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Pulmonary Langerhans' cell histiocytosis in adults

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Abstract

Pulmonary Langerhans' cell histiocytosis (PLCH) is a rare disorder of unknown cause characterised by the infiltration of the lungs and other organs by the bone marrow derived Langerhans' cells, which carry mutations of BRAF gene and/or NRAS, KRAS and MAP2K1 genes. It occurs predominantly in young smokers, without gender predominance. The disease is characterised by formation of eosinophilic granulomas with the presence of Langerhans' cells infiltrating and destroying distal airways.

High-resolution computed tomography of the chest (HRCT) plays an outstanding role in PLCH diagnosis. The typical radiological picture of PLCH is the presence of small intralobular nodules, often forming 'tree in bud' lesions, cavitated nodules, thin- and thick-walled cystic lesions frequently confluent. Definite diagnosis requires the finding of characteristic lesions in histological examination and demonstration of antigen CD1a or CD207 presenting cells in immunohistochemistry.

Smoking cessation is the most important recommendation for PLCH patients.

There are no evidence based data regarding systemic steroid therapy. The treatment of progressive PLCH is based on cladribine or cytarabine as salvage therapy. The prognosis is good, and over 85% of patients survive 10 years.

Key words: pulmonary Langerhans cell histiocytosis, pneumothorax, cladribine, BRAF

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Introduction

Pulmonary Langerhans' cell histiocytosis (PLCH) belongs to a group of rare cystic pulmonary diseases, including the following disorders: lymphangioliomyomatosis, Birt-Hogg-Dubé syndrome, light chain disease, lymphocytic interstitial pneumonia (Table 1). PLCH is of proliferative nature but its pathogenesis is also associated with a reactive, inflammatory element [1–3].

Definition

Langerhans' cell histiocytosis is a rare disorder of unknown aetiology, caused by clonal proliferation of Langerhans' cells (LC), which are geno- and phenotypically altered. LC are of myeloid origin and over half of them express BRAF V600E oncogene,

and in 25% of cases, mutations within the NRAS, KRAS, MAP2K1 kinase genes are observed. In the case of isolated involvement of the lungs in adults (pulmonary Langerhans' cell histiocytosis — PLCH) polyclonal proliferation of LC occurs with the presence of significant inflammatory process [1–7].

LCH may affect any organ. It takes the form of various size nodular lesions, infiltrating and damaging the structure of neighboring tissues. It affects most commonly the bones, lungs, skin and pituitary gland. The involvement of lymphopoietic organs (lymph nodes, liver, spleen, bone marrow), the alimentary system and central nervous system is more frequently observed in children. Pulmonary lesions in the course of LCH may take isolated forms that anticipate even for many years the occurrence of systemic changes, or from the very beginning, the lungs may be one

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of several affected organs. The isolated pulmonary form of LCH is observed in approximately 50% of patients with PLCH [3, 7–12].

In relation to organ involvement, LCH is divided into the following forms:

- **single system LCH (SS-LCH)** — single- or multiple-involvement of a single organ or system:
 - **bones** (single bone, single- or multiple, and many foci in many bones),
 - **the skin**,
 - **the lymph node** (excluding the lymph node draining the area of histiocyte infiltrate) or multiple lymph nodes (more than one lymph node group),
 - **the hypothalamus — hypophysis/the central nervous system**,
 - **isolated pulmonary involvement**,
 - **other** (the thyroid, thymus, intestines);
- **multisystem LCH (MS-LCH)**, involvement of two or more organs or systems:
 - **involvement of critical organs** (the haemopoietic system, spleen, liver and central nervous system),
 - **no involvement of critical organs**.

From the point of view of therapeutic decisions, of importance is the involvement of special areas and bones that are at risk of involvement of the central nervous system. It applies to the following bones: vertebrae (possible compression spinal fracture and damage to the spinal cord), the bones of the orbit, mastoid process, sphenoid bone, temporal bones with the transition into the soft tissue (possible injury to the nerves of the bony face and pituitary gland) [3].

Table 1 shows a new proposal of classification of histiocytosis that takes into account overlapping of the disease with myelo/lymphoproliferative changes and Erdheim-Chester disease. The common denominator of this diseases is the presence of mutations within MAP kinase pathways (Fig. 1) [1, 2, 4–6].

Epidemiology

The prevalence of LCH is estimated at 0.5–0.9/100 000 in children under 15 years of age, and 0.1/100 000 in people over 15 years of age. The persons with PLCH are considered to constitute about 5% of patients undergoing open lung biopsy. According to Japanese data, the prevalence of PLCH in women amounts to 0.07/100,000 and 0.27/100 000 in men. Due to the nature of the disorder, it is assessed that the prevalence of PLCH is underestimated [3, 7–13].

PLCH affects young people in the third and fourth decade of life, both men and women.

Table 1. The new proposition of classification of histiocytic disorders. Histiocytoses of the group L

• Langerhans cell histiocytosis (LCH)
— LCH SS
— LCH Lung+
— LCH MS-RO+
— LCH MS-RO
— Associated with other myeloproliferative/ myelodysplastic disorder
• Intermediate cell histiocytosis (ICH)
• Erdheim-Chester disease (ECD)
— ECD classical type
— ECD without bone involvement
— Associated with other myeloproliferative/ myelodysplastic disorder
— Extra-cutaneous or disseminated JXG with MAP kinase activating mutation or ALK translocations
• Mixed ECD and LCH

SS — single system; MS — multiple system; RO — risk organ; JXG — xanthogranuloma of juvenile type

Over 95% of PLCH patients are tobacco smokers. No relation between the intensity and/or duration of smoking and the occurrence of PLCH is observed [3, 7–14].

There were cases of isolated pulmonary LCH in children, and in the majority of them, the disease was associated with passive exposure to tobacco smoke.

No genetic predisposition towards LCH was found, and familial cases of PLCH occur occasionally [3, 7, 9].

Pathogenesis

Histiocytes belong to a heterogenic group of dendritic cells that process and present antigens. Langerhans' cells (LC) are a specific subclass of dendritic cells. They are present in the skin, under the epithelium of the bronchial tree and other mucosae, and they are first to react to exogenous antigens [3, 7]. LC are stimulated by Toll-like receptors, by bacterial cells or the factors released from damaged or wasting away cells. The activated LC present antigens and migrate to adjacent lymph nodes and induce a cascade of immunological response. LC also play a role in the development of tolerance to inhaled harmless antigens, thus they protect from excessive inflammatory response [7].

Tobacco smoke is considered to be a main factor inducing pulmonary form of LCH, but the mecha-

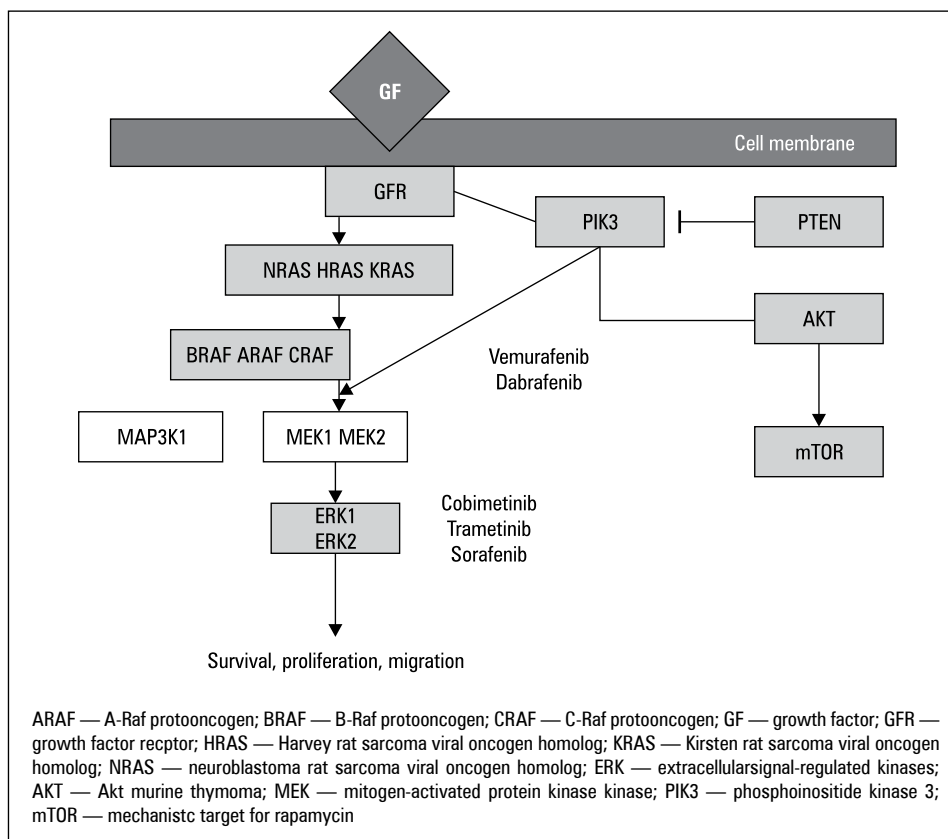


Figure 1. MEK-ERK signalling cascade of the MAPK pathway and PI3K-AKT pathway. Diagram of RAS proteins activation

nisms of the process are unclear. Tobacco smoking results in the accumulation of LC in the lungs. The phenomenon has been observed in patients with PLCH, but also in healthy smokers, people with COPD, desquamative interstitial pneumonia (DIP) or respiratory bronchitis — interstitial lung disease (RB-ILD). Tobacco smoke includes many components that induce the production of cytokines necessary to the recruitment and activation of LC. The most important among these cytokines are the following: tumour necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor beta (TGF-beta) and chemokine of dendritic cells (CCL20) [3, 5].

TNF is produced by macrophages and bronchial epithelial cells. It plays a crucial role in activation and differentiation of LC. Under the influence of tobacco smoke, bronchial epithelial cells and fibroblasts release GM-CSF, which is a strong mitogenic factor for LC. Excessive expression of this factor within histiocytic infiltrates has been shown. Whereas TGF-beta, apart from significant proliferative activity towards LC, participates in remodelling of the pulmonary parenchyma and fibrosis. A potentialising role in LC expansion play monocytes, whose recruitment is also related to exposure to tobacco smoke [5, 7].

Researches into relationship between tobacco smoking and PLCH have shown the presence of excessive osteopontin expression in histiocytic pulmonary lesions. Osteopontin is a glycoprotein with chemokine qualities inducing chemotactic activity of macrophages, monocytes and dendritic cells, including LC. Moreover, tobacco smoke promotes increased expression of anti-apoptotic protein Bcl-xL within histiocytic granulomas. Activated pathological LC display strong lymphostimulating properties and are characterised by increased expression of CD40, CD80 and CD86 antigens. To sum up, tobacco smoke induces inflammatory process in the small airways, the release of a series of proinflammatory cytokines, and the recruitment of macrophages, dendritic cells, monocytes, eosinophils and lymphocytes, which form inflammatory histiocytic granulomas. The process of tissue remodelling, which leads to the cystic destruction of the lungs, occurs probably due to activation of 2 and 9 metalloproteinases produced by dendritic cells, LC and monocytes [5, 7, 15].

The role of IL-17 in the pathogenesis of histiocytic lesions is not fully understood. IL-17 is a cytokine produced by T cells that participates in immunological response to infections, vacci-

nes and autoimmune diseases. It was shown that dendritic cells produce IL-17, which promotes the development of giant cells. The reports on the concentration of this interleukin in patients with PLCH are inconsistent [3, 7].

Pathogenesis of LCH is not established yet, and a proliferative or reactive nature of the disease due to excessive accumulation and apoptosis disorders, are still being discussed. It suggests that one of the disease mechanisms is accumulation of LC and their longer survival compared to proliferation. On the other hand, in pathological lesions obtained from children and adults with MS-LCH, the features of clonal proliferation have been observed, which argue for neoplastic nature of the lesions. Clonality is noted in 50% of pulmonary lesions, which suggests different pathogenesis of pulmonary lesions in adults and in children [3, 5].

Nevertheless, identification of the role of BRAF mutation in the development of LCH has led to a significant shift in the concept of the disorder [18]. It is believed that the central core of the disease are somatic, heterogenic mutations within MAP kinase pathways (Mitogen Activated Protein Kinase) concerning myeloid progenitors. MAP kinase regulates the activity of many enzymatic proteins and transcription factors, and covers a broad spectrum of activity. It may impact on the induction of inflammatory processes *via* recruitment of macrophages/monocytes, differentiation of T cells, proliferation of smooth muscles and the activation of endothelial cells. Mutations within MAP kinase pathways concerning precursors to macrophages of distinct origin (bone marrow or yolk bag) result in the occurrence of the overlapping syndrome of LCH and Erdheim-Chester disease or chronic myeloid leukaemia [1, 2, 4, 5, 16]. In patients with LCH, activating mutations of the BRAF, ARAF, MAP2K1, N/K/HRAS and PIK3CA genes have been found [4–6, 16–18]. The scheme illustrating signalling pathways involved in the control of histiocytic cell proliferation is shown in Figure 1. Furthermore, in patients with MS-LCH, it has been demonstrated that mutation of the BRAFV 600E gene occurs in myeloid cells, whereas in patients with SS-LCH, mutations are found solely in cells originating from infiltrates [19].

Clinical presentation

Symptoms of the disease are associated with the location of lesions.

Table 2. Examinations necessary for the evaluation of the disease

1. Full blood count
2. CRP, erythrocyte sedimentation rate
3. Blood chemistry (electrolytes, creatinine, alkaline phosphatase, ALT, AST, bilirubin, total protein, albumin,
4. Urine examination, morning urine osmolarity
5. TSH, LH, FSH, prolactin, oestrogens, testosterone,
6. Coagulation tests
7. Chest X-ray and CT scans of chest and head
8. MRI of brain and pituitary gland
9. Ultrasound of abdomen, thyroid gland and lymph nodes
10. Echocardiography, electrocardiogram
11. PET/CT or low dose whole body CT scan
12. Spirometry with bronchodilatation test, body plethysmography, diffusion lung capacity, 6 minute walk test
13. Bronchoalveolar lavage

All abbreviations in the text

Symptoms from the respiratory system

PLCH patients usually report non-productive cough, lowered exercise tolerance, exertional dyspnoea, fatigue, weight loss and night sweats. Merely in 6% of patients, haemoptysis is noted. Approximately 20% of patients do not report any symptoms, and in 10–30% of individuals, the first sign of the disorder is pneumothorax. Pneumothorax occurs in the course of the disease in 30–45% of cases. Symptoms arise 6–12 months prior to the recognition of the disorder but in some individuals, diagnosis is established after many years of observation. Dyspnoea at rest and the features of right-ventricular circulatory failure occur at late stages of the condition [3, 7–12]. More than 10% of PLCH patients develop pulmonary hypertension. It is not always related to the exacerbation of pulmonary lesions, and may be the effect of the involvement of pulmonary vessels observed in the course of the disease [3, 7–12, 20, 21].

Physical examination often does not detect significant pathological signs. The most frequently heard are the following: weakened vesicular murmur, wheezes and dry rales, and in the case of pneumothorax, the symptoms thereof.

In the course of LCH, a broad spectrum of organic lesions is observed, thus the need for thorough clinical work-up is highlighted [3]. Table 2 illustrates the scope of examinations necessary for initial evaluation of LCH patients.

Skin lesions

They usually take the form of red, brown and hard nodules, which repeatedly spontaneously



Figure 2. Histiocytic lesions on scalp, fingers and nails

regress leaving a central depression. On the hairy skin of the head, trunk and the bending areas, erythemic and pustular alterations may appear, which resemble follicular ichthyosis or acne changes. Involvement of the nails and nailfolds may also appear [3, 22] (Fig. 2).

Bone lesions — over 50% of isolated bone lesions concern children under 5 years of age. Changes in the form of painful osteolytic defects and nodulated masses spreading to the soft tissues are usually discovered in the cranial vault, bony face, particularly in the lower jaw, orbital bones, mastoid process, ribs, shoulder-blade and pelvis. Of particular danger is the involvement of the bones of the spinal column, the base of the skull and orbit, which is signaled by the pressure and damage to the surrounding structures (Figs 3–5) [3, 23].

The hypophysis — in about 10–20% of adults at various stages of the disorder, damage to the posterior lobe of the hypophysis in the form of diabetes insipidus is observed. Affected hypophysis frequently manifests itself in clinical symptoms and endocrinological disorders without changes seen on imaging tests, including magnetic resonance. Panhypopituitarism is rarely noted, but some individuals experience hormonal disorders [3, 7–11].

LCH may affect any organ: the thyroid, thymus, lymph nodes, intestines, reproductive organs. A specific form is the involvement of the liver in the form of cholangitis sclerosans [3].

Radiological findings

Table 1 shows essential radiological tests assessing particular systems that may be affected by the condition.



Figure 3. Osteolytic lesions in mandible — the picture of floating tooth

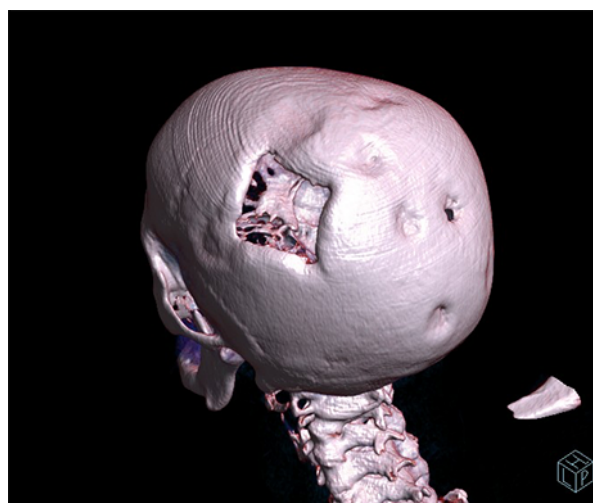


Figure 4. Osteolytic lesions in bones of scalp. Condition after surgical resection of parietal lesions (courtesy of dr I. Bestry)

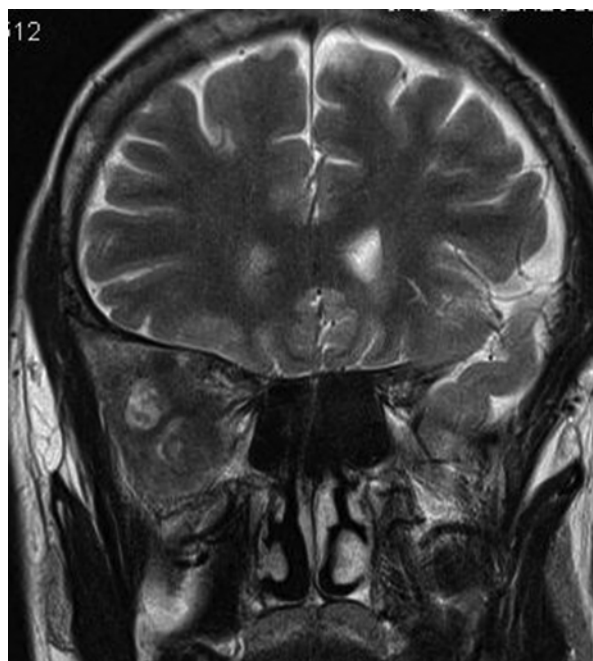


Figure 5. MRI — histiocytic infiltration in the region of the right orbit (courtesy of dr K. Błasińska-Przerwa)



Figure 6. Chest X-ray — bilateral small cysts, partially confluent nodules predominate in the upper and middle lung fields. There is opacity in the right costophrenic angle due to previous pneumothorax (courtesy of dr I. Bestry)

Due to the commonest localisation of the lesions, of particular interest is the evaluation of the skeletal system, the lungs and hypophysis. To assess the extent and activity of the disease, if available, PET/CT is recommended. In the remaining cases, low-dose CT of the entire skeleton is suggested [3, 7–13, 24, 25].

Chest radiograph

The value of standard chest radiograph is limited as multiple lesions are small and difficult to notice. In patients with advanced disease, nodular, reticular, and cystic lesions are visible in the middle and upper lung fields (Fig. 6). Lung volumes are usually normal or increased. Pleural lesions due to past pneumothorax are frequently observed. Moreover, enlargement of the hilar or mediastinal lymph nodes may occur [3, 7–12, 24–26].

Computed tomography

Computed tomography, in particular high-resolution computed tomography, is important in diagnosis of histiocystic lesions, especially in the case of the lungs [26]. The most often noted lesions are centrilobular nodules, frequently forming ‘tree-in-bud’ appearance, nodules with or without a lacuna, initially thick-walled cysts of various shape, which may be isolated or confluent with the appearance of “clover leaves”. As the disease evolves, the cysts become bigger

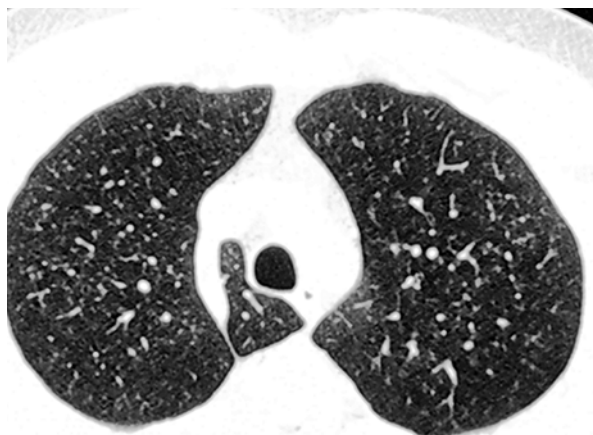


Figure 7. High resolution computed tomography — small intralobular nodules in both lung fields (courtesy of dr I. Bestry)

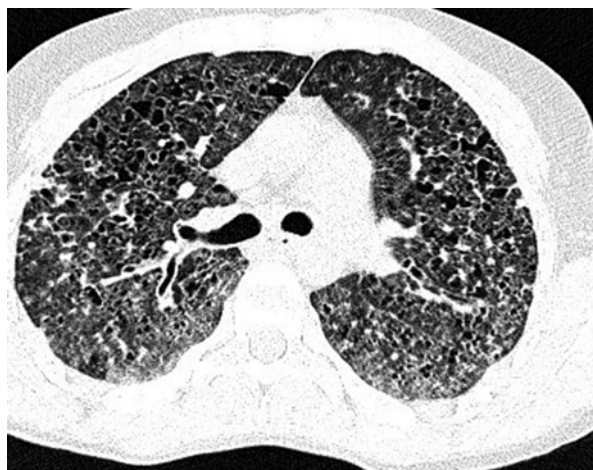


Figure 8. High resolution computed tomography – multiple nodules and cysts with thick walls, partially confluent (courtesy of dr I. Bestry)

and thin-walled. In the majority of adult patients (over 90%), the costophrenic angles are spared (Figs 7–9). Whereas in children, both lungs are symmetrically affected, lesions are found even in the lower lobes. In addition, pneumothorax is commonly present [24, 25]. In elderly heavy tobacco smokers, apart from lesions associated with PLCH, the features of COPD may be visible, including emphysematous bullae. Enlarged lymph nodes may be present. In patients with pulmonary hypertension, megalocardia and enlarged pulmonary trunk are observed [3, 27].

Positron emission tomography

PET with fluorodeoxyglucose (FDG) is more sensitive than CT in identifying bone lesions, in particular those subclinical, in the lungs, lymph nodes, liver, spleen or thyroid. PET is particularly

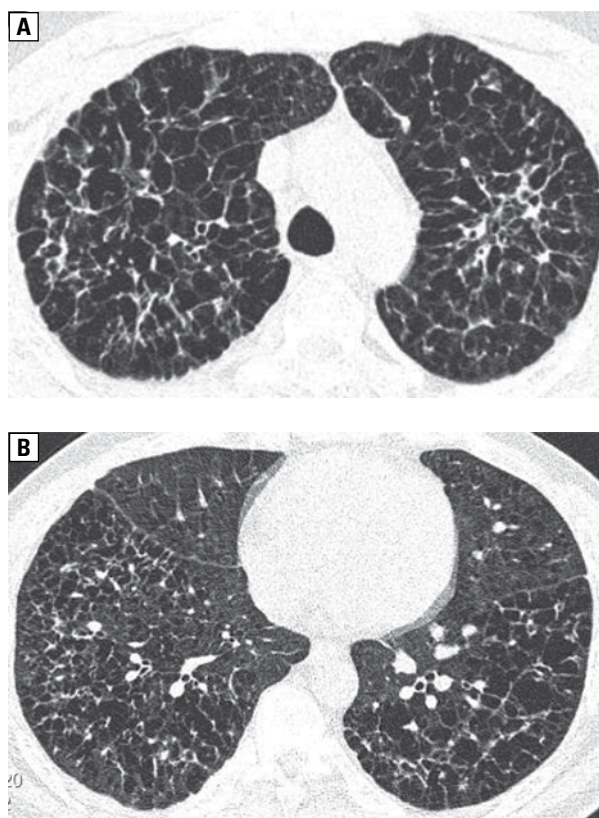


Figure 9A, B. High resolution computed tomography- multiple cysts, which predominate in the upper and middle lung zones with sparing of the costophrenic angles (courtesy of dr I. Bestry)

useful at early nodular stages of the condition, in the cases with the presence of thick-walled lacunae and in patients with MS-LCH [3]. Basing on the results observed in the group of 44 patients (41 children, 3 adults), Phillips *et al.* [28] have shown that PET is more sensitive imaging test assessing an early reaction to the applied treatment and early recurrence. However, PET has its limitations — it does not differ inflammatory and neoplastic changes from histiocytic pulmonary infiltrates.

Laboratory tests

In LCH patients, elevated serum inflammatory markers level is found. In case of patients with diabetes insipidus, serum hyperosmolarity with lower urine specific weight and its hyposmolarity are observed. Lesions in the liver manifest themselves in elevated hepatic enzymes concentration, in particular intrahepatic cholestasis and increased bilirubin level [3].

Pulmonary function testing

Patients with PLCH suffer from various ventilation disturbances. Initially, approximately 1/5 of patients do not have pulmonary function di-

sorders. In the remaining cases, obstruction with the features of pulmonary hyperinflation, often partially reversible, predominates. Lower vital capacity and total lung capacity are rarely reported, and affect mainly individuals with recurrent pneumothorax and pleurodesis. The commonest abnormality is reduced diffuse capacity of the lung for carbon monoxide, which is observed in about 70–90% of persons.

6-minute walk test (6MWT) helps to observe desaturation during exercise, and at advanced stages of the disease — a reduced walk distance [3, 7–12, 24, 25].

Bronchoscopy and bronchoalveolar lavage

Bronchoscopy does not reveal features typical of PLCH. The examination is performed in order to exclude other disorders, especially infections. The importance of transbronchial biopsy is limited and estimated at 10–50%, which is caused mainly by uneven distribution of lesions [29]. It is the most useful in the case of patients with nodular lesions seen on chest x-ray. Furthermore, there is a high probability of complication with pneumothorax during the procedure, in particular in subjects with extensive cysts. Elevated, over than 5% cells display CD1a expression in BAL with typical radiological pattern seen on chest HRCT is indicative of PLCH. However, only 10–20% of patients with PLCH show this pattern of findings. Elevated count of CD1a positive cells in BAL is not fully pathognomonic for PLCH as it may be found in healthy tobacco smokers, COPD patients and in the course of pulmonary fibrosis [30, 31].

Open lung biopsy

Open lung biopsy is often the necessary examination to definitely identify PLCH. Specimens should be taken from sites at which HRCT shows an abundance of nodules. When LCH has been confirmed by histological examination of specimens obtained from other foci (skin, bones), typical of the disease pulmonary lesions do not need to be additionally verified during biopsy [3].

Histological examination

The lungs of PLCH patients are marked with cystic and nodular lesions with a diameter up to 15 mm. In advanced forms of the condition, nodules regress and cysts are formed and pulmonary distension increases. The biggest accumulation of lesions is found in the upper and middle lung fields, and the costophrenic angles in 90% of cases remain unaffected [3, 16].

Initially inflammatory process with formation of granulomas takes place near small bronchi and bronchioles, extending to a varying degree into adjacent lung parenchyma. The presence of pigmented macrophages is frequently identified. In some cases, apart from the bronchiole-centred lesions, vascular alterations in the arterial and venous part of the vascular bed may be observed. Typical of the condition cysts develop in peribronchial space, where, apart from destroying granulomas, the bronchiole wall is destructed and the bronchioles are dilated. In consequence, polymorphic cystic formations appear with possible emphysematous changes and distension. Moreover, during fibrosis, stellar scars and fibrotic rings around the bronchioles are formed [7, 12, 29, 32].

At early stages of the disease, microscopic examination shows predominating poorly formed inflammatory nodules located in peribronchial spaces. Then, the inflammatory infiltrate extends into interalveolar spaces and blurs the lung architecture. Nodules contain a mixture of inflammatory cells, such as T cells, macrophages, monocytes and LC. Langerhans' cells are relatively large, with a pale cytoplasm and a convoluted nucleus with a longitudinal crease resembling a coffee grain. Electron microscopic evaluation shows in cytoplasm the so-called Birbeck granules, which are pathognomonic for LC. They are pentalaminar structures associated with cell membrane consisting of lectin. They may be also found in immunohistochemical examination using antibodies against langerin, *i.e.* antigen anti- CD207. LCs show expression of the S protein and CD1a antigen, whose detection is crucial for diagnosis (Figs 10–12). The structure of inflammatory granulomas varies, even within the same lung specimen. In advanced disease, in the central part of the nodule, a lacuna is formed, which is probably the part of the remaining lumen of the bronchiole or the effect of destruction mediated by cytokines and metalloproteinases. The bronchiole-centred lesions evolve forming symmetric stellar scars. Histiocytic granulomas may go along with pulmonary lesions, *e.g.* organising inflammation or lesions associated with tobacco smoke exposure, such as bronchiolitis, desquamative interstitial pneumonia, respiratory bronchiolitis with accompanying interstitial lung disease or emphysema.

In advanced disease, LCs are less abundant and the cystic and fibrotic pattern predominates.

In addition, in PLCH patients, internal wall of the vessels is thickened, both in the arteries and veins, which subsequently, results in pulmonary hypertension.

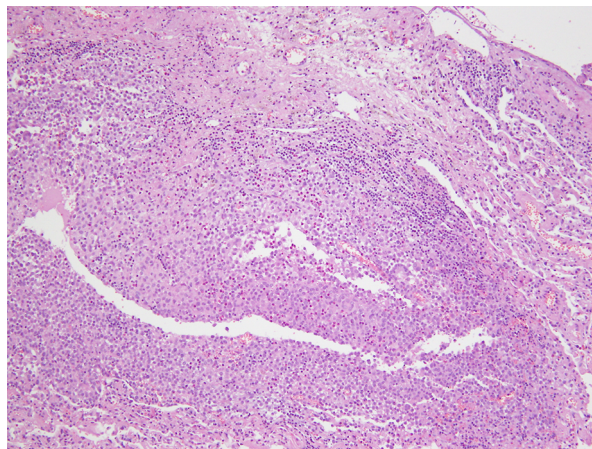


Figure 10. Langerhans cell histiocytosis. Low magnification view showing discrete nodular infiltration within lung parenchyma with the presence of central cavity (H+E × 200) (Courtesy of Prof. R. Langfort)

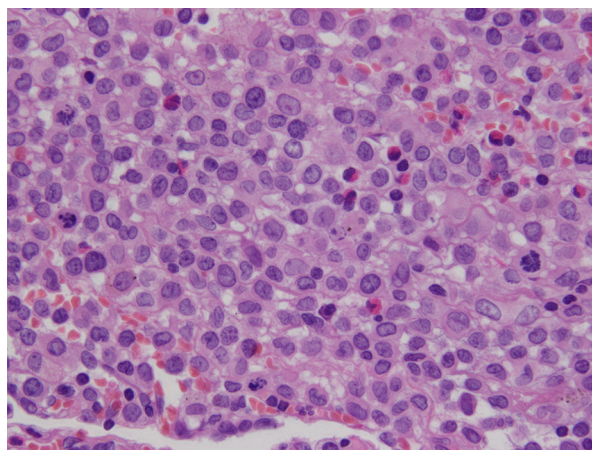


Figure 11. Langerhans cell histiocytosis. Large histiocytes with folded nuclei and few mitotic figures (H+E × 400) (Courtesy of Prof. R. Langfort)

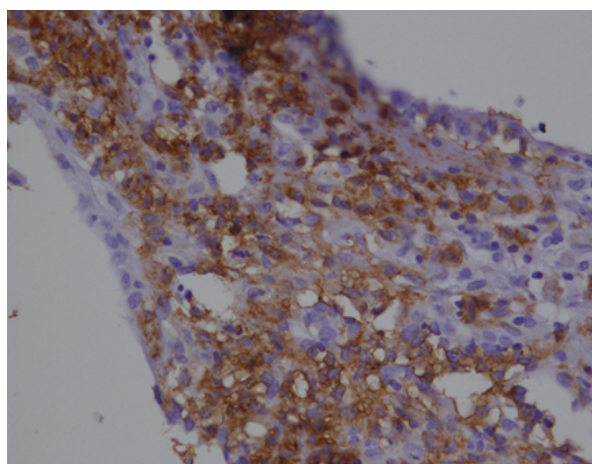


Figure 12. Immunohistochemistry for CD1a demonstrating strong positive staining in Langerhans cells (magn. × 200) (Courtesy of Prof. R. Langfort)

The patients qualified for targeted therapy need to be tested for mutations within the BRAF, ARAS, NRAS, KRAS and MAP2K genes [16–19]. Moreover, a novel diagnostic technique used in monitoring of treatment with BRAF inhibitors, is the analysis of the BRAF V600E gene mutation in circulating serum DNA [17].

Diagnosis

Diagnosis of LCH should be based on clinical and radiological tests, but the most important is histological assessment with immunohistochemical testing.

The definite diagnosis of LCH depends on adequate clinical presentation and the identification of Langerhans' cells in the biopsy material visible in electron microscopic visualisation, which show the presence of one of the following antigens: CD 207 (langerin), CD1a or Birbeck granules.

The tentative diagnosis of PLCH relies on adequate clinical presentation confirmed radiologically (chest CT scan reveals cysts and nodules seen mainly in the upper and middle lung fields).

However, any suspicious lesion found should be confirmed with histological examination.

Diagnosis needs to be validated with histological technique, in particular in patients with recommendations for systemic treatment [3, 33].

Differential diagnosis

Table 3 illustrates the list of disorders that should be taken into account while diagnosing the patients with cystic pulmonary lesions. In addition, special attention should be paid to people with solitary nodular lesions. As in such cases, the list of the reasons for the observed alterations may be longer, and may include sarcoidosis, hypersensitivity pneumonitis or infections.

Treatment

Treatment of LCH depends on the spread of the disease, affected organs, including lesions in critical organs and the degree of damage.

Smoking cessation

In case of patients with isolated pulmonary LCH (PLCH), the first recommendation is smoking cessation and detailed evaluation of the disease dynamics. In about 50% of PLCH patients, such approach leads to partial regression with a subsequent stabilisation of the disorder [3, 7–13, 20, 33–35]. To date no biological markers were found

Table 3. Diseases with cystic pattern of lung lesions

-
- Lymphangioleiomyomatosis (LAM)
 - Sporadic LAM
 - Tuberous sclerosis complex LAM
 - Pulmonary Langerhans cell histiocytosis
 - Erdheim-Chester disease
 - Birt-Hogg-Dubé disease
 - Lymphatic disorders
 - Lymphoid interstitial pneumonia
 - Light chain disease
 - Amyloidosis
 - Hyper-IgE syndrome
 - Genetic disorders
 - Ehlers-Danlos syndrome
 - Neurofibromatosis
 - Marfan syndrome
 - Proteus syndrome
 - Congenital cystic adenomatoid malformations
 - Respiratory papillomatosis
 - *Pneumocystis jiroveci*
-

identifying the patients for whom such conduct was sufficient and the patients in whom, apart from smoking cessation, the disease progressed [13].

Systemic chemotherapy

Systemic chemotherapy is recommended in the cases of MS-LCH, with or without the involvement of critical organs, SS-LCH with multiple lesions and SS-LCH with lesions in specific sites.

There is no established standard of chemotherapy to date. Although in children chemotherapy with vinblastine and prednisone proved to be effective, the results of treatment in adults turned out to be less successful [3, 7–13, 33–41]. In patients with multiple bone lesions and affected lungs, significantly higher effectiveness of treatment with cytarabine or cladribine compared to vinblastine and prednisone has been shown.

Glucocorticosteroids

Some authors recommend systemic steroid therapy in case of intensive symptoms from the respiratory system, in particular in patients with pulmonary nodular lesions. 1 mg/kg of prednisone per month with gradual reduction of a dose is suggested, so as the treatment does not exceed 6 months. Such therapy has not been confirmed by clinical trials, and recently its harmful effect have been underlined [3].

Chemotherapy

Basing on extrapolated observations made during randomised trials in children, various types of cytoreductive therapy (methotrexate, vinblastine, 6 mercaptopurine, etoposide) have been applied in adult LCH patients [3, 42–49]. However, the disease in adults runs a diverse clinical course and many drugs are differently tolerated. Tazi *et al.* [48] in a retrospective study assessed the therapy with vinblastine and steroids in 35 LCH adults, including 17 patients with pulmonary involvement. 70% of the subjects responded to the treatment but in more than 40% of patients, recurrence of the disease occurred within 5-year follow-up. The improvement in ventilation parameters due to applied treatment has not been noted in any case. In the group of 58 adult subjects with histiocytosis with multiple bone involvement, including 28% of patients with pulmonary involvement, Cantu *et al.* [38] have shown higher effectiveness of treatment with cladribine and cytarabine compared to vinblastine [38]. In the case of aggressive course of PLCH, 6 cycles of cladribine in the form of intravenous infusions, at a dose of 6 mg/m² per 5 days every 4 weeks is recommended. Effectiveness of the therapy is evaluated to exceed 75%.

In the case of progression after cladribine, salvage therapy is cytarabine administered at a dose of 100mg/m² per 5 consecutive days every 4 weeks. If the treatment is effective, next 6 cycles are administered. Another drug that proved to be effective as salvage therapy in children is clofarabine [3].

Vemurafenib and other BRAF inhibitors

These drugs offer new possibilities for targeted LCH therapy in patients with relevant mutations. The number of reports on these therapies is constantly increasing. The treatment seems to be effective but it does not fully eliminate LC, and discontinuation of treatment results in the disease progression [5, 18].

The researches conducted among French LCH children have shown that detection of BRAF mutation was associated with a weaker response not only to the first-line treatment (vinblastine and steroids) but also a weaker response to a second-line treatment and a higher proportion of recurrence [16, 19, 49].

MAP kinase inhibitors

Sorafenib, trametinib and cobimetinib have been reported to be effective in patients with aggressive form of histiocytosis. Furthermore, it

is vital to remember that presented mutations in Langerhans' cells are not excluding mutations, thus, in particular cases, there are recommendations to apply double targeted therapy [10, 16].

Single cases of the disease regression after the use of imatinib (tyrosine kinase blocker) have been reported [5].

Pneumothorax

In approximately 10-30% of patients, pneumothorax is the first symptom of the condition. It has been demonstrated that these persons have a greater probability of a consecutive recurrence. Moreover, this group often includes young men who smoke relatively less cigarettes and whose lung function is more affected by the disease. Taking into consideration the above data and clinical and financial effectiveness of HRCT in identifying PLCH patients, recommendation of HRCT in the case of the individual with spontaneous pneumothorax seems to be justified [24–26].

Pleurodesis is proposed in the case of recurrence of pneumothorax and concerns about 50% of patients in whom it occurred. It does not constitute a contraindication to possible lung transplantation [3].

Treatment of pulmonary hypertension

Pulmonary hypertension in the course of PLCH may be the consequence of progressive destruction of lung parenchyma, but in a lower proportion of cases, it also develops in the patients with stable ventilation parameters. Thus, to assess pressure in the pulmonary artery, echocardiography is advised. A positive result of drugs lowering blood pressure in the pulmonary artery, including inhibitors for phosphodiesterase and endothelin receptor in PLCH patients developing pulmonary hypertension has been observed. Treatment with prostacyclin should be applied with caution and mainly in patients with the features of venous changes (veno-occlusive disease, VOD), for episodes of severe pulmonary oedema in people using this drug have been documented. However, the main remedy is oxygen therapy and a possible and careful anticoagulation treatment [3, 21].

Lung transplantation

In patients with significantly damaged ventilatory function of the lungs, with the features of respiratory failure and those developing pulmonary hypertension, lung transplantation is an ultimate therapeutic option. Pulmonary hypertension is noted in 80–90% of subjects qualified for transplantation and constitutes an important

risk factor of the procedure. Prognosis of patients undergoing transplantation does not differ significantly from the individuals who undergo the procedure due to lymphangiomyomatosis or emphysema. Nearly 75% of patients survive 1 year, and more than 50% — 5 years. Poorer prognosis after transplantation is carried by people with MS-LCH. In about 1/5 of cases, recurrence of LCH in the transplanted organ has been found [3, 5].

Treatment of bone lesions

In some cases with solitary bone involvement, surgical removal of the focus is proposed or treatment of lesions with steroid injections. Patients with multiple bone lesions are treated systemically, surgically and/or with biphosphonates [3, 38, 40].

Hormone replacement therapy

Moreover, in patients with endocrinologic dysfunction, replacement therapy is recommended, with appropriate clinical, biochemical, enzymatic and hormone parameters being controlled [3].

Follow-up examination

The first follow-up examination should be performed after 3 months. The consecutive controls should depend on the disease activity and its advancement, but they should be performed at least every 3–12 months. It has been shown that people with isolated pulmonary histiocytosis during follow-up examinations do not need to have assessed many organs, and HRCT has a limited value in terms of the evaluation of the disorder dynamics. Of importance is the assessment of pulmonary functioning. As the patients are tobacco dependent, their participation in tobacco therapy programmes is highly recommended [3, 21, 29]. Tazi *et al.* [50] have shown that PLCH patients do not need to undergo x-ray examination of the lungs or bones every year, but only in the case of the occurrence of new signs. But the authors recommend constant monitoring of pulmonary function testing.

Prognosis

The natural course and prognosis of PLCH are unpredictable. It has been shown that PLCH patients have lower mean survival compared to people of the same sex and age [8]. Approximately 50% of patients experience spontaneous regression of the disease with improvement or stabilisation of the ventilation parameters only

after smoking cessation [3, 29, 32, 34]. In the remaining cases, the disorder gradually progresses, both in the lungs and in other organs. A lowered DLCO with stable ventilation parameters suggests increasing pulmonary hypertension and constitutes an indication to cardiac catheterisation. The presence of pulmonary hypertension worsens prognosis.

Tazi *et al.* [20] have demonstrated that the factors that impair prognosis in PLCH patients are age, exacerbation of obstruction, lowered PaO₂, a higher score obtained in SGRQ (St. George's Respiratory Questionnaire) and continued tobacco smoking (HR-3.28). An adverse effect on prognosis has the involvement of other organs [20].

A significant impact on the disease course have coexisting infections, which may lead to death.

LCH promotes the development of other neoplasms originating from the lymphatic and haemopoietic systems, including LCH overlapping with chronic myelogenous leukaemia. The condition also predisposes to developing lung cancer [1, 3, 5].

Pregnancy and labour

PLCH affects mainly young people, therefore, the approach during pregnancy and labour is crucial. Generally, pregnancy was not found to worsen the course of PLCH or diabetes insipidus. Undoubtedly, particular attention should be paid during perinatal period, and due to a greater probability of pneumothorax, caesarean section should be used [3, 51].

Conclusion

1. Langerhans' cell histiocytosis (LCH) is a rare disorder of unknown aetiology, caused by clonal proliferation of geno- and phenotypically altered Langerhans' cells (LC).
2. LCH may affect any organ. It usually involves the bones, lungs, skin and pituitary, lymphopoietic organs (lymph nodes, liver, spleen, bone marrow), alimentary system, thyroid and CNS.
3. Pulmonary lesions in the course of LCH may be as follows: isolated, anticipating even for many years the occurrence of systemic changes, or from the very beginning, the lungs may be one of the sites involved.
4. Tobacco smoke is a main causative factor for PLCH, and smoking cessation is the most vital recommendation.
5. Chest high resolution computed tomography is of particular importance in imaging

of histiocytic lesions, and the commonest pulmonary lesions are the following: centrilobular nodules, nodules with or without a central cavity, initially thick-walled cysts of various shape that may convolute forming the so-called clover leaves. As the disease evolves, cysts become bigger and thin-walled. In the majority of patients (over 90%), the costophrenic angles are not affected by the disorder.

6. The definite diagnosis of PLCH relies on adequate clinical presentation and the identification of Langerhans' cells in the examined material showing on the immunohistochemistry the presence of one of the following antigens: CD207 (langerin), CD1a or on the electron microscopic visualisation of Birbeck granules.
7. The presence of elevated by 5% the cells expressing CD1a antigen in BAL fluid, with typical radiological presentation visible on chest HRCT speaks in favour of PLCH diagnosis.
8. Treatment of LCH depends on the spread of the condition, involvement of organs, including alterations to critical organs and the degree of damage. Currently, the preferred cytostatic treatment option includes cladribine or cytarabine. In patients with isolated pulmonary involvement leading to respiratory insufficiency, lung transplantation is recommended.
9. PLCH patients have lower mean survival than individuals of the same sex and age. Adverse prognostic factors include as follows: age, tobacco smoking, severe obstruction, lowered PaO₂, a higher score in SGRQ, pulmonary hypertension and the multiple organ involvement.

Conflict of interest

The authors declare no conflict of interest.

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