Langerhans Cell Histiocytosis — Diagnosis, Classification and Prognosis

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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 which is marked by proliferation of Langerhans cells. Langerhans cells are epidermal dendritic cells and present antigens to other defense cells. Other histiocytes circulate in the peripheral blood post maturation, their depositing in different organs and organ systems, e.g. Kupffer cells of the liver, explains the variety of clinical pictures.
These are abnormal cells that are produced in the bone marrow and have the capability of moving to the lymph nodes from the skin. The disease is also known as Hand-Schüller-Christian disease, Abt-Letterer-Siwe disease, or Hashimoto-Pritzker disease.

Epidemiology of Langerhans Cell Histiocytosis

Prevalence of histiocytosis X

The incidence is 0.4-1 in 100,000 with an age-based peak for a disseminated course of the disease in infants and toddlers. Localized disease has a peak incidence between ages 5 and 15. Boys are 1.3 times more susceptible than girls.

Etiology of Langerhans Cell Histiocytosis

Causes of Langerhans cell histiocytosis

A disturbed intercellular communication between effector cells, specifically T-cells and the antigen presenting Langerhans cells is assumed as pathophysiology. Proinflammatory mediators are released which contribute to a cytokine imbalance and therefore lead to a massive proliferation and accumulation of dendritic cells. Tissue damage and ultimately fibrosis is caused by the collection of histiocytes in the organs. Although a clonal origin of the dendritic cells could be verified, certain indications of malignancy are missing.

A connection to nicotine abuse could be confirmed for isolated manifestation in the lungs.

Pathology of Langerhans Cell Histiocytosis

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. The Birbeck granules look like x-particles when examined by an electron microscope which explains the name. Furthermore, different inflammatory cells like eosinophilic and neutrophilic granulocytes, lymphocytes and plasma cells can be found in the granulomas.
Clinical Presentation of Langerhans Cell Histiocytosis

Eosinophilic granuloma as a form of Langerhans cell histiocytosis

Eosinophilic granuloma is a localized form of Histiocytosis X and largely affects bones. It accounts for 70% of Histiocytosis X cases. Above all, it 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 can often be found covering the bone. In case of spinal involvement, compression fractures with development of so-called vertebra plana and neurologic deficiencies can occur.
Lesions in the jaw bones are noted by tooth loss or premature eruption of adult teeth.

**Hand-Schüller-Christian-Disease as a form of Langerhans cell histiocytosis**

**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. In case of sella turcica involvement, children suffer from diabetes insipidus. Additional symptoms are growth abnormalities, fever, swollen lymph nodes, exophthalmos, dyspnoea and hepatosplenomegaly.

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

**Abt-Letter-Siwe-Disease as a form of Langerhans cell histiocytosis**

Occurrences affecting the skin predominantly are defined as **Abt-Letter-Siwe-Disease** which makes up 10% of Histiocystosis X cases. Skin presentation is reminiscent of seborrheic dermatitis on rump and scalp. Polymorphic maculopapular exanthema with hemorrhaging, ulceration and formation of crusts are observed. Additionally, hair may often be thinning and the children may suffer from fever. In many children, the oral mucosa is affected with 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 occurring along with infiltration of the bone marrow.

**Diagnosis of Langerhans Cell Histiocytosis**

The diagnosis of Langerhans cell histiocytosis requires:

1. Physical exam and history: this entails checking for general symptoms, which
includes the signs of the disease; history of the patient should also be asseessed.

2. Neurological exam: assessment and test to check the spinal cord and the nerve functions. Additionally, the exam aims at establishing the mental status, senses, and the function of the reflexes of the patient.

3. Complete Blood Count with differential: checks the following
   1. Amount of hemoglobin in the red blood cells
   2. Portion of the blood samples making up the red blood cells
   3. Number of red blood cells as well as the platelets.

4. Blood chemistry studies: procedure through which blood sample is examined to determine the substances released into the body by organs and tissues.

5. Urinalysis: checks the color of the urine as well as its contents.

Radiologic diagnosis of Langerhans cell histiocytosis

The main diagnostic modality is by radiologic investigations.

Eosinophilic granuloma can be observed on a skull x-ray as osteolytic lesion with 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".

Computer tomography of the lung detects the so-called Cheerio sign. A thickening in the walls of the bronchial system is akin to the breakfast cereal in appearance.

In case of liver involvement, examination of the child leads to observation of edema and
ascites formation while routine lab work will show coagulopathy, cholestasis and hyperbilirubinemia caused by a functional disturbance of the liver.

In case of involvement of the hypophyseal hypothalamic tract with diabetes insipidus as prevalent symptom, MRI will typically show a thickening of the infundibulum.

Further diagnosis of Langerhans cell histiocytosis

Completion of 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 presents proof of Birbeck granules.

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

Classification of Langerhans Cell Histiocytosis

Division of Langerhans cell histiocytosis

According to the criteria of the Histiocytosis Society, a differentiation is made between localized disease manifestation and disseminated disease. For purposes of therapy planning, patients are classified into categories of either high or low risk depending on the number of systems with evidence of disease as well as the involvement of high risk organs such as liver, lung, spleen and the hematopoietic system.

<table>
<thead>
<tr>
<th>Single system disease</th>
<th>Multi system disease</th>
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<td>Bones</td>
<td>2 or more organs or organ systems with or without organ function failure</td>
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Treatment of Langerhans Cell Histiocytosis

Surgical treatment of Langerhans cell histiocytosis

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

Diagnostic therapy of Langerhans cell histiocytosis

Disseminates 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 a stem cell transplant.

Prognosis of Langerhans cell histiocytosis

Generally, the prognosis is positive. **Spontaneous arrest** of disease is possible. Negative factors affecting prognosis are young age of the child, poor overall condition and organ infiltration. The involvement of high risk organs combined with poor therapy response within the first 6-12 weeks are independent prognosis criteria which, in about 75 % of cases, end fatally.

Malignant histiocytosis

Malignant histiocytosis is marked by **destructive infiltration** of malignant histiocytes to lymph nodes, liver, spleen, bone marrow and skin. Boys are affected more often than girls, 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 of Langerhans cell histiocytosis

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 in regular time intervals until bone reconstruction can be observed. In case of systemic disease with involvement of other organs such as the lungs, regular functional tests are to be conducted. In case of reactivation, it is recommended to conduct the entire diagnostic program as in initial diagnosis.

**Note:** Due to radiation exposure, x-ray follow-ups should only be conducted at locations showing symptomatic lesions.

Recurrent LCH

Recurrence of the condition is common and may affect the ears, skins, bones, or the pituitary gland. The commonest time of recurrence is one year after cessation of medication intake.
Review Questions

The correct answers can be found below the references.

1. Which triad is characteristic for Hand-Schüller-Christian-Disease?
   A. Bone lesion, hyperprolactinemia, diabetes insipidus
   B. Skin invasion of Langerhans cells, exophthalmos, diabetes mellitus
   C. Skin invasion of Langerhans cells, hepatomegaly, enophthalmus
   D. Bone lesion, exophthalmos, diabetes insipidus
   E. Diabetes insipidus, hepatomegaly, lung restriction

2. Which organ or organ system does not belong to the list of risk organs in Langerhans cell histiocytosis?
   A. Central Nervous System
   B. Lung
   C. Spleen
   D. Liver
   E. Hematopoietic system

3. Initial treatment of an eosinophilic granuloma of the bone as part of Langerhans cell histiocytosis involves which procedure?
   A. Radiation with 6-10Gy total dose
   B. Chemotherapy with Prednisone and Vinblastine
   C. Aggressive chemotherapy and following stem cell transplant
   D. PUVA photochemotherapy
   E. Surgical curettage and orthopedic care

References


Correct answers: 1D, 2A, 3E

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