Histiocytosis

Jan E. Drutz

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In Brief

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Jan E. Drutz, MD
Texas Children's Hospital and Baylor College of Medicine
Houston, TX

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Langerhans Cell Histiocytosis: A Review of the Current Recommendations of the Histiocyte Society. Satter EK, High WA. *Pediatr Dermatol.* 2008;25:291–295

LCH in Children. Histiocytosis Association of America. Accessed March 2011 at: http://www.histio.org/site/c.kiKTL4PQLvF/b.1764433/k.8BCD/LCH_in_Children.htm

Langerhans Cell Histiocytosis, Juvenile Xanthogranuloma, and Erdheim-Chester Disease. McClain KL. *UpToDate Online 18.3.* 2010. Accessed for subscription March 2011 at: http://www.uptodate.com/contents/langerhans-cell-histiocytosis-juvenile-xanthogranuloma-and-erdheim-chester-disease?source=search_result&selectedTitle=1%7E86

Case 16-2010: A 48-year-old Man With a Cough and Pain in the Left Shoulder. Medoff BD, Abbott GF, Louisaint A, Jr. *N Engl J Med.* 2010;362:2013–2022

The term "histiocyte" refers to a number of different cell types (monocytes/macrophages, dermal/interstitial dendritic cells, and Langerhans cells [LCs]), all believed to arise from a common bone marrow progenitor cell (CD−34+). For purposes of this review, discussion of histiocytosis is confined to Langerhans cell histiocytosis (LCH). First described at the beginning of the 20th century, LCH is considered a rare proliferative disorder that primarily affects children. LCs have the potential to accumulate in a number of different sites and organs, including the bone, lungs, liver, spleen, and lymph nodes, ultimately leading to a disease process.

To simplify confusing terminology previously used to describe LCH (eosinophilic granuloma, Letterer-Siwe disease, Hand-Schuller-Christian disease, histiocytosis X), it is preferable to define histiocytosis with regard to involvement of a single system (ie, skin, bone, lymph node), multiple systems, a single organ, or multiple organs. This perspective is extremely important in helping to determine treatment and prognosis when organs such as the liver, spleen, bone marrow, and lungs are involved.

LCs generally are localized to epithelial surfaces, particularly skin. Their primary function is to transport foreign antigens to T cells within the lymphatic system, contributing to an overall immune response.

Although the cause of LCH remains unknown, this disorder possibly is an autoimmune phenomenon. LCH is neither a cancer nor believed to be attributable to an infectious process. Of note, several studies have been unsuccessful in establishing a linkage between human herpesvirus 6 and LCH.

Every year, LCH affects nearly 200,000 individuals, particularly children 1 to 15 years of age. Among those younger than 4 years of age, 50% to 70% present with multiorgan involvement. Symptoms in children vary and may include abdominal pain, bone pain, or other complaints; those younger than 5 years generally present with bone pain only. Of the bone sites in children, the most frequent finding is a lytic scalp lesion. Such a lesion may be accompanied by a mass impinging on the dura. The most common endocrine abnormality associated with LCH is diabetes insipidus.

Diagnosis of LCH requires the identification of specific clinical features as well as characteristic histopathologic and immunohistochemical findings. In more than 50% of affected patients, skin findings are evident. A diffuse, vesicular (herpes simplex virus-like) or excoriated exanthem may be present at birth. In older infants, LCH may present with scaling of the scalp, suggestive of seborrhea. In addition to the skin findings and bone pain, other clinical features can include abdominal pain, pulmonary infiltrates, gingival hypertrophy and ulcerations, exophthalmos, destructive damage to the mandible, and marked developmental delay.

Definitive diagnosis is dependent upon specific characteristics of cell staining and the identification by electron microscopy of Birbeck granules. The number of LCs containing these granules varies, depending on the organ from which the tissue specimen is obtained. Whether the patient has single-site or multiorgan involvement, evaluation should include a skeletal survey, skull radiographic series, bone scan, chest radiograph, computed tomography (CT) head scan (if there is orbital or mastoid involvement), and CT scan of the spine or pelvis if there is neurologic dysfunction. In neonates, a CT scan of the lungs should be performed.

Treatment consists primarily of corticosteroids or immunosuppressive agents, such as 6-mercaptopurine, vinblastine, or methotrexate. Individual treatment protocols should be tailored to specific risk factors. Those patients who have only single-system involvement should be subcategorized according to the number of sites involved within that system. For those who have multiorgan disease, treatment should be determined in relation to whether organ dysfunction is present.

In general, no therapy is required for individuals whose involvement is limited to the skin. Treatment is somewhat controversial for those who have multiorgan disease. Some experts advocate high-dose prednisone as first-line therapy; others advocate single-agent chemotherapy. A review of a large number of cooperative studies revealed that multiagent chemotherapy, administered over a long period of time, resulted in a greater response with fewer recurrences.

The prognosis for patients who have LCH depends on the number of organ systems involved and the degree of organ dysfunction. To a less significant degree, the patient's age may be a factor. Mortality is greater for the young child who has multiorgan involvement and organ failure. Involvement of the spleen, lung, liver, or hematopoietic system portends a poor prognosis. Newborns who have isolated cutaneous lesions do exceptionally well. The best indicator for a favorable prognosis is the patient's response to chemotherapy during the first 6 weeks of the induction phase. Those who respond to initial chemotherapy have an 88% to 91% survival rate; those who do not exhibit an early response have only a 17% to 34% survival.

Comment: LCH is a fascinating disease. I have been involved with two cases: a neonate who had an enlarged inguinal lymph node without a perineal rash, thus having no readily apparent reason for the adenopathy, and a 2-year-old child initially believed to have periorbital cellulitis who subsequently developed proptosis and was found to have an orbital bone lesion. These diagnoses were challenging to make because the patients presented with more common initial symptoms that became atypical over time. Because of the multiple sites and organs in the body that can be involved, pediatricians need to have knowledge of this disease and consider it when what initially appear to be common symptoms recur or do not resolve in the expected time frame.

Janet R. Serwint, MD
Consulting Editor, In Brief

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