Langerhans Cell Histiocytosis
A Clinicopathologic Review and Molecular Pathogenetic Update

Charles M. Harmon, MD; Noah Brown, MD

Langerhans cell histiocytosis (LCH) is a rare disease marked by proliferation of Langerhans-type cells that share immunophenotypic and ultrastructural similarities with antigen-presenting Langerhans cells of mucosal sites and skin.1 Given this resemblance, it was hypothesized that the disease originated from epidermal Langerhans cells.2 However, more recent studies using cell-specific gene expression profiling suggest that LCH arises from bone marrow–derived immature myeloid dendritic cells rather than from epidermal Langerhans cells.3 Langerhans cell histiocytosis occurs most often in children and in white individuals of northern European ancestry.1 The broad clinical spectrum that is encompassed by LCH is reflected in the many synonyms for this disease, which include eosinophilic granuloma (unifocal LCH), Hand-Süller-Christian disease (multifocal unisystem LCH), and Letterer-Siwe disease (disseminated multiform multisystem LCH). In single-system LCH, bone is the most common site of involvement followed by skin, lymph node, and lung.4,5 Pulmonary LCH seems to be a distinct entity, as it occurs almost exclusively in smokers and may resolve with cessation of smoking.6 Sites that may be involved in multisystem disease include skin, bone, liver, spleen, and bone marrow.7 Liver, spleen, and bone marrow are considered “risk organs,” involvement of which by LCH places patients at higher risk of mortality.8

The lesions of LCH are composed of cells that are 12 to 15 μm in diameter with abundant eosinophilic cytoplasm. The nuclei of LCH cells are irregular with prominent folds and grooves, fine chromatin, and indistinct nucleoli (Figure, A and B). Background eosinophils, lymphocytes, histiocytes, and neutrophils are often present in variable quantities. When present within lymph nodes, LCH is often characterized by sinusoidal involvement. The characteristic immunophenotype of LCH includes expression of CD1a, S100 protein, and langerin (CD207).1 Expression of CD68 is variable. On electron microscopy, elongated, zipperlike cytoplasmic structures measuring 200 to 400 nm × 33 nm, known as Birbeck granules, are observed.

The differential diagnosis for LCH may include other histiocytic/dendritic lesions, lymphoma, and Langerhans cell sarcoma. In most cases, LCH can be definitively diagnosed by the distinctive morphologic and immunohistochemical features described above. Langerhans cell histiocytosis shares some clinical and immunohistochemical features with sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). However, Rosai-Dorfman disease does not show expression of CD1a or langerin, and large histiocytic cells are present that engulf lymphocytes, plasma cells, and erythrocytes (emperiplois).9 Erdheim–Chester disease shares some clinical features with LCH, including involvement of bone and multiple other sites, but tends to occur at an older age and is histologically characterized by foamy histiocytes without expression of CD1a or S100.10 Juvenile xanthogranuloma may enter the differential diagnosis of LCH presenting in the skin. However, juvenile xanthogranuloma is also characterized by foamy histiocytes as well as Touton giant cells. Dendritic neoplasms such as follicular dendritic cell sarcoma and interdigitating dendritic cell sarcoma can generally be easily excluded on clinical, morphologic, and immunohistochemical grounds. Likewise, lymphoma may enter the differential diagnosis on the basis of morphology, but it generally displays more cytologic atypia and can be quickly differentiated from LCH by immunophenotype. The differential diagnosis may also include nonneoplastic proliferations of Langerhans cells. Dermatopathic lympho-
adenopathy is characterized by an expanded paracortex with small lymphocytes and scattered Langerhans cells and histiocytes, sometimes accompanied by pigment. Langerhans cell hyperplasia can be seen in the skin as part of reactive lesions such as eczema. The immunophenotype of the Langerhans cells in these nonneoplastic lesions will be the same as in LCH. However, the extent of the Langerhans cell infiltrates as well as the clinical context can be helpful in making this distinction. Finally, Langerhans cell sarcoma may be considered but can be distinguished from LCH by the presence of overtly malignant cytologic features and a high mitotic rate.

Because of the wide clinical spectrum of LCH, conventional therapy is tailored to match the site and extent of disease. For treatment purposes, patients are generally stratified into single-system LCH and multisystem LCH. Patients with multisystem LCH are further divided into low-risk and high-risk categories on the basis of involvement of the “risk organs” mentioned previously. The current standard of care for patients with low-risk multisystem LCH is 1 year of systemic therapy with vinblastine and prednisone. Patients with high-risk multisystem LCH are treated with mercaptopurine in addition to vinblastine and prednisone for 1 year. Although disease refractoriness and reactivation are not infrequent, cladribine and cladribine have been reported as options for salvage therapy. In contrast, the type of therapy used in single-system LCH depends on the location of disease. Although unifocal bone lesions are usually treated effectively by curettage, systemic therapy with vinblastine and prednisone may be considered in cases of multifocal bone involvement. Treatment options for patients with single-system cutaneous LCH include topical nitrogen mustard, topical corticosteroids, and oral methotrexate. Although smoking cessation is the cornerstone of treatment for pulmonary LCH, case reports have described disease improvement following therapy with cladribine. Patients with single-system LCH have an excellent prognosis with more than 80% remaining disease free after initial therapy. The question of whether LCH is a neoplasm or a reactive process has long been debated. Evidence of clonality in LCH was reported more than 20 years ago, supporting the notion that LCH is a neoplastic process. More recently, the identification of oncogenic BRAF V600E mutations in 25% to
64% of cases of LCH has provided additional evidence that LCH is a neoplasm. Although it was previously thought that pulmonary LCH represents a nonclonal, reactive process, BRAF V600E mutations have been detected in a similar percentage of pulmonary LCH cases and extrapolunary LCH cases. In cases of multifocal pulmonary LCH with BRAF V600E, the mutation is in all concurrent nodules, providing further confirmation that pulmonary LCH is a clonal proliferation. Although the BRAF V600E mutation results in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, it has been observed that the MAPK pathway is also activated in cases of LCH without mutations of BRAF. Mutations in MAP2K1, which encodes the dual-specificity kinase MEK1 protein in the MAPK pathway, were subsequently identified in 27.5% of LCH cases, thus explaining MAPK pathway activation in the absence of BRAF mutation. According to the degree of differentiation (hematopoietic cell progenitors versus mature dendritic cells) at which the BRAF V600E mutation can be detected is strongly associated with pulmonary LCH. As mentioned above, in cases of multifocal pulmonary LCH with BRAF mutations and BRAF mutations were found to be mutually exclusive, as would be expected since MEK1 is directly targeted dendritic cells tend to have a low-risk phenotype. Inhibitors of BRAF and MEK may prove to be effective options in treatment of LCH.

CONCLUSION
Langerhans cell histiocytosis is a rare disease that includes a wide range of clinical manifestations. The recent identification of either BRAF or MAP2K1 mutations in most cases of LCH provides additional evidence of the neoplastic nature of the disease and has important implications for potential risk stratification and treatment. Patients who have the BRAF V600E mutation present in hematopoietic cell progenitors have high-risk LCH, while those patients in whom the BRAF V600E mutation is restricted to differentiated dendritic cells tend to have a low-risk phenotype. Inhibitors of BRAF and MEK may prove to be effective options in treatment of LCH.

References


