually treated by surgical curettage.[23] Other investigators have suggested that monostotic bone disease usually does not require specific treatment due to the possibility of spontaneous healing after incisional biopsy.[24] However, a more conservative approach was the preferred treatment due to the presence of CDI, relative risk of pathological fracture caused by disease progression, and unfavorable location of the biopsy site, which was close to the mandibular ossification center in this young patient. We believe that psychological aspects such as the wishes and expectations of the patient and his parents should be taken into account when choosing the most adequate treatment. In this respect, parents were not in favor of a surgical approach. Possibility of injury to permanent dental follicles and the particular risk of malignant development in children, contra-indicated low-dose radiotherapy as a treatment option.[25]

Systemic chemotherapeutic agents administered alone or in combination, such as vinblastine, vincristine, methotrexate, alkylating agents, cyclophosphamide, 6-mercaptopurine, and anthracyclines, are useful for controlling LCH.[11] Recently, an etoposide (VP16) has emerged as one of the most active and least toxic chemotherapeutic drugs.[26] In the present case, multi-agent chemotherapy was the treatment of choice based on the recommendations of the Histiocyte Society, that has reported a high recurrence rate when single-agent chemotherapy is used, compared to a multi-agent therapeutic strategy.[7] In addition, conservative treatment of the mandible in this 5-year old patient with a vinblastine-prednisone association may avoid damage and loss of teeth.[27]

Important multicenter therapeutic studies have shown that the patient's initial response to chemotherapy during the 6-week induction phase is the hallmark of a favorable prognosis. After chemotherapy, most patients respond satisfactorily, with an expected survival rate of 88 to 91%, as observed in the present case.[28,29] Corticosteroid therapy improved the pituitary lesion in this case report; however, hormone replacement therapy was essential because of the presence of CDI. Therefore, the observed damage to the hypothalamus-pituitary axis will probably result in the need for lifelong hormone replacement therapy. Continuous follow-up is mandatory in this case.

CONCLUSION

Monostotic LCH arising in the mandibular ramus in the absence of visceral involvement is an uncommon entity. Its association with CDI, though uncommon, should be considered by clinical professionals that treat the pediatric population, in the differential diagnosis of bone lesions that occur in young patients. Nevertheless, the present case report demonstrated the importance of a multidisciplinary approach for the early diagnosis and appropriate management of LCH associated with CDI. Although chemotherapy generally leads to cure, the lack of complaints and recurrence of the mandibular lesion after one year of follow-up do not invalidate recommendations for long-term monitoring, particularly when intervening at a young age.

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