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Review

LANGERHANS-CELL HISTIOCYTOSES – EPIDEMIOLOGY, CLASSIFICATION, CLINICAL FEATURES, DIAGNOSIS, COMPLICATIONS, TREATMENT AND PROGNOSIS

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Summary

Histiocytoses comprise a group of diverse diseases of unknown etiology with various clinical presentation and evolution. The underlying pathology is characterised by accumulation and infiltration of variable numbers of cells of the monocyte-macrophage line in the affected tissues and organs. Histiocytoses are divided into three major classes: Langerhans cell histiocytosis (LCH), non-Langerhans cell histiocytosis, and malignant histiocytic disorders. The term LCH (also known in the past as histiocytosis X) encompasses the following rare diseases: Eosinophilic Granuloma, Hand-Schuller-Christian disease, Letterer-Siwe disease, Hashimoto-Pritzker disease, in which accumulation of pathologic Langerhans cells (LCs) leads to tissue damage. LCs usually reside in the skin and ensure protection against infections by destroying foreign substances. LC accumulation is caused by antigen stimulation and inadequate immune response. Thus, clinical LCH manifestations range from isolated disease with mono- or multifocal bone lesions to disseminated multisystem disease. LCH is a rare disease, affecting mainly children and young smokers, aged 20-50 years. Lung involvement in LCH usually presents as a mono-system disease and is characterized by Langerhans cell granulomas (LCG) infiltrating and impairing the distal bronchioles. The definite diagnosis is based on lung biopsy of CAT selected LCG areas. So far, there is no an effective treatment, but the better understanding of the mechanisms involved in the pathogenesis of the disease would help in the development of effective therapeutic strategies in the future.

Key words: Langerhans cells, granuloma, bone, skin, lung, histiocytosis

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Introduction

Histiocytoses (histiocytosis X, reticulo-endotheliosis) encompass a group of various diseases, characterized by pathologic accumulation and infiltration of variable numbers of cells from mononuclear phagocyte system (MPS) in different organs and systems. This pathologic process occurs without any relation to infection or to a primary defect in the metabolism of lipids. Heterogeneity of these disturbances is a direct result from the biological variability of MPS cells and the tissues in which they reside, so research in histiocytoses is still provoking interest and is yet acomplicated issue in contemporary hematology [1].

Histiocytosis was initially described in 1883 by Hand [2]. Historically, there were numerous difficulties in creating a system for classifying this group of entities. In 1987, the Working Group of the Histiocyte Society proposed a classification, which was adopted by the World Health Organization (WHO). In this classification, different entities were divided based on the origin of cells from normal histocytes [3, 4]:

Class I – Langerhans cell histiocytosis (LCH)

Class II non-Langerhans cell histiocytosis

- Hemophagocytic lymphohistiocytosis – HLH
- Virus-associated lymphohistiocytosis – Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes simplex virus (HSV), Adenovirus
- Rare hemophagocytic syndromes Rosai-Dorfman, Kikuchi syndrome

Class III malignant histiocytic disorders

- Acute monocyte leukemia M5
- Malignant histiocytosis Robb-Smith syndrome
- True histiocytic lymphoma – histiocytic sarcoma

In 1997, the classification is revised according to the biologic behavior of each type. Currently we have two big groups:

- with a variable course;
- with a malignant course.

Each group is further divided according the relationship of the cell substrate with dendritic or monocyte-macrophageal cells.

Classification of histiocytic disorders (FAB, French – American – British):

Class I: dendritic cell histiocytoses

- Langerhans cell histiocytosis
- Secondary dendritic cell processes
- Juvenile xanthogranuloma and related disorders
- Erdheim-Chester disease
- Solitary histiocytomas of various dendritic cell phenotypes

Class II: nondendritic cell histiocytoses

- Primary hemophagocytic lympho-histiocytosis
- Familial hemophagocytic lympho-histiocytosis
- Secondary hemophagocytic lympho-histiocytosis
- Infection associated
- Malignancy associated
- Rosai-Dorfman disease (sinus histio-cytosis with massive lymphadenopathy)
- Solitary histiocytoma with macrophage phenotype

Class III: malignant histiocytoses

- Monocyte related
- Leukemias (FAB and revised FAB classification)
- Monocytic leukemia M5A and M5B
- Acute myelomonocytic leukemias M4
- Chronic myelomonocytic leukemias
- Extramedullary monocytic tumor or sarcoma
- Dendritic cell-related histiocytic sarcoma
- Macrophage-related histiocytic sarcoma

Langerhans cell histiocytosis

The old term "Liechtenstein's histiocytosis X", dating back from 1953 (now replaced by "Langerhans cell histiocytosis") is part of the big group of rare diseases. In LCH there is a clonal proliferation and tissue infiltration in different tissues and organs of activated CD1a+/CD207+ cells, bearing phenotype and ultra-structure characteristics of Langerhans cells (LCs), with variable biological and clinical behavior [5, 6].

Langerhans cells, first described in 1968 by Paul Langerhans (medical student), are 15 μм in diameter. LCs are dendritic cells that regulate the pulmonary response to inhaled antigens or noxious particles. They are big, ovoid mononuclear phagocytes with a rather large amount of eosinophlic cytoplasm, indented or lobulated nuclei, small nucleoli and finely dispergated chromatin. The so called Birbeck granules (X-bodies) in LC cytoplasm are visible under an electron microscope. Bribeck granules are 5-layer cytoplasmic inclusions with a unique tennis-racket appearance. Immuno-histochemically, LCs express CD1a antigen and are positive on staining for S100 protein, which suffices to make a definite diagnosis. Besides CD1a, LCs express CD4, CD1c and B7 antigens. LCs usually do not exhibit dysplasia or atypical features (signs of malignant cells). The most important characteristics include antigen presence: CD1a, CD 207 (Langerin), CD 68, major histocompatibility complex molecules (MHC class II), S-100 antigen, CAM-1+, and Birbeck granules (Figure 1, 2).

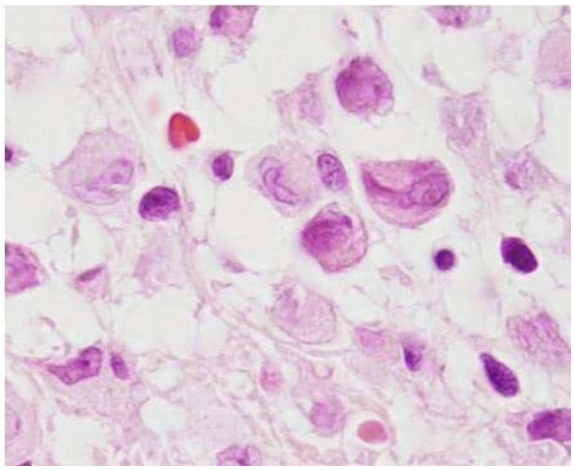

Figure 1. Histological features of LCs cells with grooved nuclei (hematoxylin-eosin staining)

The basis for understanding the disease is in LCs ontogenesis. LCs are cells from the monocyte-macrophage system, and originate from one pluripotent stem cell. These cells leave bone marrow to circulate as monocytes in blood vessels in order to complete their maturation in the tissues. Once they have invaded the connective tissue, they become histocytes and define two cell lines: a cell line of monocyte-macrophages with basic function into phagocytosis; and a line of dendritic cells. Some of the dendritic cells differentiate into LCs and play a major role in antigen-presenting to T-lymphocytes. Initially, LCs were described in epidermis but they could be also found in mucosa, lymph nodes, the thymus, spleen and lung [3].

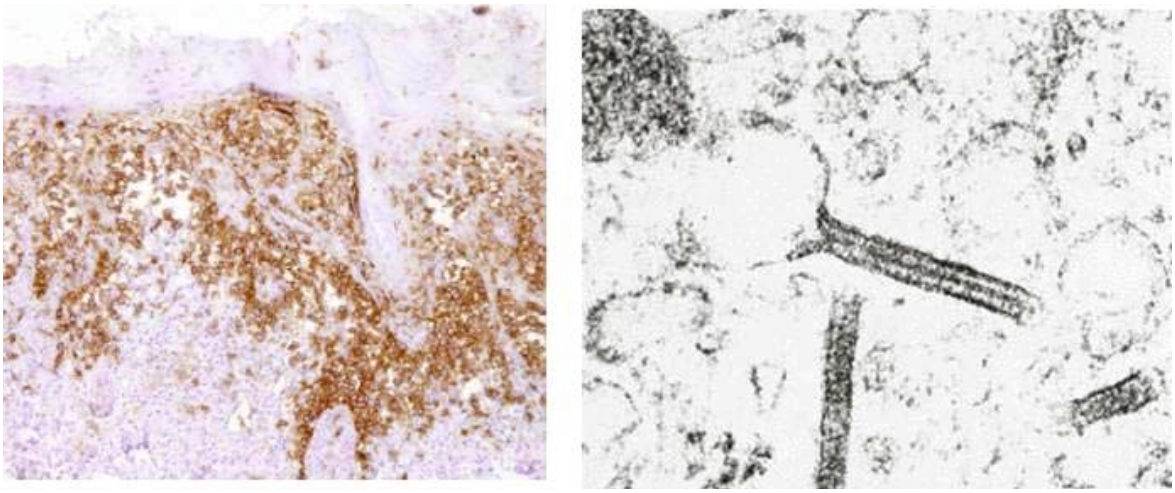

Figure 2. Characteristic findings for LCs: CD1a positivity of LCs (Streptavidin-Biotin method) – left; electron microscope image of Bribeck granules right [7]

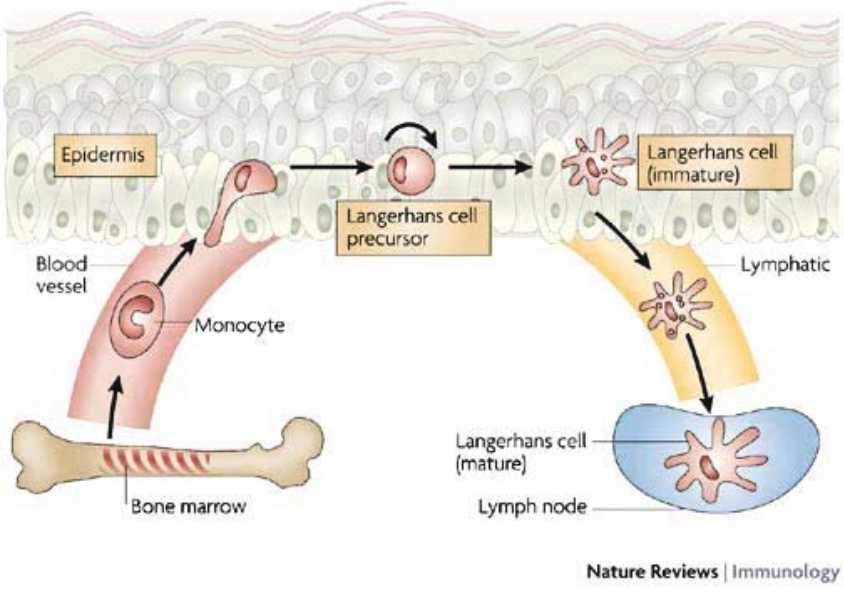

Figure 3. Langerhans cells ontogenesis [8]

Tumor or reactive proliferative origin of LCs is still a topic of unsolved debate. A clonal proliferation of LCs, but not a malignant transformation has been proved. Uncontrolled production of some cytokines plays part in the genesis of LCs: GM-CSF, IL-1, IL-3, IL-4, TNF-α, IL-8. Among these cytokines, the key factor for survival, accumulation, proliferation, maturation and activation of LCs is the granulocyte-macrophage colony-stimulating factor (GM-CSF). Higher levels of GM-CSF are established in children with LCH, confirming autocrine/paracrine stimulation on LCs by GM-CSF. In these cases viral etiology (CMV; Human herpes virus (HHV)-6, HHV-8; EBV; human immunodeficiency virus, HIV) has not been proved. The monocytes circulating in the blood are also highly modifiable cells, which could be other multipotent precursors of LCs under the effect of cytokines as IL-4, GM-CF and mainly transforming growth factor beta 1 (TGF-β1) synthesized in large quantities in epidermis by keratocytes.

After antigen exposition, LCs in epidermis have the ability to internalize and present the antigen. After leaving the epidermis through the lymph vessels (filamentous cells), LCs populate T-zones of the draining ganglia (interdigitating dendritic cells), where they present the antigen to the T-cells and express membrane co-activation molecules (CD40, CD80). In contrast to normal LCs, LCs in LCH can infiltrate almost every organ in the body: spleen, liver, gut, CNS, bones, etc. Expression of specific adhesive molecules and their modulation from LCs is perhaps the reason for these specific localization and dissemination (E-cadhérine) [9, 10].

In patients with LCH high levels of the proinflammatory cytokine IL-17A have been detected, which served as a base for suspecting the role of IL-17A in the pathogenesis of the disease. More detailed studies proposed the hypothesis of IL-17A-induced cell fusion of dendritic/LCs into giant cells with multiple nuclei, which further attract other cells of inflammation leading to local tissue destruction, characteristic of LCH [11, 12].

Other studies found that vascular endothelial growth factor (VEGF) expression, as well as the one of proteins from Bcl-2 family and proteins from Fas signaling pathway (FADD, FLIP and FLICE) are probably also involved into LCH pathogenesis [13].

In 57% of LCH biopsy samples, mutation of the BRAF gene (a protooncogene in the Raf family) was detected, with mutations being more prevalent in the patients younger than 10 years (76%) versus those found in the older patients (44%). These findings provided scientific proof of the myeloproliferative nature of LCH.

There has been a major debate regarding classifying LCH as an inflammatory or neoplastic disease due to incomplete understanding of its pathogenesis. Nowadays, a significant improvement in outcome and prognosis of the disease has been achieved through empiric therapeutic strategies and multicenter randomized clinical trials. Recently published data from genetic, molecular and functional studies support a hypothesis, according to which LCH is a consequence of errors in the differentiation of myeloid dendritic cell precursors. One of the critical mechanisms - activation of the Mitogen-activated protein kinases (MAPK) signaling pathway, together with the discovery of recurrent somatic mutation in genes of this pathway serve as a basis for developing novel approaches to diagnosis and therapy [14-17].

Etiology

LCH etiology remains unknown. The proliferation of LCs may be due to viral infection, a shortage in T cell-macrophage interaction, and/or tumor necrosis factor, IL-11 and leukemia inhibitory factor mediated cytokine-driven process. Recently, HHV-6 was found to contribute in the modulation of LCH, but the results are controversial. Another noxious factor could be cigarette smoking as a chronic irritant in the process of development of eosinophilic granuloma of the lung [18, 19].

Epidemiology

LCH is a rare disease that affects all age groups and races with predominance of the Caucasian race. The reported annual incidence varies from 0.5 up to 5.4 cases per million persons. Every year approximately 1 200, 160 and 60 new cases respectively are diagnosed in the United States, Japan and France. The disease is more often diagnosed in children aged younger than 15, with reported incidence of 3-4 cases per million. Different manifestations and variants affect predominantly particular age groups, as follows: Letterer-Siwe prevails in children under 2 years of age; the onset of chronic multifocal form

ranges from 2nd to 10th year of life; localized eosinophilic granuloma affects mainly children aged 5 to 15 years, while pulmonary LCH is predominant after the third and even forth decade of life [20].

LCH is more common in males, with a male:female ratio of 1.3:1. Less than 5% of females with diffuse lung pathology are positive for LCH in the USA. Incidence of 90-100% in smokers (over 20 cigarettes/daily) is a major epidemiological characteristic of lung LCH.

Lung LCH has been reported in patients with lymphoma, mainly with Hodgkin disease [18].

Prognosis in different forms of LCH varies from self-limited, as in congenital self-healing histiocytosis and most cases of unifocal LCH, to more than 50% deaths in disseminated LCH in children less than 2 years old. Usually multifocal chronic LCH tends to be self-limited, but in infants with pulmonary impairment there are even death cases [21, 22].

Classification

The oldest classification is the one used by Osband. It is based on 3 variables: age (<2 years – yes/no), number of affected organs (<4 – yes/no) and dysfunction of the affected organ (yes/no).

The Histiocytosis Association suggested an even simpler classification, based only on the number of affected organs: 1 or 2 organs - localized form; 3 and more affected organs - disseminated (generalized) form. The latter is more common in children [23-25].

Immunohistochemical comparison between LCH in children and adults is described in table 1.

Table 1. Comparison between LCH in children and adults (immunohistochemistry)

Children	Adults
All lesions are clonal	Some lesions are not clonal
LCs are more immature : CD86-	LCs are more mature: CD86+
IL -10 expression from macroph ages	No IL -10 expression from macrophages

Historical terms

Eosinophilic Granuloma (single organ involvement) is a slowly progressing, usually isolated lytic lesion due to an expanding proliferation of LCs in different bones. It could be monostotic (affecting one bone) or polyostotic (affecting multiple bones) without any extraskeletal damage.

Hand-Schuller-Christian disease (multiple organ involvement) - usually fatal if not treated disease with onset ranging from 3 to 6 years of age, with the characteristic triad of cranial lesions, exophthalmos and diabetes insipidus (1893).

Letterer-Siwe disease (multiple organ involvement) - a rare, usually fatal condition, mimicking systemic infection of neoplastic disease. It presents with a seborrheic rash, bleeding predisposition, hepatosplenomegaly, enlarged lymph nodes and progressive anemia. The lung involvement is seen mostly in children, rarely after 18 months of age (1924).

Hashimoto-Pritzker disease presents with lesions predominantly on the scalp skin. It is the most benign, self-limited form of LCH. Nowadays it known as Congenital self-healing reticulohistiocytosis.

These terms are relatively rigid and patients often present with a clinical course, demonstrating overlapping of these forms [26].

Chronic unifocal LCH (eosinophilic granuloma of bone)

Chronic unifocal LCH in one-third of the cases occurs in young adults with a solitary lesion of the calvaria, but other bones such as the scapulae, femur, ilium, mandible, vertebrae and ribs can also be affected. Although the initial changes are mostly asymptomatic, sometimes bone pain or

soft tissue mass could be present. So far no bacterial cause has been found in the bone affected. Some authors believe there is a hidden allergic trigger. Disease peak age is 13-14 years and it affects both sexes equally.With the extension of the affected area in the cranium more symptoms appear. The involvement of the nervous system manifests as a variety of neurologic symptoms. The destruction of the mastoid part of the temporal bone leads to otitis media. Orbital mass protrusion can be suspected in the presence of proptosis, while loose teeth testify for mandibular involvement. In cases, in which the sella turcica is involved, dysfunction of the pituitary gland is the main finding. Spontaneous fractures are rare and they could be due to osteolytic changes in the long bones. Some cases with spinal cord compression because of vertebral collapse or single lesions in less common sites (e.g. scapula) have been described [27].

On X-ray examination, bone defects with sharp edges without reactive changes are visualized. In these cases, Ewing sarcoma, cystic angiomatosis, multiple myeloma, metastatic carcinoma, primary lymphoma of the bone and osteomyelitis should be ruled out. Ewing sarcoma has similar radiolograhic changes in long bones, cystic angiomatosis presents with multiple widespread skeletal and visceral lesions, and soft tissue lesions may present with phlebitis. In multiple myeloma, "punched-out" lytic lesions mainly in the skull and axial skeleton, bones could have diffuse osteopenia are characteristic findings. In metastatic carcinoma, radiographs reveal mainly lytic lesions in bones, predominantly in older patients. Primary lymphoma of the bone manifests as aggressive lytic lesions. A serpiginous lytic pattern and sequestrum could be seen in cases with osteomyelitis and, when present, they are more specific for infection. The lesion has a regular surrounding enhancement due to inflammatory changes. Laboratory data is usually without deviations from the normal limits, but sometimes elevated erythrocyte sedimentation rate (ESR) is found. The disease initiates from the bone marrow and gradually affects the bone. The formation has a brownish color due to scattered hemorrhages. Histology findings are characterized with histiocytes, eosinophils and specific "foamy cells" that carry lipids (cholesterol). The disease has a good prognosis due to its benign course with a self-healing tendency, and gradual but slow recovery. In younger children (under 3 years) there might be multiple bone involvement and transition into other form of LCH.

The treatment of eosinophilic granuloma is a combination of corticosteroids with radiotherapy, but due to proclivity towards self-healing, the effect is disputable.

Some rare locations of eosinophilic granuloma have also been described. They include the gastro-intestinal form (polypus-like formation mainly in pylorus or diffuse infiltrations in small intestine), which is thought to be allergic in nature because of lack of histiocytes in the infiltrates), a cutaneous form, granuloma in the salivary glands, thymus and lung [28, 29].

Letterer-Siwe disease

It is also known as acute disseminated histiocytosis X, aleukemic reticulosis, non-lipid reticuloendotheliosis. It is an acute, disseminated and rapidly progressive form of LCH (multiorgan involvement) with unknown etiology, seen mainly in children less than 2 years of age. Histology findings include infiltration of non-lipid carrying histiocytes (big cells with one or two nuclei) in all internal organs, the skin and bone marrow. The clinical presentation includes a skin rash (papule-like rash similar to an insect bite rash), fever, hematological changes (anaemia and thrombocytopenia), lung infiltrates, enlarged lymph nodes and hepatosplenomegaly. Skin lesions appear as the first sign in almost 80% of the patients. The eruption could spread to the face, scalp, trunk, intertriginous areas and the gluteal zone. The rash is mainly petechial, with yellow-brown papules, sometimes with crusts. The papules can fuse to form a rash mimicking seborrheic dermatitis. The changes in intertriginous zones are usually exudative and sometimes with secondary infection or ulceration. As the diseases progresses, complications arise such as pneumonia, progressive anemia and thrombocytopenia. Osteolytic changes are rare in the disseminated form of LCH, but mastoid involvement presents as otitis media as onset. Conductive hearing loss, aural discharge and postauricular swelling have been reported. Bone changes are similar to those in the eosinophilic granuloma form. In the sub-acute course, the disease can be similar to the Hand-Schuller-Christian form. This type of LCH is treated with antibiotics, immunosuppressants,

cytostatics, and sometimes radio therapy is included. Only short-term remissions are achieved [30].

Hand-Schuller-Christian disease

This form is named after three scientists: Alfred Hand, Artur Schüller and Henry Asbury Christian. It is also known as chronic disseminated histiocytosis X, cranio-pituitary xanthomatosis, cholesterol granulomatosis, and chronic lipoid granulomatosis. In chronic cases, histology is similar to chronic unifocal LCH, while in sub-acute forms it overlaps with Letterer-Siwe disease. It is almost twice as common in males, and is rare in children younger than 2 years. The triad of exophthalmos, osteolytic lesions (mainly in the cranium) and diabetes insipidus (from sella turcica involvement) is characteristic for the disease. One of the most affected bones is sphenoid bone near the sella turcica. Retro-orbital proliferation of the formation is the cause for uni- or bilateral exophthalmos. The optic nerve is rarely damaged. Progression towards the sella turcica leads to pituitary dysfunction. In cases with temporal bone involvement, the middle ear is affected, leading to deafness. Enlarged liver and lymph nodes could be found in acute forms, while enlargement of the spleen is rare. Some cases are described in patients with Marfan syndrome. Skin lesions include papular or seborrheic rash and xanthelasma palpebrarum. Treatment with corticosteroids and antimetabolites is used. In some cases radiotherapy of the pituitary yields good results. Symptomatic treatment for diabetes insipidus with synthetic replacement for vasopressin is administered [31].

Hashimoto-Pritzker disease

This is a form of self-healing congenital histiocytosis with onset in the early neonatal period. It presents with are red-brown, firm, painless papulonodules 1 to 10 mm in diameter, vesicles and crusts all over the skin of the body, mainly on the face and scalp. The lesions could be solitary, or may ulcerate. Residual hypo-pigmented or hyperpigmented macules are found on the site of the lesions after recovery [26].

Snapper syndrome

This is an extremely rare, slow progressing disease with unknown etiology. Snapper syndrome is allotted to histiocytoses due to cholesterol accumulation of macrophages and histiocytes in bone formations. The disease affects only bones in adults. Some cases with engaged long bones have been reported. Well-delineated bone defects without adjacent bone reaction could be seen on X-ray images [23].

Pulmonary LCH (PLCH)

PLCH is characterized with lung infiltration from histiocytes (LCs) with granuloma formation. It affects the lungs with or without involvement of other organs in adults of both sexes, mainly Caucasians. Only in less than 10% of cases, there is a no smoking-related correlation to the disease, while in the rest of patients there is a positive smoking history (active or past smokers). In other words, PLCH is a one of the "smoking-related pulmonary diseases". In case of smoking-cessation, there occurs complete recovery in some patients, while others suffer certain long-term complications such as pulmonary hypertension and fibrosis.

Immune response towards cigarette smoke, initiated and mediated by LCs plays a major role in the pathogenesis of PLCH [32]. Cigarette smoke stimulates cytokine production by macrophages and epithelial cells (TNF-α, GM-CSF, TGF-β), which are responsible for LCs accumulation. This leads to hyperplasia of neuroendocrine cells in the lungs (NEC) by elevating the levels of bombesin-like peptides in lower airways (confirmed by biopsies). NECs, through bombesin-like peptides, contribute for accumulation and activation of mononuclear phagocytes and LCs, and stimulate the growth of fibroblasts. It has been confirmed that asymptomatic smokers have larger numbers of LCs. LCs multiply in alveolar structure and sustain alveolar inflammation in PLCH. LCs cooperate with lymphocytes, plasmocytes, eosinophils and macrophages through cytokines. Immune complexes against smoke antigens also take part in the pathogenesis of PLCH. Smoke glycoprotein stimulates lymphocyte differentiation and lymphokines production. In PLCH lesions there are a lot of lymphocytes (CD4+), which suggests formation of (unknown so far) antigen in lesion areas. Probably it is an antigen that originates from the airway epithelium damaged by cigarette smoke. A lot of smokers, however, do not develop PLCH. Thus,

the hypothesis for a "second hit" in the pathogenesis of the disease is highly probable.

Features, characteristic of PLCH histology include:

- formation of badly shaped delimited nodules in peribronchiolar space, from inflammatory cells – mainly LCs, surrounded by eosinophils (predominant in early stage), lymphocytes, plasmocytes, fibroblasts; central fibrosis (in advanced disease);
- star-shaped (stellate) fibrosis after infiltration of LCs, which aggregate in the inter-alveolar interstitium;
- cyst formation in damaged bronchial wall;
- bronchiolitis;
- macrophages in alveolar spaces and interstitium;
- intraluminal "buds" of connective tissue;
- cytological findings: blood, eosinophils, histiocytes with lobulated nuclei, foamy macrophages, solitary giant multinuclear cells (Figures 4 and 5).

Pathoanatomical differential diagnosis includes mostly chronic eosinophilic pneumonia, desquamative interstitial pneumonia and cryptogenic organizing pneumonia. Eosinophil infiltration is predominant in the early stages, while in the late stages cells infiltration is relatively reduced, with prevailing fibrosis, cysts and "honeycomb" changes.

Progress of the disease is characterized by elevated number of nodular lesions, cavitating granulomas and star-shaped cicatrices rich in fibroblasts. In the end stage of the disease, there are vast areas with honeycomb transformation

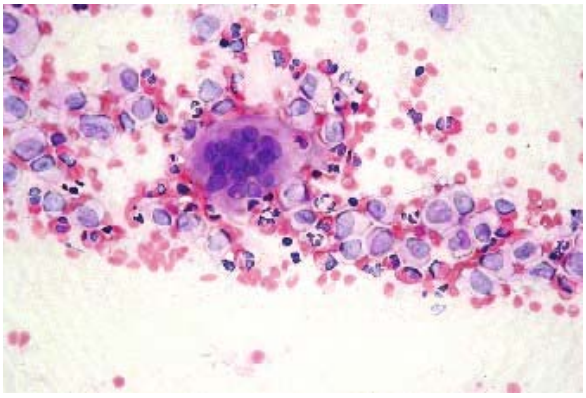

Figure 4. Chest wall tumor sample (hematoxylin-eosin x 1000)

and paracicatricial emphysema mainly in upper lung lobes. Combined involvement of the lungs and other organs is reported in about 20% of the patients.

The clinical course of PLCH is variable and unspecific. In more than 50% of the patients the onset is gradual and unnoticed, with dry cough and progressive dyspnea (in the beginning it is exercise-induced). In 30% there are general symptoms as fever, fatigue, weight loss, anorexia. Rarely, hemoptysis and wheezing are present. One quarter of the patients are accidentally diagnosed after random X-ray. In 20% of patients PLCH debuts with pneumothorax. In generalized forms other organs are also affected. Bone cystic lesions are found in 20% of patients with PLCH, while such lesions are found in 50% of LCH patiens.

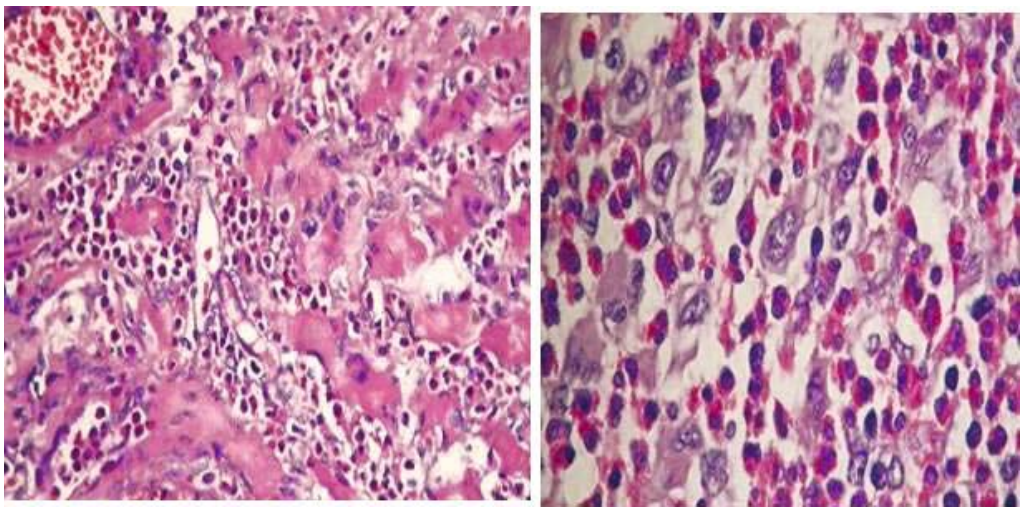

Figure 5. Rib sample: hematoxylin-eosin x 400 (left); hematoxylin-eosin x 1000 (right)

X-ray features of PLCH include diffuse reticular, reticulo-nodular or cystic lesions mainly in upper or middle parts; pleural thickening (rarely effusion); rarely mediastinal and hilar lymph nodes involvement (1/3 of the patients).

High resolution computed tomography (HRCT) is crucial for the diagnosis. The most common findings include combination of thin-walled cysts (over 85% of the patients) and nodules (1-15 mm) in zones of healthy lung tissue. Cysts are usually round, under 10 mm in diameter but could merge and reach 3 cm. Nodules are situated around bronchioles as peribronchiolar granulomas, which are replaced by cysts as the disease progresses. HRCT changes evolve from nodules to cavitating nodules, then to cysts and merged cysts. In 3-20% of the patients changes are found like ground glass opacities (Figure 6).

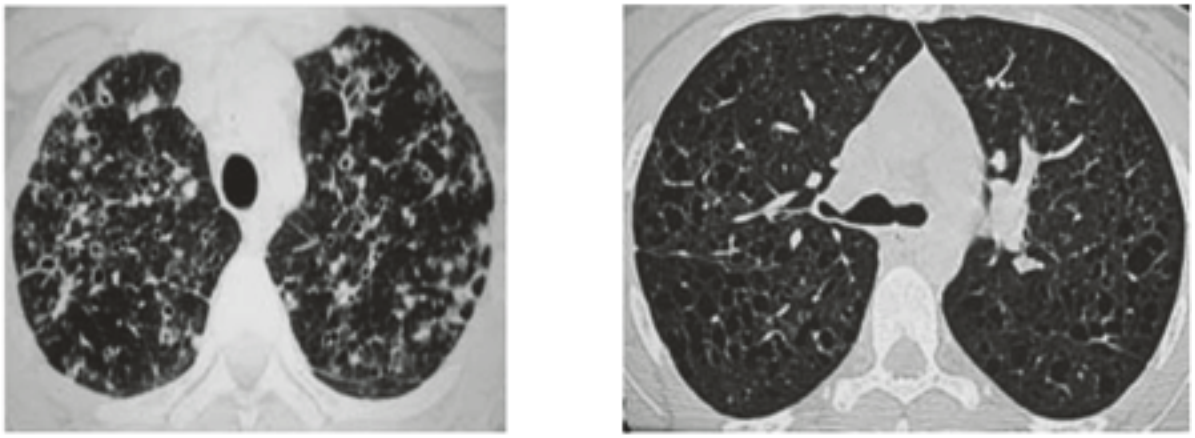

Figure 6. HRCT images in PLCH

Main imagining differences between PLCH, lymphangioleiomyomatosis, bronchiectasis and emphysema are shown in table 2.

Table 2. Differential table of PLCH

	X-ray	CT
PLCH	Normal or multifocal contiguous cysts (2-3 cm in diameter) End stage of the disease - reticular areas of opacity predominantly in the upper and middle lung lobes Rarely spontaneous pneumothorax	Early stage - multiple nodules predominantly in the upper lobes Progressed disease - diffuse, large and irregular cysts (honeycomb lung)
Lymphangio-leiomyomatosis	Normal to large lung volumes and subtle interstitial reticular opacities Unilateral or bilateral pleural effusions	Bilateral diffuse thin-walled cysts surrounded by normal lung parenchyma May be associated with pleural effusion
Bronchiectasis	Varies from linear pulmonary markings and mucus-filled bronchi to cystic spaces and honeycombing	Irreversible bronchial dilation which remains in subsequent images (“railroad track”)
Emphysema	Hyperinflation signs, cystic cavities, honeycombing, reticulations, and in some cases pneumothoraces	The cystic areas represent foci of lung destruction that typically lack perceptible walls There are four categories: • centrolobular (centroacinar) • panlobular (panacinar) • paraseptal • paracicatricial

On pulmonary function tests, there are changes without correlation to imaging findings in over 80% of the patients. The affected area of the cystic lesions is in reverse correlation with FEV1/FVC (forced expiratory volume in one second/forced vital capacity ratio), PaO2, DLCO (diffusing capacity of the lungs for carbon monoxide). Diminished DLCO is found in more

than 75% of the patients and is an early marker for alveolar-capillary membrane engagement by diffuse interstitial process in the lung. Severe DLCO changes are associated with a poor prognosis. In 50 to 80% of the patients total vital capacity (TVC) is diminished and residual volume is elevated in almost in 50%, while hyperinflation (TVC>110%) is a very rare finding. Almost one-third of the patients have obstructive or mixed ventilator defect, while restriction prevails in the later stages.

The lesions typical of PLCH are in peripheral zones, therefore quite often for diagnostic purposes thoracoscopic biopsy is enough, while in some patients fibrobronchoscopy with trans-bronchial biopsy could be necessary.

Diagnosis of PLCH is based on the clinical course, imaging findings and more than 5% cells positive for CD1a in broncho-alveolar lavage liquid (BALL).

Differentials of PLCH include mycobacterial infections, septic emboli, cavitating P. carinii pneumonia, sarcoidosis, Wegener granulomatosis, cavitating lung metastases, bronchio-alveolar cancer, lymphangioleiomyomatosis (LAM, in females) [33-37].

Therapeutic options for LCH

At present, there is no consensus on universal LCH therapy, especially in multisystem variants. The choice of medication and regimen is made depending on the disease severity and extension. The International LCH Study of the Histiocyte Society proposes a stratification of LCH cases by the number of systems involved. The cases with only one system involved are further assorted by the number of the zones affected in the system (e. g. single bone or multiple bone involvement). The presence of risk-organ dysfunction is also a maker for poor prognosis in patients with multisystem disease. An important measure in cases of PLCH is smoking cessation. In single system PLCH cases promising results have been demonstrated with cladribine (a purine analogue, 2-chlorodeoxyadenosine) by dramatic improvement of lung function. In patients with severe pulmonary hypertension specific therapies (inhibitors of phosphodiesterases, anti-endothelin receptors) could be used with caution.

Non-responsive single-system cases and multisystem variants of the disease require systemic chemotherapy. A combination of systemic steroids (prednisone) and cytotoxic medication (methotrexate, vinblastine) are effective in most cases. In cases of resistant LCH, a combination of cyclosporine A, prednisolone and antithymocyte globulin could be used if bone marrow transplant is not an option (no matched donor). In low-risk patients with only skin or bone systems affected, thalidomide has shown some efficacy but the drug is known for its significant side effects like pancytopenia and pulmonary failure.

The patients should have their complete blood count (CBC) and liver enzymes regularly monitored, as well as X-ray (thorax and all affected bones), abdominal echography, pulmonary function test (PFT), BALL studied, computerized axial tomography scan (CAT scan), magnetic resonance imaging (MRI) and myeolgram for CD1a+ cells.

For patients not eligible for clinical trial protocols, the Histiocyte Society provides guidelines for management (Table 3).

Table 3. Treatment guidelines

Therapy		Drug name and dosing	Frequency	Length of treatment
First line Pediatric LCH	Induction	Vinblastine 6 mg/m^2 IV	Weekly	6 wks
		Prednisone 1 mg/kg PO	Daily	4 wks, with 2-wk taper
	Maintenance	Vinblastine 6 mg/m^2 IV	Every 3 wks	12-24 mo
		Prednisone 1 mg/kg PO	5 days every 3 wks	
		6-Mercaptopurine 3 mg/m^2 PO	daily	
First line Adult LCH		Cytarabine (Ara-C) 100 mg/m^2 IV	5 days every 4 wks	6-12 cycles
Salvage		Cladribine (2CdA) 5-7 mg/m^2/d IV over 2 hrs	5 days every 4 wks	4-6 cycles
		Clofarabine 25-30 mg/m^2 IV		6 cycles
		Cladribine (2CdA) 9 mg/m^2/d continuous IV		3-5 cycles
		Cytarabine (Ara-C) 1 g/m^2/d IV over 2 hrs		6-12 cycles
Targeted		Vemurafenib, Dabrafenib – still under investigation		

Abbreviations: IV – intravenous; PO – per os (by mouth); hr – hour; wk – week; mo – month

The prognosis for patients with a disease, which is refractory to commonly used chemotherapy for LCH is poor. Two promising strategies for high-risk patients are currently on clinical trials – a combination of cladribine and cytarabine, and allogenic stem cell transplantation [38, 39].

Evolution

LCH is a disease with a heterogeneous clinical presentation and variable evolution. In 50% of patients, a favorable evolution is described: whether spontaneous or due to corticosteroid treatment. In case of cystic changes, however, no such favorable course is expected. The best prognosis is for patients with single bone lesions. In around 20% of cases with multisystem involvement the disease progresses despite aggressive treatment. Complications arise in up to 30-50% of patients, most commonly diabetes insipidus, orthopedic invalidation, hearing impairment or loss, skin scarring and psychologic disorders (e.g. depression, anxiety or decreased intellect).

Patients with multisystem disease and cranial involvement are at increased risk for developing diabetes insipidus. Therefore, regular neurological examination and brain MRI are indicated to evaluate CNS involvement and evidence of neurodegeneration.

Liver cirrhosis, growth retardation, pulmonary dysfunction and secondary neoplasms (solid tumors, acute lymphoblastic leukemia) are less common sequelae.

In 10-20% of the patients with PLCH, recurrent pneumothorax, progressing respiratory failure and cor pulmonale are found. Such patients should be monitored closely for years, since "silent" disease lung function can deteriorate very quickly. Among the most reliable prognostic factors in multifocal LCH is the response to induction chemotherapy (in the first 6 weeks). The patients who respond well during this period have a significantly improved survival. Worse long-term outcome is associated with hematologic involvement or involvement of lungs, spleen, and liver. Sclerosing cholangitis with jaundice and pruritus is found in about 1% to 6% of children with LCH. In adults, the combination of sclerosing cholangitis and LCH is more sporadic, and with a high mortality.

The mortality of Letterer-Siwe disease is high – over 50%, and the prognosis depends on the age of the patient, extent of organ dysfunction and spread of the disease.

The congenital self-healing form resolves spontaneously within weeks to months, although some cases of relapse up to 5 years after the initial disappearance of the disease have been reported. Some cases initially diagnosed as chronic unifocal LCH may progress to multifocal or even to a disseminated form of the disease.

Poor prognostic factors are:

- disease onset very early or very late in life;
- extrathoracic localization (excluding bones);
- involvement of at least 3 organs with organ failure (lung, liver, spleen);
- hematologic involvement;
- lung involvement (interstitial X-ray syndrome, diffuse cystic image, dyspnea and/or cyanosis, PFT-restrictive changes, low DLCO and/or pneumothorax);
- liver involvement (enlarged liver with cholestasis over 2 times above the normal range and/or cytolysis, and/or low albumin level <25 g/l);
- bad initial response to chemotherapy (patients with involvement of lung, liver or spleen without response after 3 months of therapy account for 75% of lethal outcomes).

Five-year relative survival (RS) is over 90.0%. Important differences in survival are noted according to age (<1 year: RS=78.5%, 1-4 years: RS=95.6%, 5-19 years: RS=100%). Mean survival nowadays is 13 years after diagnosis [40-43].

Other histiocytoses

Familial reticuloendotheliosis

Familial reticuloendotheliosis is also known as familial reticuloendotheliosis with eosinophilia, familial hemophagocytic lymphohistiocytosis, familial Letterer-Siwe syndrome, familial histiocytic reticulosis.

Inappropriate prolonged activation of lymphocytes and macrophages lead to an aggressive and potentially fatal disease. Histologically, there is histocyte proliferation with eosinophilic infiltration. Characteristic, but not diagnostic are pathological findings of haemophagocytosis (macrophages engulfing and destroying all types of blood cells) in the bone marrow, lymph nodes, spleen or liver. The

condition is seen mainly in young children of both sexes under 3-4. Familial cases are associated with autosomal recessive inheritance of known mutation. If the mutation is unknown, the disease is defined as "secondary" or "acquired", due to infection (such as caused by Epstein-Barr virus). The clinical presentation includes fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, and a skin rash.

This form of histiocytosis is uniformly fatal if not treated. It requires aggressive chemotherapy followed by bone marrow transplantation (BMT). Without treatment, the reported median survival time is 2-6 months after diagnosis. In cases treated only with chemotherapy, a temporary remission is possible, but the 5 year survival rate is less than 30%. Even with a successful BMT, the reported median 3-year survival rate is 55% due to post-BMT complications (fungal infections, acute respiratory distress, and graft-versus-host disease). In cases of "secondary" disease, good results are achieved with an 8-week regimen of steroids, cyclosporine and intrathecal methotrexate (in case of CNS impairment). If disease reactivation occurs or a decision to proceed with BMT is made, then the aforementioned combination therapy could be continued.

Reticulohistiocytoma (giant cells)

It is a benign, probably reactive proliferation of histocytes with unknown etiology. Characteristic for the disease is a firm, solitary skin lesion (less than 1 cm in diameter) found usually in females of middle age or young adults. The most affected areas are the head, neck and upper part of the trunk. Sometimes certain vasculitides or neoplasms can be also found. The disease is described in about 30% of patients with xanthelasmata. Histologically, the lesions are in the upper and middle layers of the dermis and do not tend to ulcerate. Cellular profile is characterized by big epithelial-like histocytes and various numbers of neutrophils and lymphocytes, CD3+ T cells, B cells, as well as plasmocytes,eosinophils and scarce mast cells.

Usually it is a "silent" non-recessive disease, but it should be differentiated from Rosai-Dorfman disease, juvenile xanthogranuloma, different granulomatous diseases and some neoplasms, including melanoma and sarcoma.

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

It is a rare benign disease of unknown etiology, with lymph nodes crowded with histiocytes typically found. The most commonly affected lymph nodes are the one on the neck, but histiocytes can infiltrate not only these lymph nodes but the surrounding tissue, skin, sinuses, upper airways and CNS in 25-40% of cases.

The clinical course is variable and depends on the localization. Many cases are self-healing but in the presence of large lymph nodes, symptomatic surgery treatment may be useful. Patients with multi-organ involvement or dysfunction require treatment, including steroids and chemotherapy (methotrexate/mercaptopurine, cladribine and venorelbine/methotrexate).

Juvenile xanthogranuloma

Juvenile xanthogranuloma is histiocytosis without LCs, affecting mainly infants, but onset is possible at any time during childhood: 80-90% of all cases are children younger than 2 years.

It is a rare disorder, in which solitary skin nodules of the same color as the surrounding skin or yellowish are found on the head, neck, or trunk. Sometimes the nodules may be deeper in the subcutaneous fat, soft tissue, or in muscles. Extracutaneous involvement is usually restricted to the eye. These infiltrations can affect the function of internal organs (spleen, pancreas, lung, liver, adrenal, intestines, kidneys, heart), bones (including the bone marrow), CNS, as well as the patient's immune system. So far no relationship with lipid metabolism defects has been found.

Skin biopsy is sufficient to make the diagnosis. Findings include histocytic infiltration, and some older lesions have foam-like cells and giant cells.

Patients presenting with only skin or soft tissue involvement have very good prognosis, and the majority of lesions spontaneously disappear with time. Some patients may require topical steroid therapy. In single or only a few lesions, excisional biopsy could be used for cosmetic reasons. Patients with systemic disease and risk organ involvement (CNS, liver, bone marrow) should be treated with steroids and chemotherapy. The systemic form is associated with other diseases such as neurofibromatosis type 1 and juvenile chronic myelogenous leukemia. Café au lait spots are found in 20% of the patients.

Conclusions

Histiocytoses present a group of diverse diseases of unknown etiology with various clinical presentation and evolution. Although knowledge of these disease dates back almost a century, the underlying pathophysiology remains a mystery and the treatment is not specific. So far there is no effective treatment, but a better understanding of their pathogenesis could be of help to develop effective therapeutic strategies in the future.

References

1. Badalian-Very G, Vergilio JA, Degar BA, Rodriguez-Galindo C, Rollins BJ. Recent advances in the understanding of Langerhans cell histiocytosis. Br J Haematol. 2012;156(1):163-72.
2. Hand A. General tuberculosis. Trans Pathol Soc Philadelphia. 1883;16:282.
3. Favara BE, Feller AC, Pauli M, Jaffe ES, Weiss LM, Arico M et al. Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol. 1997;29(3):157-66.
4. Writing Group of the Histiocyte Society. Histiocytosis syndromes in children. Lancet. 1987;1:208-9.
5. Oreshkov K Stoeva N. [How far we have come in understanding Langerhans histiocytosis]. Medinfo. 2008;12:35-40. Bulgarian.
6. Lynch JP. Rare interstitial lung diseases: pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, and cryptogenic organizing pneumonia. In: ACCP Pulmonary Medicine Board Review. 25th ed. Northbrook, IL: American College of Chest Physicians; 2009.
7. Kissenpfennig A, Aït-Yahia S, Clair-Moninot V, Stössel H, Badell E, Bordat Y, et al. Disruption of the langerin/CD207 gene abolishes Birbeck granules without a marked loss of Langerhans cell function. Mol Cell Biol. 2005;25(1):88-99.
8. Shortman K, Naik SH. Steady-state and inflammatory dendritic-cell development. Nat Rev Immunol. 2007;7:19-30.
9. Berres ML, Merad M, Allen CE. Progress in understanding the pathogenesis of Langerhans cell histiocytosis: back to Histiocytosis X? Br J Haematol. 2015;169(1):3-13.
10. Csire M, Mikala G, Jako J, Masszi T, Janosi J, Dolgos J. Persistent long-term human herpesvirus 6 (HHV-6) infection in a patient with langerhans cell histiocytosis. Pathol Oncol Res. 2007;13(2):157-60.
11. Allen CE, Li L, Peters TL, Leung HC, Yu A, Man TK. Cell-specific gene expression in Langerhans cell histiocytosis lesions reveals a distinct profile compared with epidermal Langerhans cells. J Immunol. 2010;184(8):4557-67.
12. Allen CE, McClain KL. Interleukin-17A is not expressed by CD207(+) cells in Langerhans cell histiocytosis lesions. Nat Med. 2009;15(5):483-5.
13. Bank MI, Gudbrand C, Rengtved P, Carstensen H, Fadeel B, Henter JI et al. Immunohistochemical detection of the apoptosis-related proteins FADD, FLICE, and FLIP in Langerhans cell histiocytosis. J Pediatr Hematol Oncol. 2005;27(6):301-6.
14. da Costa CE, Szuhai K, van Eijk R, Hoogeboom M, Sciot R, Mertens F, et al. No genomic aberrations in Langerhans cell histiocytosis as assessed by diverse molecular technologies. Genes Chromosomes Cancer. 2009;48(3):239-49.
15. Haroche J, Charlotte F, Arnaud L, Von Deimling A, Hélias-Rodzewicz Z, Hervier B, et al. High prevalence of BRAF mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood. 2012;120(13):2700-3.
16. Nelson DS, van Halteren A, Quispel WT, van den Bos C, Bovée JV, Patel B, et al. MAP2K1 and MAP3K1 mutations in langerhans cell histiocytosis. Genes Chromosomes Cancer. 2015;54(6):361-8.
17. Satoh T, Smith A, Sarde A, Lu HC, Mian S, Trouillet C, et al. B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease. PLoS ONE 2012;7(4):e33891.
18. Cerri S, Spagnolo P, Luppi F, Richeldi L. Smoking-related interstitial lung disease. In: Cordier JF, editor. Orphan Lung Diseases: Volume 54 of European Respiratory Monograph. Plymouth: European Respiratory Society; 2011. 376 p.
19. Strenger V, Urban C. Chromosomal integration of the HHV-6 genome as a possible cause of persistent HHV-6 detection in a patient with langerhans cell histiocytosis. Pathol Oncol Res. 2010;16(1):125-6.
20. Ribeiro KB, Degar B, Antoneli CB, Rollins B, Rodriguez-Galindo C. Ethnicity, race, and socioeconomic status influence incidence of Langerhans cell histiocytosis. Pediatr Blood Cancer. 2015;62(6);982-7.
21. Delobbe A, Durieu J, Duhamel A, Wallaert B, the Groupe d'Etude en Pathologie Interstitielle de la Societe de Pathologie Thoracique du Nord. Determinants of survival in pulmonary Langerhans' cell granulomatosis (histiocytosis X). Eur Respir J. 1996;9:2002-6.
22. Watanabe R, Tatsumi K, Hashimoto S, Tamakoshi A, Kuriyama T. Clinico epidemiological features of pulmonary histiocytosis X. Intern Med. 2001;40:998-1003.
23. Ivanov S. [Sarcoidosis and other granulomatoses]. Sofia: Nasko-1701; 2000. Bulgarian.

24. Gaensler E, Carrington C. Open biopsy for chronic diffuse infiltrative lung disease: clinical, roentgenographic, and physiological correlations in 502 patients. Ann Thorac Surg. 1980;30:411-26.
25. Haupt R, Minkov M, Astigarraga I, Schafer E, Nanduri V, Jubran R, et al. Langerhans cell histiocytosis (LCH): Guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2013;60(2):175-84.
26. Lampert F. Langerhans cell histiocytosis. Historical perspectives. Hematol Oncol Clin North Am. 1998;12(2):213-9.
27. Kluge G, Sorge I, Bierbach U, Hirsch W. Scapula as an uncommon site of Langerhans cell histiocytosis in an infant. Pediatr Int. 2010;52(1):142-4.
28. Friedman PJ, Liebow AA, Sokoloff J. Eosinophilic granuloma of lung. Clinical aspects of primary histiocytosis in the adult. Medicine (Baltimore). 1981;60:385-96.
29. Unger J, England D, Collins J. Miliary nodules, Hodgkin's disease, and eosinophilic granuloma. J Thorac Imaging. 1994;9:71-3.
30. Lahey ME. Prognosis in retinucloendotheliosis in children. J Pediatr. 1962;60:664-71.
31. Arico M, Haupt R, Russotto VS, Bossi G, Scappaticci S, Danesino C. Langerhans cell histiocytosis in two generations: a new family and review of the literature. Med Pediatr Oncol. 2001;36:314-6.
32. Marinova D, Titorenkov P, Slavova Y. [Pulmonary Langerhans Cell Histiocytosis]. Inspiro. 2013;4(24):39-42. Bulgarian.
33. Chaowalit N, Pellikka PA, Decker PA. Echocardiographic and clinical characteristics of pulmonary hypertension complicating pulmonary Langerhans cell histiocytosis. Mayo Clin Proc. 2004;79:1269-75.
34. Crausman RS, Jennings CA, Tuder RM, Ackerson LM, Irvin CG, King TE Jr. Pulmonary histiocytosis X: pulmonary function and exercise pathophysiology. Am J Respir Crit Care Med. 1996;153:426-35.
35. Fridlender ZG, Glazer M, Amir G, Berkman N. Obstructing tracheal pulmonary Langerhans cell histiocytosis. Chest. 2005;128:1057-8.
36. Sundar KM, Gosselin MV, Chung HL, Cahill BC. Pulmonary Langerhans cell histiocytosis: emerging concepts in pathobiology, radiology, and clinical evolution of disease. Chest. 2003;123:1673-83.
37. Vassallo R, Ryu JH, Colby TV, Hartman T, Limper AH. Pulmonary Langerhans'-cell histiocytosis. N Engl J Med. 2000;342:1969-78.
38. Simko SJ, McClain KL, Allen CE. Up-front therapy for LCH: is it time to test an alternative to vinblastine/prednisone? Br J Haematol. 2015;169(2):299-301.
39. Veys PA, Nanduri V, Baker KS, He W, Bandini G, Biondi A, et al. Haematopoietic stem cell transplantation for refractory Langerhans cell histiocytosis: outcome by intensity of conditioning. Br J Haematol. 2015;169(5):711-8.
40. Arico M, Astigarraga I, Braier J, Donadieu J, Gadner H, Glogova E, et al. Lack of bone lesions at diagnosis is associated with inferior outcome in multisystem langerhans cell histiocytosis of childhood. Br J Haematol. 2015;169(2):241-8.
41. Egeler RM, Neglia JP, Puccetti DM, Brennan CA, Nesbit ME. Association of Langerhans cell histiocytosis with malignant neoplasms. Cancer. 1993;71:865-73.
42. Vassallo R, Ryu JH, Schroeder DR, Decker PA, Limper AH. Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. N Engl J Med. 2002;346:484-90.
43. Thomeer M, Demedts M, Vandeurzen K. Registration of interstitial lung diseases by 20 centres of respiratory medicine in Flanders. Acta Clin Belg. 2001;56:163-72.