Clinical Characteristics and Treatment of Langerhans Cell Histiocytosis

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KEYWORDS

• Langerhans cell histiocytosis • Neurodegeneration • Oncogenes • BRAF
• Chemotherapy

KEY POINTS

- Langerhans cell histiocytosis (LCH) is a neoplasm of myeloid origin characterized by a clonal proliferation of CD1a+/CD207+ cells. In a little more than half of the cases, *BRAF* mutations, predominantly encoding BRAF V600E, are identified; mutations of other members of the MAPK/ERK pathway, such as *MAP2K1* or *ARAF*, are present in another 10% to 25%.
- LCH affects individuals of all ages, although infants more often present with multisystem disease. The disease can affect many tissues and organs of the head and neck. Bony lesions are most common; but the skin, lymph nodes, and brain can also be involved.
- Patients with involvement of only one organ system can often be treated with surgery alone and have excellent outcomes. Patients with multisystem disease, especially with risk-organ involvement, need multimodality treatment and have variable prognoses.
- Treatment with BRAF inhibitors has shown to induce complete and durable responses, and the role of BRAF and MEK inhibitors is currently being investigated.
- LCH neurodegeneration, a devastating long-term complication of LCH, represents one of the major challenges in clinical and translational research of LCH.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a disease characterized by clonal proliferation of CD1a+/CD207+ myeloid dendritic cells that presents at all ages and with different degrees of systemic involvement. Almost any organ can be affected, and the clinical presentation reflects the tissue-specific inflammatory phenomena. For several

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decades, LCH has been considered to be a reactive clonal proliferation of Langerhans cells; however, in recent years, LCH has been defined as a neoplasm of myeloid origin, with a significant inflammatory component that defines some of the acute and long-term manifestations. This evolution from an immune disorder to a neoplasia has reframed the disease and opened the door for the development of targeted therapies.

BIOLOGY

The pathogenic cells are known to originate from a myeloid-derived precursor and are uniformly characterized by activation of the MAPK/ERK signaling pathway; ERK activation is documented in all cases.[1,2] In up to two-thirds of cases, pathway activation is secondary to a somatic mutation in *BRAF (BRAF^{V600E})*; in other cases, mutations in *MAP2K1*[3] or less frequently in other members of the pathway, such as *ARAF*,[4] have been described. About one-quarter of cases have no known genomic abnormalities.

EPIDEMIOLOGY

The estimated incidence of LCH is 8.9 cases per million children younger than 15 years per year, with a median age at diagnosis of 3 years old.[5] The causes and risk factors for developing LCH are unclear.[6] However, the unique patterns of presentation, ranging from localized bone lesions with spontaneous regression to disseminated forms with multiorgan involvement, suggest a complex pathogenesis. Familial associations, particularly the observation of increased incidence in monozygotic twins of affected patients, have suggested the presence of a germline predisposition at least for a proportion of cases.[7] Also, population-based studies have shown differences in the incidence of disseminated LCH by race and ethnic group; a higher incidence has been reported for Hispanics and a lower incidence for blacks.[8] Studies have also shown a correlation with maternal and neonatal infections,[6,9,10] lack of childhood vaccinations,[6,9] family history of thyroid disease,[6] in vitro fertilization,[11] and feeding problems and transfusions during infancy.[10] Finally, lower socioeconomic conditions have been associated with an increased incidence of disseminated LCH.[8]

PATHOLOGY

Since pathologic Langerhans cells activate other immunologic cells, microscopic examination of diseased tissue shows eosinophils, neutrophils, lymphocytes, and histiocytes in addition to the LCH cells; this appearance is what has been traditionally described as eosinophilic granuloma. Abscesses and necrosis may be present. LCH cells are large, oval , and mononuclear, with a prominent nucleus and eosinophilic cytoplasm. They do not have dendritic cell processes like cutaneous Langerhans cells. They stain positive for protein S-100, CD1a, and CD207 (langerin) and contain cytoplasmic rod-shaped inclusions called Birbeck granules. A diagnosis of LCH is made by typical positive staining with CD1a or CD207.[12]

With the development of new technology for accurate detection of cell-free DNA, *BRAF^{V600E}* mutation analysis in plasma and urine has shown to be an effective tool for diagnosis and monitoring of disease activity in patients with LCH.[13]

CLINICAL PRESENTATION

Classically, LCH was defined as 3 distinct diseases; eosinophilic granuloma, Hand-Schüller-Christian disease, and Abt-Letterer-Siwe disease were different clinical descriptions within the same spectrum of progressive system involvement. *Eosinophilic granuloma*, whether solitary or multifocal, is found predominantly in older children as