Langerhans cell histiocytosis in children

Diagnosis, differential diagnosis, treatment, sequelae, and standardized follow-up

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Learning objectives
After completing this learning activity, participants should be able to recognize the recommended approach to initial evaluation and diagnosis, treatment, and follow-up in LCH patients; contrast the recommended treatment of single system as compared to multisystem disease and of children as compared to adults; identify and distinguish alternative diagnoses from LCH; and discuss the risk factors and management of potential sequelae.

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A definitive diagnosis of Langerhans cell histiocytosis (LCH) requires a combination of clinical presentation, histology, and immunohistochemistry. The inflammatory infiltrate contains various proportions of LCH cells, the disease hallmark, which are round and have characteristic "coffee-bean" cleaved nuclei and eosinophilic cytoplasm. Positive immunohistochemistry staining for CD1a and CD207 (langerin) are required for a definitive diagnosis. Isolated cutaneous disease should only be treated when symptomatic, because spontaneous resolution is common. Topical steroids are first-line treatment for localized disease of skin and bone. For multifocal single-system or multisystem disease, systemic treatment with steroids and vinblastine for 12 months is the standard first-line regimen. Current research is seeking more effective regimens because recurrence rates, which increase the risk of sequelae, are still high (30-50%) in patients with multisystem disease. An active area of research is the use of targeted therapy directed at the mitogen-activated protein kinase pathway. Adequate follow-up to monitor for disease progression, relapse, and sequelae is recommended in all patients. (J Am Acad Dermatol 2018;78:1047-56.)

Key words: BRAF; cladribine; clofarabine; cytarabine; diabetes insipidus; Langerhans cell histiocytosis; steroids; vinblastine.

DIAGNOSTIC CRITERIA

Key point

- **A definitive diagnosis is made by the combination of clinical presentation, histology, and immunohistochemistry**

Obtaining a biopsy specimen is mandatory for a diagnosis of Langerhans cell histiocytosis (LCH), and the skin is an easily accessible site in patients presenting with cutaneous signs; however, because Langerhans cell reactivity is not specific for LCH, the

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diagnosis should be reserved for the appropriate clinical context. Bone marrow aspiration and biopsy specimens are indicated in patients suspected of having multisystem disease presenting with cytopenia to rule out other causes of bone marrow failure.[1]

Histology reveals an inflammatory infiltrate of eosinophils, macrophages, regulatory T lymphocytes ($FoxP3^+$ and $CD4^+$), and multinucleated giant cells. Though eosinophilia is typically a prominent finding (particularly in bone lesions), the presence of eosinophils is not essential for diagnosis. LCH cells have a "coffee-bean" cleaved nuclei, rounded shape, and eosinophilic cytoplasm. Mitotic features and binucleate cells may occasionally be identified, but atypical mitosis and pleomorphism are typically not observed and should raise suspicion towards an alternative diagnosis, particularly Langerhans cell sarcoma.[2]

Skin biopsy specimens reveal predominant involvement of the papillary dermis with minimal involvement of the epidermis. Sinus involvement is essential for diagnosis when biopsy specimens are obtained from the lymph nodes.[2] Megakaryocyte dysplasia, emperipolesis, and myelofibrosis are prevalent findings on bone marrow specimens, while $CD1a^+$ LCH cells are less frequently identified.[3]

Though the detection of Birbeck granules by electron microscopy was once the criterion standard for diagnosis, it was laborious and difficult to reproduce.[4] It became obsolete with the development of staining for CD207 (langerin), which is a monoclonal antibody against Birbeck granules. Diagnosis is now confirmed by positive staining for CD1a and CD207 on immunohistochemistry.[5] Other useful markers include S100, CD68, peanut agglutinin, placental alkaline phosphatase, interferon-gamma receptor, human leukocyte antigen–antigen D related, and CD4. Nevertheless, none of these markers, including CD207 and CD1a, are exclusively specific to LCH, because they are expressed by mononuclear precursors and other derivatives. Therefore, the diagnosis requires a combination of clinical presentation, histology, and immunohistochemistry.[2,6-9]

DIFFERENTIAL DIAGNOSIS

Key points

- **The diverse cutaneous presentation of LCH generates a broad differential**
- **Techniques to distinguish LCH from alternative diagnoses include immunohistochemistry, electron microscopy, and cultures**

The differential diagnosis of LCH can be broad based on clinical presentation. Histology, immunohistochemistry, electron microscopy, Tzanck preparations, bacterial, viral, and fungal cultures, and serology can be used to distinguish LCH from alternative diagnoses (Table I).

EVALUATION AT INITIAL PRESENTATION, RELAPSE, OR PROGRESSION

Key point

- **A thorough history and physical examination for extracutaneous manifestations is indicated in all patients with LCH**

The distinction between single-system and multisystem LCH is essential for prognosis and treatment, yet a physical examination and histology are not sufficient for reliable stratification.[2] The uncertainty of clinical course based on clinical and histologic findings warrants thorough evaluation and regular follow-up.[24]

A standardized initial evaluation is mandatory in all patients with LCH to define disease extent and tailor treatment intensity.[25] It includes a thorough history and physical examination with special attention to the skin, lymph nodes, ears, oral cavity, bones, lungs, thyroid, liver, central nervous system, and spleen. Assessment for stunted growth and symptoms of polyuria and polydipsia is also indicated. Recommended laboratory tests include a complete blood cell count, liver function tests, and electrolyte assessment. The minimal requirements for imaging assessment include a skeletal survey, chest radiography, and sonography of the liver and spleen. Additional laboratory tests and imaging are recommended upon specific indications (eg, endocrine evaluation and a magnetic resonance imaging scan of the brain in patients presenting with polyuria and polydipsia[26]).

CONTEMPORARY TREATMENT APPROACH

Treatment of cutaneous single-system LCH

Key points

- **Topical steroids are first-line therapy for lesions few in quantity**
- **Systemic steroids with vinblastine (12 months) are first-line therapy for diffuse disease**

There is no treatment protocol for isolated cutaneous disease. Recommendations are mainly based on case series rather than prospective controlled trials. In children with isolated cutaneous LCH, systemic therapy is only indicated for symptomatic or progressive disease, because isolated cutaneous involvement often resolves spontaneously.[27,28]