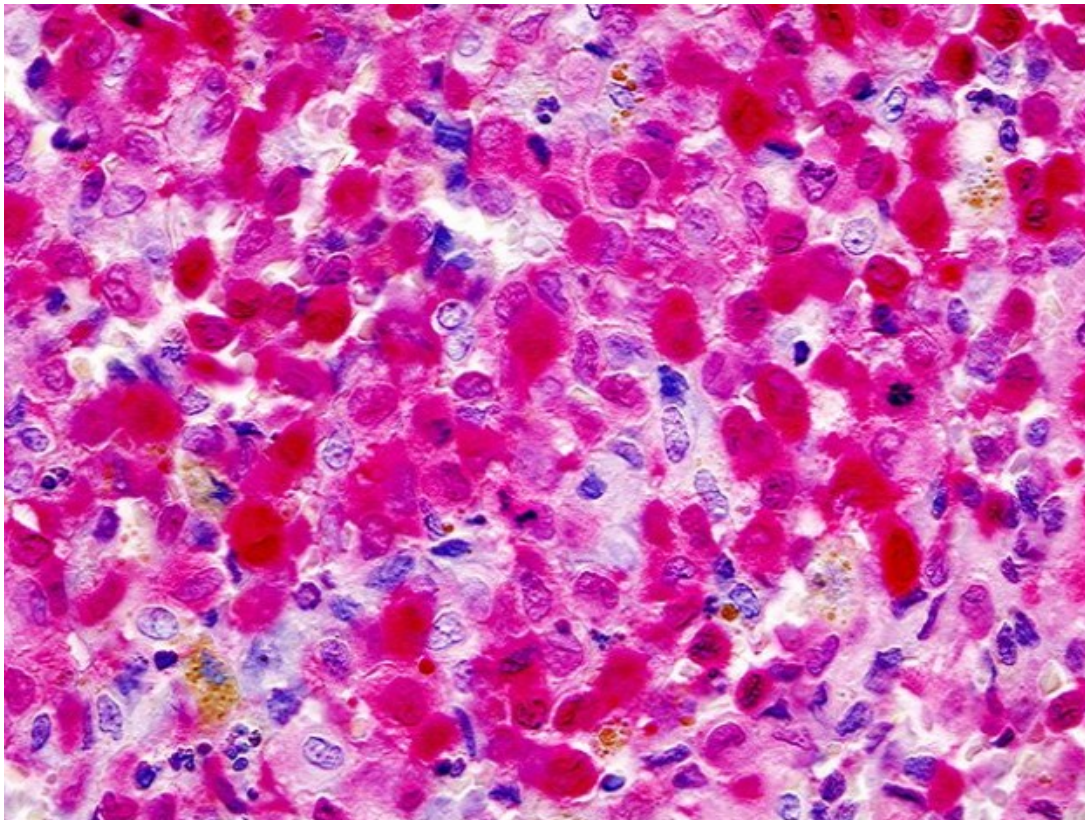


Langerhans Cell Histiocytosis: Diagnosis, Classification, and Prognosis

[See online here](#)

Langerhans cell histiocytosis occurs with granulomatous infiltration in various organs and tissues. Hence it is present in multiple clinical appearances with variable course and outcome. For that reason, it is important to approach Langerhans cell histiocytosis as a differential diagnosis since late effects are not uncommon. While localized disease has an excellent prognosis, involvement of high risk organs often ends fatal in spite of research regarding new therapies such as stem cell therapy or immunotherapy.



Definition of Langerhans Cell Histiocytosis

Histiocytosis X

Langerhans cell histiocytosis (LCH), also called **histiocytosis X**, is a nonmalignant disease marked by proliferation of Langerhans cells. Langerhans cells are epidermal **dendritic cells** and present antigens to other defense cells. Dendritic cells are a form of histiocytes. In this condition, histiocytes circulate in the peripheral blood post-maturation, depositing in different organs and organ systems. Therefore, the disease may present as

different syndromes, including [Hand-Schüller-Christian disease](#), Abt-Letterer-Siwe disease, and Hashimoto-Pritzker disease.

Epidemiology

Prevalence of histiocytosis X

The incidence is 0.4-1 in 100,000. Incidence of the disseminated course of the disease peaks in **infants and toddlers**. Incidence of localized disease peaks between **ages 5 and 15**. Boys are 1.3 times more likely to have the disease than girls are.

Etiology

Causes

The assumed pathophysiology is **disturbed intercellular communication** between effector cells, specifically T cells and antigen-presenting Langerhans cells. Proinflammatory mediators are released, contributing to **cytokine imbalance** and therefore massive proliferation and accumulation of dendritic cells. Tissue damage and ultimately fibrosis are caused by collection of histiocytes in organs.

Although a clonal origin of dendritic cells has been verified, certain indications of malignancy are missing. Some research has explored a connection between LCH and nicotine abuse, finding isolated manifestation in the lungs.

Pathology

Histiocytosis X on a cellular level

Dendritic cells are marked by a tender eosinophilic cytoplasm and a nucleus akin to a coffee bean. Langerhans cells show typical **Birbeck granules** and typical antigen patterns. They are **positive for** S100, vimentin, and **CD1a**. Birbeck granules look like X particles under an electron microscope. Furthermore, different inflammatory cells, such as eosinophilic and neutrophilic granulocytes, lymphocytes, and plasma cells, can be found in the granulomas.

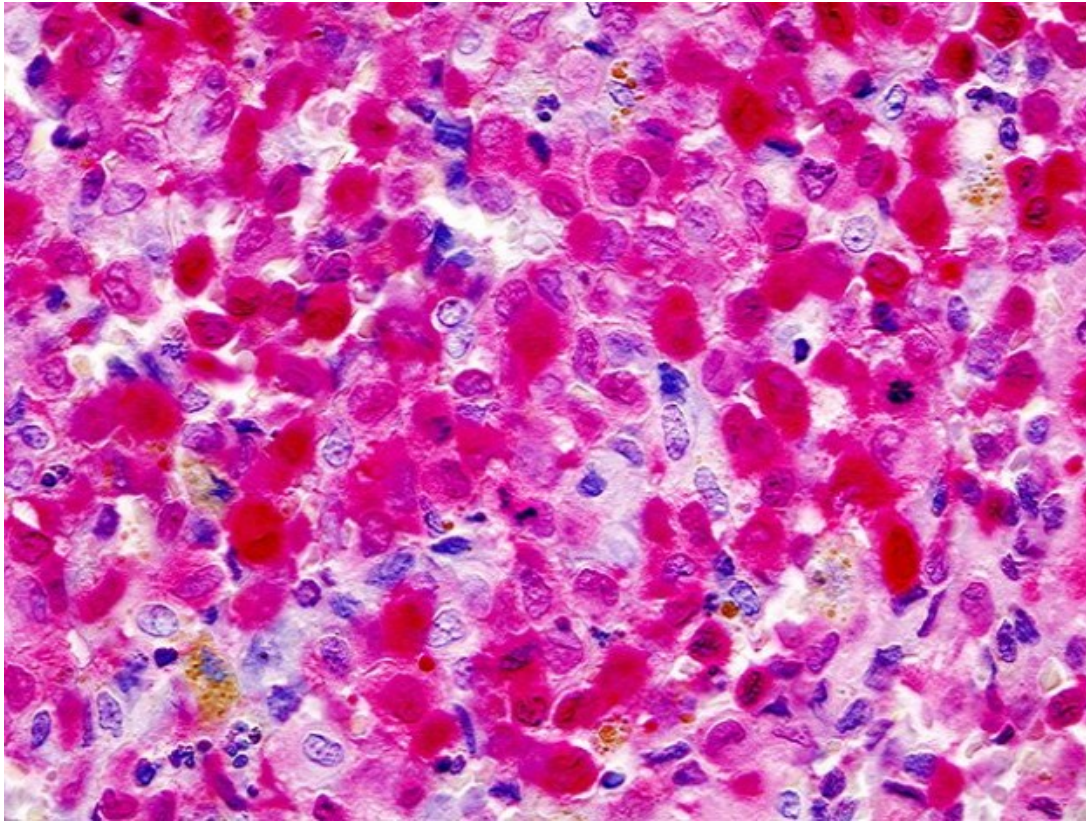


Image: "Histopathologic image of eosinophilic granuloma of the jaw." License: [CC BY-SA 3.0](#)

Clinical Presentation

Eosinophilic granuloma



Image: "CT of periorbital Langerhans cell histiocytosis," by BetacommandBot. License: [CC BY 2.5](#)

Eosinophilic granuloma is a localized form of histiocytosis X and largely affects bones. Eosinophilic granuloma accounts for **70%** of histiocytosis X cases. Eosinophilic granuloma arises in the **skull, spine, pelvis, and long bones**, with the possibility of disease in more than one bone at the same time. A painful, pliable swelling often covers the bone(s). With spinal involvement, compression fractures and development of so-called vertebra plana and neurologic deficiencies can occur.

Lesions in jaw bones can be accompanied by tooth loss or premature eruption of adult teeth.

Hand-Schüller-Christian disease

Hand-Schüller-Christian disease is marked by **multiple eosinophilic granulomas** of the bone, in addition to **soft tissue involvement**. It makes up **15%-40%** of all Langerhans cell histiocytoses. With sella turcica involvement, children suffer from **diabetes insipidus**. Additional symptoms are growth abnormalities, fever, swollen lymph nodes, exophthalmos, dyspnea, and hepatosplenomegaly.



Image: "A rare case of 'switch on and off' multisystem Langerhans cell histiocytosis in an adult patient," by *J Med Case Rep* (2011). License: [CC BY 2.0](#)

Note: The classical Hand-Schüller-Christian triad with bone lesion, exophthalmos, and diabetes insipidus is rather rare.

Abt-Letter-Siwe disease



Image: "Langerhans cell histiocytosis: an illusion of hope," by *Int J Clin Pediatr Dent* (2013). License: [CC BY 3.0](#)

LCH affecting the skin is predominantly defined as **Abt-Letter-Siwe disease**, which makes up **10%** of histiocytosis X cases. Skin presentation is reminiscent of **seborrheic dermatitis** on the buttocks and scalp. Polymorphic maculopapular exanthema with hemorrhaging, ulceration, and formation of crusts are observed. Additionally, hair may be thinning, and affected children may suffer from fever. In many children, the oral mucosa is affected by whitish granulomatous plaques, which exhibit a tendency for ulceration and bleeding. Generalized lymphomas and hepatosplenomegaly are observed. Also, thrombopenia with petechiae, anemia, and granulocytopenia are possible symptoms, along with infiltration of the bone marrow.

Diagnosis

Diagnosis of LCH requires:

1. Physical examination and history.
2. Neurological exam to check the spinal cord and nerve functions. Additionally, the neurological exam should establish mental status, senses, and reflexes.
3. Complete blood count with differential: amount of hemoglobin in the red blood cells, number of red blood cells, and platelets.
4. Blood chemistry studies to determine the substances released into the body by

organs and tissues.

5. Urinalysis to check the color of urine as well as its contents.

Radiologic diagnosis

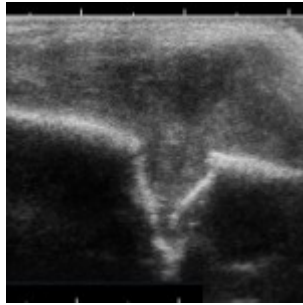


Image: "Ultrasound of eosinophilic granuloma in a 1-year-old," by Kinderradiologie Olgahospital Klinikum Stuttgart. License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

The main diagnostic modality is radiologic investigation.

On skull X-ray, an eosinophilic granuloma appears as an **osteolytic lesion with a punched-out appearance** and clear margins, surrounded by a sclerotic area or periosteal reaction. Observation of several lesions of the skull in Hans-Schüller-Christian disease is referred to as **geographic map skull**.

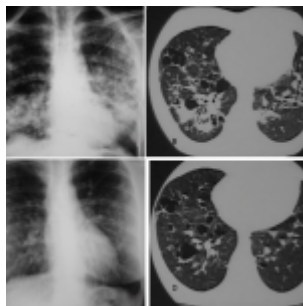


Image: "A rare case of 'switch on and off' multisystem Langerhans cell histiocytosis in an adult patient," by Karpathiou G, Koutsopoulos A, Froudarakis ME. License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Computed tomography of the lung can detect the so-called **Cheerio sign**, a thickening in the walls of the bronchial system that looks like the breakfast cereal.

With **liver** involvement, examination of a child will lead to observation of **edema and ascites formation**, and routine laboratory tests will show coagulopathy, cholestasis, and hyperbilirubinemia caused by a functional disturbance of the liver.

When involvement of the hypophyseal hypothalamic tract occurs, with diabetes insipidus as the prevalent symptom, magnetic resonance imaging will typically show a thickening of the infundibulum.

Further diagnosis

Skeletal scintigraphy, bone marrow aspiration, and lumbar puncture procedures, as well as testing of endocrinological functioning of the hypophyseal anterior and posterior lobes, serve to exclude disseminated disease.

Diagnosis is completed via biopsy, which can present proof of **Birbeck granules**.

Note: Per recommendation of the Histiocytosis Society, definitive diagnosis of LCH is based on immunohistochemical proof of CD1a antigens or observation of Birbeck granules by electron microscope.

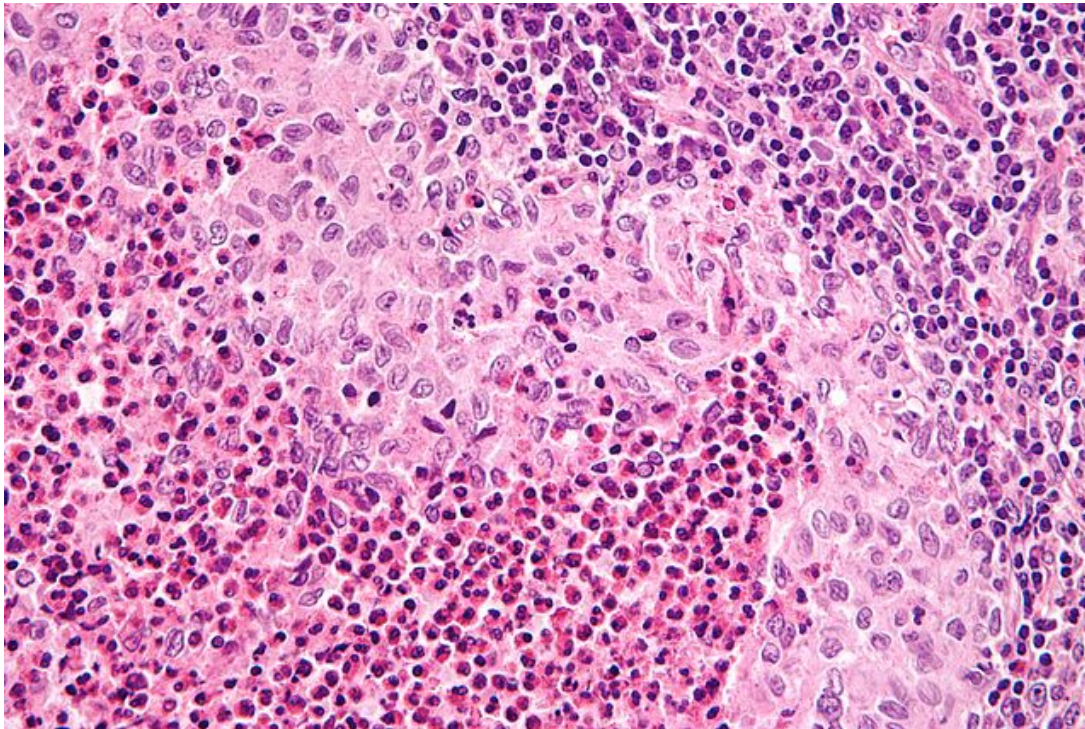


Image: "Very high magnification micrograph of Langerhans cell histiocytosis," by Nephron. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Classification

Division of Langerhans cell histiocytosis

According to criteria from the Histiocytosis Society, differentiation should be made between localized disease and disseminated disease. For purposes of therapy planning, patients should be classified into categories of either high or low risk, depending on the number of systems with evidence of disease as well as involvement of **high-risk organs** (e.g., liver, lung, spleen) or the hematopoietic system.

Single-system disease	Multisystem disease
Bones	2 or more organs or organ systems with or without organ failure
Skin	High-risk patients with involvement of high-risk organ system
Lung	Low risk; no involvement of high-risk organ system
Lymph nodes	
Central nervous system	

Treatment

Surgical treatment

Treatment of eosinophilic granulomas consists of **surgical curettage** of the lesion. **Radiation** is justified in cases of inoperable or recidivating lesions.

Diagnostic therapy

Disseminated courses are treated with cytostatic therapy including **prednisone** and **vinblastine**, which also minimizes delayed damage such as diabetes insipidus, stunted growth, and deafness. Abt-Letterer-Siwe disease may necessitate stem cell transplantation.

Prognosis

Generally, prognosis is positive. **Spontaneous arrest** of disease is possible. Factors negatively affecting prognosis are young age, poor overall condition, and organ infiltration. Involvement of high-risk organs combined with poor response to therapy within the first 6–12 weeks are independent prognostic criteria associated with fatality in about 75% of cases.

Malignant histiocytosis

Malignant histiocytosis is marked by **destructive infiltration** of malignant histiocytes into lymph nodes, liver, spleen, bone marrow, and skin. Boys are affected more often than girls are; the rapidly progressing disease can occur at any age. Differentiation from benign histiocytosis is essential. Treatment is similar to B-cell lymphoma via **chemotherapy**.

Follow-up care

Follow-up care over the course of many years is important for all LCH patients. Follow-up care includes checking of known bone lesions via X-ray at regular time intervals until bone reconstruction is observed. In case of systemic disease with involvement of other organs such as the lungs, regular functional tests should be conducted. In case of reactivation, the entire diagnostic program should be conducted as if it were the initial diagnosis.

Note: Due to radiation exposure, X-ray follow-up should be conducted only at locations that have symptomatic lesions.

Recurrent LCH

Recurrence of LCH is common and may affect the ears, skins, bones, or pituitary gland. The most common interval of recurrence is one year after cessation of medication.

References

S. H. Chou, G. Kicska, J. P. Kanne, S. Pipavath: *Cheerio sign*. In: *Journal of Thoracic Imaging*.

28, Januar 2013, S. W4.

Favara BE, Feller AC, Pauli M et al (1997) A contemporary classification of histiocytic disorders. The WHO Committee on Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocytic Society. *Med Pediatr Oncol* 29:157-166

Gadner H, Grois N (1993) The histiocytosis syndromes. In: Fitzpatrick TB, Eisen AZ, Wolff KF et al (eds) *Dermatology in general medicine*, pp 1002-2017. McGraw-Hill, New York

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