Langerhans cell histiocytosis in children

History, classification, pathobiology, clinical manifestations, and prognosis

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Learning objectives
After completing this learning activity, participants should be able to discuss historical perspectives, previous and current classification systems, and former and current perspectives of pathobiology, particularly as they pertain to novel treatment approaches and recognize specific cutaneous and systemic clinical manifestations and the wide range of potential disease courses, ranging from spontaneous resolution to life-threatening multisystem involvement.

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Langerhans cell histiocytosis (LCH) is an inflammatory neoplasia of myeloid precursor cells driven by mutations in the mitogen-activated protein kinase pathway. When disease involves the skin, LCH most commonly presents as a seborrheic dermatitis or eczematous eruption on the scalp and trunk. Evaluation for involvement of other organ systems is essential, because 9 of 10 patients presenting with cutaneous disease also have multisystem involvement. Clinical manifestations range from isolated disease with spontaneous resolution to life-threatening multisystem disease. Prognosis depends on involvement of risk organs (liver, spleen, and bone marrow) at diagnosis, particularly on presence of organ dysfunction, and response to initial therapy. Systemic treatment incorporating steroids and cytostatic drugs for at least one year has improved prognosis of multisystem LCH and represents the current standard of care. (J Am Acad Dermatol 2018;78:1035-44.)

Key words: *BRAF*; Langerhans cell histiocytosis; MAPK; pathway myeloid neoplasia.

INTRODUCTION

Key points

- **Langerhans cell histiocytosis is a rare neoplasm of hematopoietic myeloid precursor cells that most commonly affects white male children, with a peak incidence of 1 to 3 years of age**
- **Cutaneous involvement, which is observed in 40% of cases, typically reflects multisystem disease with a 20% mortality**

Abbreviations used:

ECD: Erdheim–Chester disease
LCH: Langerhans cell histiocytosis

The histiocytoses are a group of rare disorders characterized by pathologic accumulation of cells derived from the monocyte, macrophage, and dendritic cell lineage. In 1987, the Working Group of the

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Histiocyte Society classified the histiocytoses as Langerhans cell–related, non-Langerhans cell–related, or malignant,[1] and this classification has been in place for 3 decades. A new classification has been elaborated upon and recently published, and it accounts for the current breakthrough in understanding the molecular mechanisms of most entities.[2] The new classification attempts to integrate clinical and imaging features with pathology and molecular findings.

Histiocytes (tissue macrophages) derive from hematopoietic myeloid progenitors, which further differentiate into monocytes, macrophages, and dendritic cells.[3,4]

Despite their phenotypic resemblance to normal Langerhans cells, which are dendritic cells of the skin and mucosa, the pathologic cells in Langerhans cell histiocytosis (LCH) derive from immature myeloid precursor cells.[5] In the past, they had been erroneously thought to derive from Langerhans cells, the normal dendritic cells of the skin and mucous membranes, because of their phenotypic resemblance and shared markers (eg, positive staining for CD1a, human leukocyte antigen–antigen D related, S-100, and cytoplasmic Birbeck granules).

Among histiocytic disorders, LCH is the most common one, affecting an estimated 4 to 5 per million children 0 to 15 years of age each year.[6,7] Because localized disease often spontaneously regresses, the prevalence is probably higher than reported.[8] The median age of diagnosis is 3.5 years, and the highest incidence rate is observed before 1 year of age, with a decreased incidence observed thereafter.[6] While most prevalent in children, the disorder presents in all ages and has also been reported in the elderly.[9,10] There is a 2:3 male:female ratio.[6,11]

The clinical presentation and subsequent course may vary remarkably, from single-system disease that may resolve spontaneously to treatment refractory multisystem involvement with a 20% mortality.[12] Two thirds of children present with single-system involvement, most commonly of the bone, but also of the skin or lymph nodes.[12] LCH involves the skin in about 25% of cases.[13]

Significant risk factors for LCH include maternal urinary tract infection during pregnancy, feeding problems or blood transfusions during infancy,[14] Hispanic ethnicity, crowding, low education level,[15] neonatal infections, solvent exposure, family history of thyroid disease,[16] and in vitro fertilization.[17] Protective factors include black race,[15] childhood vaccinations,[16] and supplemental vitamins.[14] Association of LCH with other neoplasms has been reported in rare cases.[18]

Table I. Histiocytoses classification*

Disease
Langerhans
Langerhans cell histiocytosis
Erdheim–Chester disease/extracutaneous juvenile xanthogranuloma
Indeterminate cell histiocytosis
Cutaneous and mucocutaneous
Juvenile xanthogranuloma
Adult xanthogranuloma
Solitary reticulohistiocytoma
Benign cephalic histiocytosis
Generalized eruptive histiocytosis
Progressive nodular histiocytosis
Xanthoma disseminatum
Cutaneous Rosai–Dorfman disease
Necrobiotic xanthogranuloma
Multicentric reticulohistiocytosis
Cutaneous histiocytoses not otherwise specified
Malignant
Histiocytic sarcoma
Indeterminate cell sarcoma
Langerhans cell sarcoma
Follicular dendritic cell sarcoma
Rosai–Dorfman disease
Rosai–Dorfman disease
Noncutaneous, non-LCH not otherwise specified
Hemophagocytic lymphohistiocytosis and macrophage activation syndrome
Hemophagocytic lymphohistiocytosis/macrophage activation syndrome

*Data from Emile et al.[2]

HISTIOCYTOSES CLASSIFICATION

Key point

- **A recent (2016) histiocytoses classification system divides the histiocytoses into 5 categories: Langerhans (L), cutaneous and mucocutaneous (C), malignant (M), Rosai–Dorfman disease (R), and hemophagocytic lymphohistiocytosis and macrophage activation syndrome (H)**

Emile et al[2] recently proposed a new classification of the histiocytic disorders that takes into consideration current knowledge from dendritic cell biology and integrates molecular findings from lesion tissues. Therefore, based on clinical manifestation(s), imaging, histology, and molecular genetics, the histiocytoses are divided into 5 groups (Table I): Langerhans (L), cutaneous and mucocutaneous (C), malignant (M), Rosai–Dorfman disease (R), and hemophagocytic lymphohistiocytosis and macrophage activation syndrome (H).[2]

LCH is assigned to the Langerhans (L) group, together with Erdheim–Chester disease (ECD),