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A unique case of polyostotic Langerhans cell histiocytosis

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INTRODUCTION: Langerhans cell histiocytosis (LCH) is a relatively rare dendritic cell disorder with an unclear etiology. The incidence is 2:1 million and it is most commonly seen in children from 5 to 10 years of age. The diagnosis is confirmed by biopsy with treatment options varying from simple observation to systemic chemotherapy. The four-year event-free survival for patients with solitary bone disease approaches 90% compared with 58% of those with polyostotic bone disease.

CASE DESCRIPTION: A 10-month-old female was brought to her pediatrician with a 2-month history of a mass of the left temporal area. The physical examination was remarkable only for a 4-cm nodule over the left temporal bone.

RESULTS: Laboratory values revealed a microcytic anemia with an alkaline phosphatase of 1994 and lactate dehydrogenase (LDH) of 536. Multiple skull defects were found on computed tomography and magnetic resonance imaging, with increased activity on bone scan and skeletal survey. A bone biopsy was CD1a- and S100-positive, consistent with LCH. The patient was started on the LCH-3 protocol with positive results and is currently in 5 years of remission.

CONCLUSIONS: Although cases of LCH are rare, they do occur in primary care settings; hence it is important to recognize it quickly. This case demonstrates how a timely diagnosis and treatment can lead to a good clinical outcome. Not all cases, however, have an equally favorable result and therapy may be ineffective or include many potential side effects. Furthermore, investigation and research is needed for improved treatment protocols for LCH.

Case description

A 10-month-old Hispanic female was brought to a pediatric office with a two-month history of a left temporal region mass. The patient's birth history was remarkable for an exchange transfusion at 6 days of age; medical history and family history were noncontributory. The physical examination was remarkable only for the left temporal mass, which was negative for tenderness upon palpation; there was also no lymphadenopathy or hepatosplenomegaly. Laboratory data were only significant for microcytic anemia, alkaline phosphatase level of 1994, and lactate dehydrogenase (LDH) level of 536. The pediatrician referred the patient for a head computed tomography (CT) scan, which described three soft tissue masses: the first in the region of the left temporalis muscle, the second located more superiorly over the left parietal bone, and the third over the left occipital bone. Each lesion was also found to have underlying skull erosions. The working differential diagnoses were histiocytosis X, eosinophilic granuloma, neuroblastoma, and metastatic disease. The patient was sent to a pediatric hematologist-oncologist for further workup and was subsequently scheduled for a skeletal survey, bone scan, and magnetic resonance imaging (MRI) of the brain with contrast. The bone scan and skeletal survey showed increased activity in three discrete bony lesions of the skull. The MRI of the head demonstrated multiple calvarial lesions without intracranial extension. The patient was then

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sent to a pediatric neurosurgeon and underwent a left temporal craniectomy with biopsy of the skull tumor. The biopsy of the bone mass was CD1a- and S100-positive. The clinical presentation, imaging studies, and biopsy results were consistent with Langerhans cell histiocytosis (LCH) multifocal bone disease. The patient was started on the LCH-3 protocol, which included six-month systemic therapy with vinblastine and prednisone. The patient did well during the course of chemotherapy and has been in remission for 5 years to present.

Discussion

Histiocytosis is an umbrella term for disorders of abnormal proliferation of monocytes/macrophages or Langerhans cells. The former is known as non-X histiocytosis. The latter is known as LCH, or is historically known as histiocytosis X, meaning "unknown." Langerhans cells originate from the bone marrow and are normally found in the epidermal layer of the skin. They function as antigen-presenting cells to T-lymphocytes, thus serving an important role in the cutaneous immunologic response.[1] LCH encompasses three subclasses of disorders. These are classified as either single-organ involvement (low-risk patients) or multisystem disease (high-risk patients), or these can be divided into Abt-Letterer-Siwe syndrome (multifocal, multisystem); Hand-Schuller-Christian syndrome (multifocal, unisytem); or eosinophilic granuloma (unifocal disease).[1]

LCH is considered a relatively rare disorder, with incidence reported as 2 per 1 million people, and is most commonly seen in children from 5 to 10 years of age, with prevalence greater in males. It is less common in adults and presents at a mean age of 33 years.[2,3]

The pathogenesis of LCH remains unclear. It is classically described as an abnormal clonal proliferation of Langerhans cells, which cluster and infiltrate surrounding tissues such as skin or bone. The debate remains unclear on whether the disease arises from a neoplastic or a reactive process. A neoplastic hypothesis is supported by the evidence of monoclonal proliferation of Langerhans cells, infiltration of organs, and a response to chemotherapy, as opposed to a reactive hypothesis, which is supported by involvement of cytokines and either a spontaneous remission of the disease or a chronic course with survival.

The clinical presentation of LCH depends on the extent of the disease. The organs most commonly involved are the skin followed by bone. Fifty percent of LCH cases in children have skin involvement.[1] Skin lesions vary in appearance (red to yellow papular or nodular plaques) and favor the intertriginous areas, behind the ears and the scalp. Between one- and two-thirds of pediatric LCH cases and 12% of adult LCH cases have bone involvement.[1] The bones most often affected include the skull, ribs, and pelvis.[4] The presenting symptom is usually a painful swelling at the affected bone site. Pathologic fractures are common. Localized skin and bone disease appears to be more common in children. In adults, multisystem disease is more common.

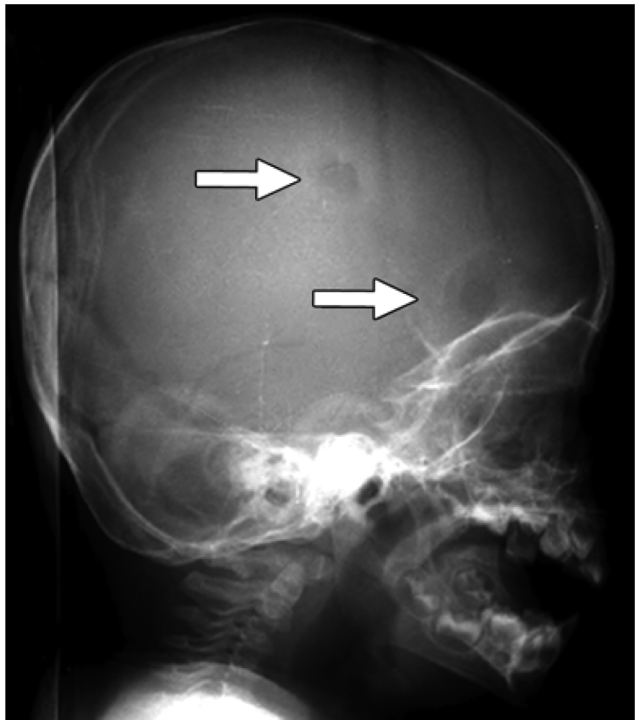

Figure 1 Lateral skull radiograph shows two well-defined lytic lesions (*arrows*) with characteristic beveled edges.

Initial diagnosis is made on the basis of clinical suspicion and imaging studies. Conventional radiographs and skeletal surveys have been used to identify and follow LCH bone lesions.[4] The classic manifestation is a punched-out, lytic lesion with an associated beveled-edge appearance (Figure 1).[4] CT scans are useful for categorizing the extent of bone destruction in the head and neck (Figure 2).[4] MRI and positron emission tomography scans can identify and give information regarding the activity of bone lesions.[5] A chest radiograph is necessary to evaluate for possible pulmonary involvement. Histologic confirmation is necessary and obtained when the fine-needle aspirate or core biopsy of the suspected lesion returns with staining positive for CD1a and/or CD207.[6] Electron microscopy will demonstrate the presence of Birbeck granules, which are characteristic of Langerhans cells.[1]

Treatment of LCH is a multidisciplinary approach. According to the Histiocyte Society, treatment depends on the classification of LCH, in terms of low- vs. high-risk patients. The criteria for high-risk patients includes skeletally mature bones; involvement of more than one bone; involvement of high-risk skull bones (orbit, mastoid, or temporal); and multisystem involvement. These patients are considered to have a high risk of recurrence and complications such as pulmonary disease and diabetes insipidus. The latter is the result of the skull masses causing direct impingement of the underlying dura matter. Treatment of low-risk, solitary bone lesions can vary from simple observation only to local surgical curettage and/or intralesional injection of glucocor-

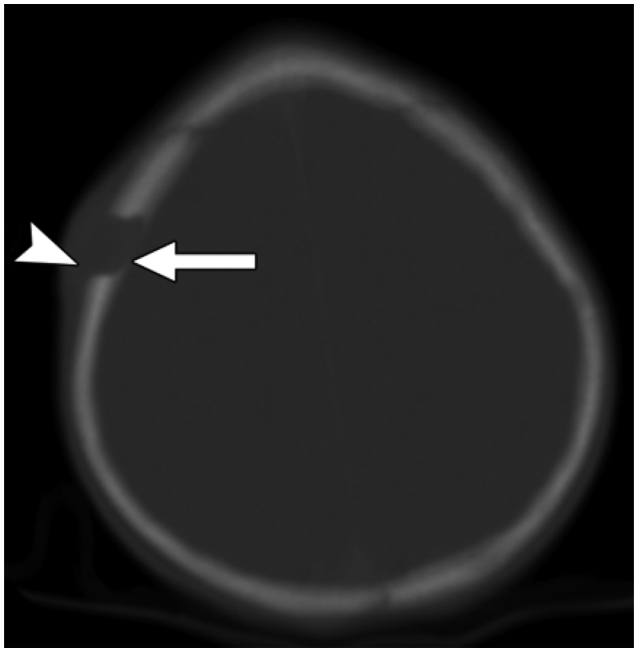

Figure 2 Axial CT shows unequal destruction of outer bone surface (*arrowhead*) and inner bone surface (*arrow*), which produces a beveled-edge appearance.

ticoids and/or radiation therapy. According to the LCH-III 2008 treatment recommendations, high-risk lesions are treated with six-month systemic therapy with vinblastine and prednisone. Radiation therapy is generally reserved for symptomatic lesions, which are persistent or recurrent after chemotherapy.[7] Surgical resection is reserved for patients with neurologic symptoms or unstable lesions.[7] Patients with bone involvement only have a good prognosis: most are ultimately cured of their disease. The four-year event-free survival for patients with solitary bone disease approaches 90% compared with 58% of those with polyostotic bone disease.[8] Poor prognostic factors include lack of rapid response to chemotherapy, multisystem disease, and age of onset younger than 2 years.

Conclusions

This case was unique and deserves attention because the patient was a 10-month-old female at the time of diagnosis who was found to have multiple skull bone lesions. She underwent and completed a six-month course of systemic therapy and has been free of LCH for 5 years to present. The goals of this case study are to improve the state of knowledge of histiocytoses as well as to emphasize the importance of identifying high-risk patients, such as the very young child in this case, because these patients are at risk for recurrence and complications.

Although cases of LCH are rare, they do occur in primary care settings and it is important to recognize them and initiate appropriate therapy. The present case is a great example of timely diagnosis and treatment in which the patient had a good outcome. However, not all cases have a favorable prognosis and the therapeutic options might be ineffective with several adverse side effects. Furthermore, investigation and research is required for proper therapeutic protocol in the treatment of many subtypes of LCH.

There is ongoing research in the development of innovative treatments for LCH. It has been noted that in patients with chronic LCH or LCH with bone involvement, an accumulation of immature and poorly immunogenic Langerhans cells were seen. Thus, the development of drugs that enhance maturation of Langerhans cells or induce their apoptosis may be beneficial in the treatment of LCH.[9] Currently, the new LCH-IV guidelines and recommendations for the treatment of high-risk LCH patients are under development.

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