

# LANGERHANS CELL HISTIOCYTOSIS IN A 3-YEAR-OLD GIRL: A CASE REPORT AND LITERATURE REVIEW

JOANNA DUDA-SZYMAŃSKA, AGNIESZKA WIERZCHNIEWSKA-ŁAWSKA

Chair and Department of Pathomorphology, Medical University of Lodz

The report presents a case of Langerhans cell histiocytosis with diagnostic problems and fatal outcome in a 3-year-old girl, as well as a short literature review.

**Key words:** histiocytes, Langerhans cells, Langerhans cell histiocytosis, histiocytic neoplasms, CD1a.

## Introduction

Langerhans cell histiocytosis (LCH) is a neoplastic proliferation of Langerhans cells, with an expression of CD1a, S-100 protein, and the presence of Birbeck granules by ultrastructural examination (WHO 2001) [1].

Langerhans cell histiocytosis is a rare condition, but the most common neoplastic proliferative process of dendritic cells. In most cases it affects children and young adults (peak incidence: 1-3 years of age). Rare cases of congenital LCH were described, too [2]. It can occur in older individuals (> 65 years of age) [3]. The incidence is about 2-5 per million, with a male predilection (M : F = 1.5 : 1) [2].

The first clinical description of Langerhans cell histiocytosis was published over 100 years ago [4], but etiology of the disease still remains unclear. It is supposed to result from some immunologic dysregulation leading to excessive production of cytokines and prostaglandins (IL-1, IL-2, IL-4, IL-8, GM-CSF, TNF- $\alpha$ , TGF- $\beta$ ) [5] that damage various internal organs. The monoclonal character of Langerhans cell proliferation has been proved quite lately and this has allowed to consider LCH as a neoplastic process [1, 6]. The disease (especially its disseminated form) frequently precedes or accompanies other hemopoietic or lymphatic neoplasms, such as acute lymphoblastic leukemia or Hodgkin and non-Hodgkin lymphoma [1, 7, 8]. There may be an association with a history of neonatal infections, solvent

exposure, thyroid gland diseases and the lack of childhood vaccination. The infection with adenoviruses, parvoviruses, and such viral agents as HHV-6, EBV, HSV, CMV, HTLV 1 and 2 and HIV may bring about a special risk [1, 9]. Kallen *et al.* [10] observed a higher incidence of LCH in children from *in vitro* fertilization. In adult patients there is an association between LCH (pulmonary type) and tobacco and marijuana smoking [1]. There is a hypothesis of genetic background of the disease, associated with the occurrence of some HLA antigens (Bw61 and Cw7) [11]. Additionally, Rust *et al.* [12] proved that the expression of MMP12 gene in Langerhans cells could play a role in disease progression.

Langerhans cell histiocytosis can be local (e.g. isolated bone lesion) or can affect multiple organs and systems. Clinical manifestation depends on the site of the lesion, organs and systems involved and the deficiency of their function [1, 3].

There are three distinctive clinical forms of Langerhans cell histiocytosis: eosinophilic granuloma, Hand-Schüller-Christian syndrome and Letterer-Siwe syndrome. Diagnostic criteria are established by the Histiocyte Society [13]:

- presumptive diagnosis – light microscope morphological characteristics,
- designated diagnosis – light microscope morphological characteristics and 2 or more supplemental positive reactions to the following: adenosine triphosphatase, S-100 protein,  $\alpha$ -D-mannosidase, peanut lectin,

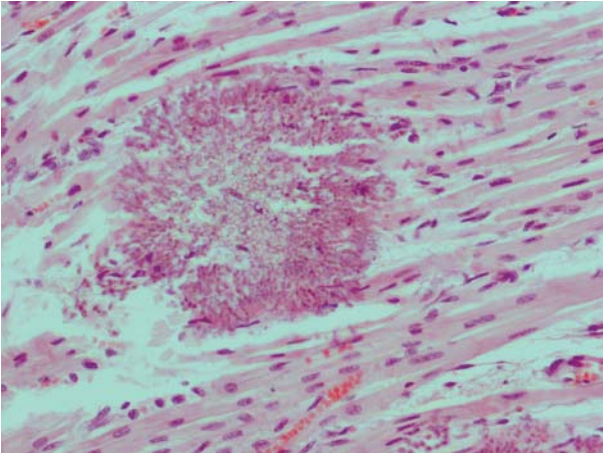


Fig. 1. Fungal colony in myocardium. H&E, magnification 400×

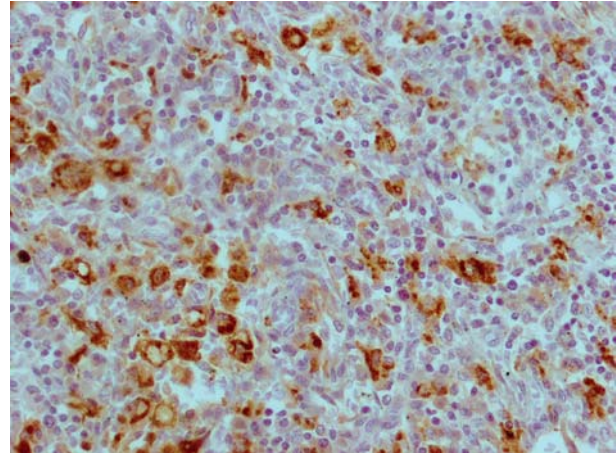


Fig. 2. CD1a positive cells in lymph node, magnification 400×

- definitive diagnosis – light microscope morphological characteristics and positive staining for CD1a antigen on the lesion cells and/or Birbeck granules in the ultrastructural examination.

We want to present and discuss a case of generalized LCH with associated fungal sepsis.

### Case report

A 3-year-old girl was admitted to the hospital because of rhinitis, massive dyspnea and fever. The patient had the history of generalized lymphadenopathy, hepatosplenomegaly, various blood abnormalities (anemia, hypoplastic picture of lymphoid cell line, increased serum calcium level), heart hypertrophy, recurrent upper respiratory tract and lung infections. Langerhans cell histiocytosis was suspected. During the first hospitalization (about 2 years before), a surgical biopsy of axillary lymph node was done and the specimen was examined at the same time by two independent histopathology centers. The diagnosis was: 1) non-specific reactive lymphadenopathy, 2) Gaucher disease. For the purpose of differential diagnosis, various tests were done and, eventually, Gaucher disease, bacterial, viral and protozoan infections were excluded. Polymyositis was suspected and the clinical improvement was observed after the corticosteroid therapy. Another hospitalization, due to pneumonia, took place about 3 months before. Fungal infection was proved and the patient underwent a successive course of antibiotic therapy.

At that moment, on physical examination, the girl had generalized lymphadenopathy and hepatosplenomegaly. On auscultation, multiple ruffles were heard over the right suprascapular region. Laboratory test results revealed a decreased number of white blood cells and lack of neutrophils, as well

as increased serum C-protein, gamma-globulin and IgM and IgG levels. The ultrasound examination showed enlargement of periaortic and splenic lymph nodes. In spite of antibiotic therapy, respiratory symptoms and laboratory abnormalities remained unchanged and after a few days clinical symptoms of mononucleosis occurred. Blood test results (decreased number of red and white blood cells and thrombocytopenia) worsened progressively. A bone marrow biopsy showed an aplastic picture in all cellular series (erythroid, lymphoid and platelets). Serum presence of antinuclear and antimitochondrial antibodies was observed and because of this fact, immunoglobulin and corticosteroid therapy was administered. Within the next days, gastrointestinal bleeding symptoms appeared. In spite of intensive supporting care and transfusion therapy, the patient's general condition worsened continuously. Massive dyspnea and symptoms of CNS injury occurred. A possible CNS hemorrhage was excluded in a CT examination. After a few days the patient died.

Autopsy findings: brain edema and multiple ecchymoses and necrotic foci in the central nervous system; hepatosplenomegaly and the presence of an additional spleen; generalized abdominal and thoracic lymph node enlargement; multiple white infarcts in the spleen; inferior lobe pneumonia with pleuritis; hypertrophic heart with mural thrombus in the left ventricle; ulceration of gastric and esophageal mucosa; fibrinous inflammation in the oral cavity, caries, and multiple petechiae on skin and serous membranes, mesentery and kidneys. General cachexia.

Microscopic findings: fungal colonies and fungal emboli in blood vessels of the heart muscle, lungs, kidneys, and thyroid gland as well as in lymphatic vessels of lymph nodes (Fig. 1); fibrinous-purulent pericarditis; multiple lung and spleen infarcts; recent kidney infarct; chronic active gastritis with

ulceration; lymphatic periportal inflammatory infiltrates in the liver.

Central nervous system: multiple fungal colonies visible in the tissue of the brain and cerebellum as well as fungal emboli with thrombosis in blood vessels. Inflammatory tissue reaction in the neighborhood of fungal colonies slight or absent. Perivascular infiltrates. The fungi were identified as *Candida*.

Immunohistochemical stain for CD1a antigen in histiocytic cells of the lymph node positive (Fig. 2).

## Discussion

In the light microscope the key feature of Langerhans cell histiocytosis is a neoplastic, monoclonal Langerhans cell that is about 10-15  $\mu\text{m}$  and has a characteristic grooved, folded or lobulated nucleus with fine chromatin and inconspicuous nucleolus. The cytoplasm is usually moderately abundant and slightly eosinophilic [14]. Some nuclear atypia can be observed, but if severe cytological features of malignancy are seen, one should consider the diagnosis of Langerhans cell sarcoma rather than LCH. Mitotic activity is variable, usually not more than some mitotic figures/10 HPF. Neoplastic infiltration contains also a various number of eosinophils, histiocytes, neutrophils, small lymphocytes and, sometimes, multinucleated macrophages [1]. Seldom, eosinophilic abscesses with central necrosis can appear. In early changes Langerhans cells, neutrophils and eosinophils predominate while in older lesions foamy macrophages and fibrosis are mostly seen. Lymph node involvement starts from sinuses with secondary infiltration of the paracortical regions. In the spleen the red pulp involvement is observed. In the bone marrow focal infiltrates and fibrosis occur [1]. Some researchers point out the usefulness of the fine needle aspiration biopsy of the lymph node in LCH diagnostics [15]. In our case such biopsy was performed, but the results were misleading.

Some authors suggest that the correct diagnosis of LCH is possible only on the basis of routine hematoxylin-eosin stain but with the full knowledge of all clinical data and imaging test results [16]. But according to newer data most of researchers agree that for final diagnosis immunohistochemical stains (S-100 protein, CD1a, HLA-DR) and ultrastructural examination (Birbeck granules) are necessary [1, 3]. There are studies claiming that marked eosinophilia is a good prognostic factor [17], but others do not find any relationship between the microscopic picture and survival time [16]. In our case the diagnosis was established too late (*post mortem*). However, the treatment (symptomatic) raises no reservations, because there is no evidence that the type of the therapy influences the clinical course and progression of the disease [16]. In 10-20% of patients spontaneous regression is observed [18]. The therapeutic strategy depends on the site and size of involvement as well as the patient's age [17, 19].

For staging LCH and planning the therapy the staging system proposed by Greenberger *et al.* in 1981 [19] is used (Table I).

In the case of a single monostotic lesion a widely accepted way of treatment is surgical resection of the involved area. If disease symptoms persist or progression is observed adjuvant radiotherapy is recommended. Primary radiotherapy is used when bone lesions are large, painful or a life (or health) threatening risk of surgery is present [20]. In patients older than 18 the results of such treatment are worse than in younger individuals. However, in children some disturbances of bone growth are possible after radiotherapy [21]. In general, the results of this treatment are good: 90-100% of patients survive 10 years [20, 21].

Combined chemotherapy is not useful in cases of LCH limited to bones, but is recommended in a disseminated multisystemic disease or when recurrence or progression takes place [20]. In the latest studies there are reports about benefits of

Table I. Staging system for Langerhans cell histiocytosis

STAGE I	a) single monostotic bone lesion b) multiple lesions in one or more bones
STAGE II	age > 24 months, one or more symptoms or organs involved: teeth, gingivae, lymph nodes, skin, diabetes insipidus, lungs (mild, i.e. RTG infiltrates without pulmonary symptoms or gross consolidation), focally positive bone marrow
STAGE III	a) age < 24 months, with any of systems involved in stage II b) age > 24 months, involvement of: liver and/or spleen, lymph nodes (nodes > 5 × 5 cm, in several sites above or below diaphragm), "honeycomb lung", bone marrow packed
STAGE IV	spleen > 6 cm (palpable below costal margin), fever longer than 1 month, with or without any or all of the above systems involved
STAGE V	stage III or IV and "special monocytosis" in peripheral blood > 20% of differential cell count



steroids administered separately or in combination with chemotherapy [17].

Prognosis in Langerhans cell histiocytosis depends on dissemination of the disease. It is the best in cases of single monostotic lesions [17, 20], when a risk of progression to a systemic disease is low, and so is probability of death [3]. The survival rate decreases when the number of involved organs increases [1]. In most cases recurrences in bones appear within 2 years (range: 2 months – 13 years) from the first diagnosis, and they are more often seen in adults (15%) than children (5%). The long lasting follow-up is recommended [20].

In patients with a disseminated systemic disease the prognosis remains poor. Spontaneous regression is rarely seen. Total remission is observed in 20-30% of patients, while 10% of patients die. The others (60-70%) progress to a chronic disease with involvement of consecutive organs [3]. The patient's age is a minor prognostic factor. Below 2 years of age mortality reaches up to 50% [1]. The poor prognosis is observed also in patients over 65 [3].

In our case disseminated fungal infection and not systemic insufficiency of affected organs was the direct cause of death. It suggests that serious immunodeficiency can accompany LCH. However, there is no evidence that it exclusively results from the disease.

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## Address for correspondence

Agnieszka Wierchniewska-Ławska  
 Chair and Department of Pathomorphology  
 Medical University of Lodz  
 ul. Pomorska 251  
 92-213 Łódź  
 phone +48 42 675 76 36, +48 42 675 76 38  
 e-mail: aggie.lawska@gmail.com