Cell(s) of Origin of Langerhans Cell Histiocytosis

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KEYWORDS

• Langerhans cell histiocytosis • BRAF • MAPK signaling • Dendritic cell • Myeloid differentiation

KEY POINTS

- Dendritic cells (DCs) are immune cells that arise from different lineages with a shared function of presenting antigen and activating adaptive immunity.
- Langerhans cell histiocytosis (LCH) arises from myeloid DC precursors. Mitogen-activated protein kinase (MAPK) activation is a universal feature of $CD1a^+$ $langerin^+$ LCH cells. The clinical extent of LCH is related to the stage of development in which somatic MAPK mutations arise, either self-renewing progenitors or committed precursors.
- Activating MAPK mutations in hematopoietic stem cells and committed myeloid precursors support classification of LCH as a myeloid neoplasia.

INTRODUCTION TO LANGERHANS CELL HISTIOCYTOSIS

The Histiocytoses

The spectrum of histiocytic diseases is characterized by collections of abnormal histiocytes or, literally, tissue cells related to myeloid cells of the mononuclear phagocyte system (MPS).[1–4] LCH is defined by the presence of a large pale-staining histiocyte

The Texas Children's Cancer Center Histiocytosis Program (C.E. Allen and K.L. McClain) is supported by the HistioCure Foundation. Grant support includes NIH R01 (CA154489) (C.E. Allen and K.L. McClain), NIH SPORE in Lymphoma (P50CA126752) (C.E. Allen), and the St. Baldrick's Consortium Grant for the North American Consortium for Histiocytosis Research (C.E. Allen and K.L. McClain). M. Collin is supported by the Histiocytosis Research Trust (UK), the Leventis Foundation, and the Histiocytosis Association. V. Bigley is a Wellcome Trust Intermediate Fellow (WT088555MA).
The authors have no conflicting financial interests.
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Hematol Oncol Clin N Am 29 (2015) 825–838
http://dx.doi.org/10.1016/j.hoc.2015.06.003 **hemonc.theclinics.com**
0889-8588/15/$ – see front matter

with high expression of CD1a and langerin (CD207) and containing Birbeck granules (Fig. 1). These features, shared with Langerhans cells (LCs) of the epidermis, are the basis of classifying the disease as an LCH. Prior to this, LCH was known as histiocytosis X, a disease entity incorporating historically described syndromes: Hand-Schüller-Christian disease, characterized by lytic bone lesions and mucosal lesions; Letterer-Siwe disease, a fatal hepatosplenomegaly; and eosinophilic granuloma of bone. The discovery of the Birbeck granule in LCs in 1961 and identification of the same organelle in histiocytosis X by Nezelof and colleagues[5] in 1965 formed the basis for modern models of LCH. Another influence driving this model of LCH at the same time was the model of the MPS in which peripheral macrophages were thought to be continually renewed from bone marrow–derived monocytes.[1] LCs had recently joined the MPS by virtue of their expression of MHC class II, complement and Fc receptors, and repopulation by bone marrow–derived cells after transplantation. The formation of LCH was, therefore, perceived to be an aberration of this development, leading to the accumulation of abnormal LC-like cells in inappropriate locations.

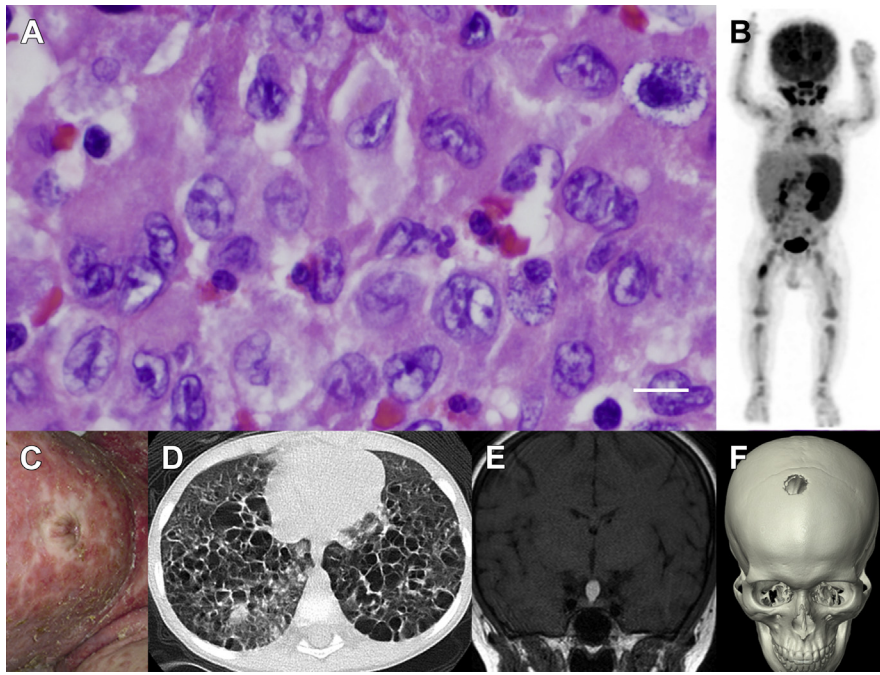

Fig. 1. LCH: common histology and clinical heterogeneity. (*A*) Hematoxylin-eosin staining of a typical LCH lesion, demonstrating the classic large histiocytes with grooved coffee bean nuclei and abundant eosinophilic cytoplasm. The inflammatory infiltrate varies but typically includes lymphocytes, eosinophils, and macrophages. Histologic features have not been associated with specific clinical presentations. Scale bar is 10 microns. (*B–F*) This biopsy could have come from any of the cases presented. (*B*) PET scan of a 1 year old with high-risk LCH: PET-avid R femur lesion, spleen, bone marrow, and cervical lymph nodes are evident in this image. (*C*) Infant with severe LCH skin lesions. In infants, skin LCH may be self-limiting and spontaneously resolve or may be part of life-threatening, multisystem, high-risk disease. (*D*) CT scan demonstrating innumerable cysts and lung lesions in a 3 year old with LCH involving lung, pituitary, and skin. (*E*) Brain MRI in a teenager with an isolated pituitary LCH lesion. (*F*) CT scan of a teenager with an isolated skull LCH lesion.