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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Lymphangioleiomyomatosis and Langerhans cell histiocytosis – two case reports from our practice

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SUMMARY

Introduction Lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis are the most common pulmonary cystic diseases. Although they differ in pathogenesis, they share several features. The aim of this paper is to present the similarities and differences between these diseases, as well as to describe two cases from our practice.

Outlines of cases The patient with lymphangioleiomyomatosis (43 years old) had pulmonary changes detected during a regular examination within the underlying disease – tuberous sclerosis. Four years after starting therapy with everolimus, she was still respiratory asymptomatic, a slight radiological deterioration of cystic changes was registered, the diffusion capacity was declining (by 12%).

The second patient (23 years old) was admitted due to bilateral radiological lung changes and symptoms in the form of dry cough, quick fatigue, and chest pain. Pathohistological examination of the transbronchial biopsy showed numerous large-core histiocytes, immunohistochemically positive for CD1a and S100, so it was concluded that it was Langerhans cell histiocytosis. Cessation of smoking was advised. The follow-up examinations showed withdrawal of symptoms and an orderly finding of lung function, chest high-resolution computed tomography indicated slight regression of changes. In the meantime, the patient gave birth to a healthy child, the pregnancy and prenatal period were uneventful.

Conclusion These diseases are extremely rare and in cooperation with other specialties should be distinguished from diseases that mimic lung cysts.

Keywords: lymphangioleiomyomatosis; pulmonary Langerhans cell histiocytosis; cystic lung disease

INTRODUCTION

Diffuse cystic lung diseases are a group of disorders of different pathophysiological mechanism of occurrence, which is characterized by the presence of multiple lung cysts [1]. There are conditions that mimic lung cysts, both in clinical and radiological terms, and these are emphysema, bronchiectasis, cavitation, honeycombing, localized pneumothorax [2]. Individual cysts in the lungs may be present in healthy individuals, as well as a result of aging, previous infections, or trauma. In the past decade, owing to the development of high-resolution computed tomography (HRCT), the level of knowledge about these diseases has increased and disease evaluation is performed based on the radiological appearance of cysts (shape, size, wall thickness, and distribution) [1, 3].

Lymphangioleiomyomatosis (LAM) and pulmonary Langerhans cell histiocytosis (PLCH) are the most common pulmonary cystic diseases. Although they differ in pathogenesis, they share several features. Both diseases act as neoplastic disorders, have a cystic radiological pattern, affect young people in generative period, and can have extrapulmonary involvement.

The aim of the paper is to present the similarities and differences between these diseases as well as to describe two cases from our practice.

REPORTS OF CASES

The patient with lymphangioleiomyomatosis

Female patient (43 years old) was referred to the Institute of Pulmonary Diseases of Vojvodina in 2016 by a competent neurologist to clarify the etiology of bilateral diffuse pulmonary changes, detected during regular systematic physical examination within the underlying disease – TSC, which was diagnosed in her fourth month of life. Within her underlying disease, the patient had occasional epileptic seizures of the petit mal type, mild mental retardation, changes in the skin of the face and torso, previously ultrasound-verified tumor-altered structures of the kidneys and uterus (myomas).

Upon admission, the patient was asymptomatic; auscultatory finding was normal. X-ray of the chest showed no pathological changes on the lungs. HRCT verified bilateral and diffusely increased density of the lung parenchyma, which showed smooth thickening of the interlobular septa and a large number of clearly demarcated, randomly distributed hypodense

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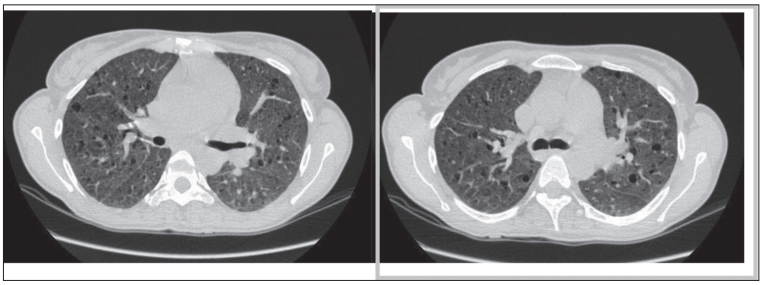


Figure 1. Chest high-resolution computed tomography of the patient with lymphangioleiomyomatosis before therapy

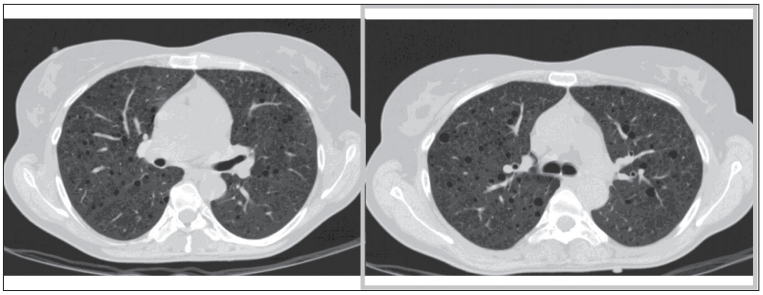


Figure 2. Chest high-resolution computed tomography of the patient with lymphangioleiomyomatosis after four years of therapy

Table 1. Findings of spirometry, diffusion capacity, and six-minute walk test at the first and control examination in a patient with lymphangioleiomyomatosis

Parameter	First examination		Control	
	[l]	%	[l]	%
FVC	3.25	89.29	3.66	103.7
FEV 1	2.75	87.58	2.93	96.38
FEV1/FVC		84.62		80.05
DLCO	7.61	82.09	6.35	69.93
6MWT	420 m	57%	350 m	47%

FVC – forced vital capacity; FEV1 – forced expiratory volume in one second; DLCO – diffusion capacity; 6MWT – six-minute walk test

(cystic) smooth-walled lesions of various shapes and diameters (up to 16 mm in diameter) (Figure 1). The pulmonary gas exchange was preserved at rest, while during exercise of two floors oxygen dropped by 1.3 kPa. The spiroplethysmographic finding was normal. During the six-minute walk test the patient walked 420 m (57%). Mild pulmonary hypertension (right ventricular systolic pressure – RVSP 35 mmHg) was verified by echocardiography (ECHO). Based on the clinical and radiological findings, the patient was diagnosed with LAM within tuberous sclerosis (TSC) complex. The patient started using everolimus (5 mg/day) in consultation with a neurologist and an immunologist.

The patient reported four years after the first examination (she had not reported for the advised annual check-ups at her own initiative). She denied respiratory problems, auscultatory finding was normal. HRCT indicated a discrete increase in the number of multifocal thin-walled cystic changes (Figure 2). The spirometric finding was normal, the diffusion capacity was declining compared to the first examination (Table 1). The ECHO finding was stationary. The use of everolimus was continued.

The patient with Langerhans cell histiocytosis

The patient (23 years old) was admitted to the Institute of Pulmonary Diseases of Vojvodina in 2018 due to bilateral radiological lung changes and symptoms (dry cough, chest pain and quick fatigue) that appeared two weeks before admission. She was a smoker (5 packs/year), without comorbidities.

The X-ray of the chest verified reticular changes in the upper and middle lung fields on both sides. Chest HRCT indicated bilateral diffuse, more pronounced in the upper and middle parts, thin-walled cystic lesions of various sizes, up to 15 mm in size (Figure 3). Spiroplethysmographic finding indicated a slightly reduced diffusion capacity (64%). The gas exchange was normal. Pulmonary hypertension (RVSP 43 mmHg) was registered on the ECHO. Pathohistological examination of the transbronchial biopsy showed numerous large-core histiocytes, immunohistochemically positive for CD1a and S100. It has been concluded that it is PLCH and additional examination (ultrasound and CT of the abdomen, endocrinological examination) ruled out systemic spread of the disease. The therapy included advice on the cessation of smoking, which the patient did.

The six-month follow-up examinations showed a good general condition of the patient and an orderly finding of lung function. In the meantime, the patient gave birth to a healthy boy, the pregnancy and perinatal period were uneventful. Chest HRCT three years after diagnosis (Figure 4) indicated slight regression of the bilateral cystic changes. ECHO showed an improvement, RVSP was within the reference limits. Diffusion capacity was not done due to the COVID-19 pandemic (the Institute of Pulmonary Diseases of Vojvodina was in the COVID system).

The paper was approved by the Ethics Board of the Institute for Pulmonary Diseases of Vojvodina and written consent was obtained from the patients for the publication of this case report and any accompanying images.

DISCUSSION

Pulmonary LAM is a disease involving the proliferation of smooth muscle cells of the blood and lymph vessels of the pulmonary interstitium, which leads to the formation of thin-walled cysts, pulmonary hemorrhage, and the involvement of lymph nodes can lead to chylous pleural effusions [4].

PLCH is a disease of former or current smokers, where cigarette smoking triggers abnormal proliferation and migration of dendritic cells, followed by the activation of the immune system, which lead to the formation of peribronchiolar nodules and later lung cysts [1]. These two diseases are reclassified from interstitial diseases into

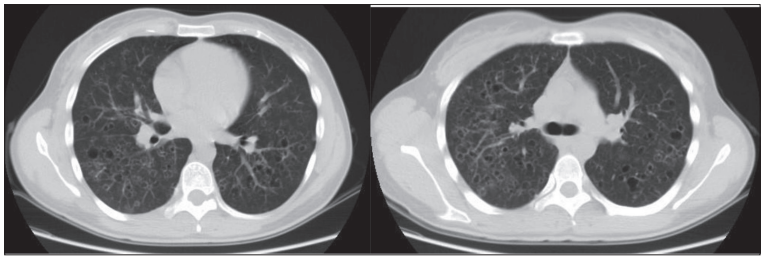


Figure 3. Initial chest high-resolution computed tomography of the patient with pulmonary Langerhans cell histiocytosis

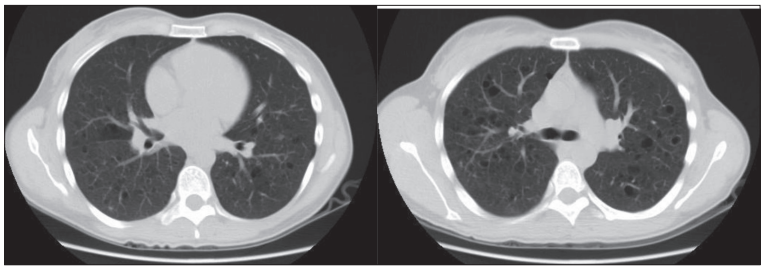


Figure 4. Chest high-resolution computed tomography of the patient with pulmonary Langerhans cell histiocytosis after three years

tumors – LAM belongs to perivascular epitheloid cell tumors (PEComa), classified as low-grade connective tissue neoplasms, and PLCH is classified as a bone marrow-derived dendritic cell tumor according to the World Health Organization [4].

Both diseases can occur in isolated or systemic form. LAM exists in a sporadic form (s-LAM) or within the tuberous sclerosis complex (TSC/LAM). Likewise, Langerhans histiocytosis may have its own isolated-pulmonary form (PLCH), or multisystem form (MS-LCH) [1].

These diseases are extremely rare. The annual incidence of PLCH is 2.2 per million, while the incidence of LAM is 1–7 per million inhabitants [3]. There are no official data for either Serbia or the region [5, 6]. PLCH is equally represented by sexes, s-LAM occurs only in women, a small percentage of men with TSC (13%) will develop LAM [4, 7]. Age at diagnosis is similar for both diseases (32–35 years) [4, 7]. Smoking is 90–100% present in PLCH, while LAM occurs mainly in non-smokers [4, 7]. Our patients were females in generative period (the PLCH patient was 23, the LAM patient was 43 years old). The patient with PLCH was a smoker; the patient with LAM was a non-smoker.

In clinical terms, both diseases may be asymptomatic when detected as an incidental finding, or may be accompanied by nonspecific symptoms (cough and/or difficulties in breathing), while acute shortness of breath is a consequence of pneumothorax [3]. In our cases, the patient with LAM was asymptomatic, previously diagnosed with TSC, which urged further diagnosis. The patient with PLCH had dry cough, chest pain and fatigue symptoms.

The radiograph in both diseases shows the changes primarily in the upper and middle thirds of the lungs, in the form of discrete cystic changes of the interstitium. HRCT is essential in diagnosing and monitoring both diseases. According to the criteria of the European Respiratory Society for the diagnostic algorithm of LAM, the finding of HRCT with the data on previously proven TSC may be sufficient to give a diagnosis, as was the case with our patient. HRCT findings in LAM describe multiple (more than 10), diffusely distributed, thin-walled (up to 2 mm), round, clearly demarcated, air-filled cysts with preserved or increased lung volume without other interstitial damage except for the possible presence of micronodular epithelial hyperplasia in TSC [7].

The HRCT findings of PLCH patients depend on the stage of the disease. In the early phase of the disease, it is dominated by centrilobular nodules, 1–10 mm in diameter. In the later stages of the disease, thin-walled cysts of different sizes develop. In most patients, a combination of nodular and cystic parenchymal lesions is registered. Both nodules and cysts follow the apicobasal distribution, they are larger and more numerous in the upper than in the lower lung parts [8].

Spirometry tests can be normal in early stages (both LAM and PLCH patients); however, as diseases progress, airflow obstruction and decreased lung diffusion capacity occur [1]. Our patient with LAM had a normal spiroplethysmographic finding, while 6MWT distance was reduced. The PLCH patient had slightly decreased diffusion capacity. With regard to pregnancy, a study showed that it is safe in woman with PLCH and not associated with deterioration of pulmonary function or blood oxygenation [9]. The pregnancy and perinatal period in our patient were uneventful.

PLCH cells (Langerhans cells) are 12–15 μm in diameter, with eosinophilic cytoplasm. Immunohistochemical staining of these cells showed the expression of CD1a, S100 protein and CD207 (langerin) [10, 11, 12]. The characteristic finding consists of granulomas composed of the Langerhans cells described above and infiltrates of inflammatory cells (eosinophils, lymphocytes, neutrophils). Granulomas can occur in any organ (most commonly in the skin, bones, the pituitary gland, the liver, and the lungs).

Current therapy for LAM are mTOR inhibitors – sirolimus and everolimus [13]. Sirolimus is indicated in patients with FEV1 ≤ 70%, chylous effusions, or a rapidly progressive form of the disease [1]. The drug sirolimus is registered under the name Rapamune® (Pfizer Manufacturing Deutschland GmbH, Freiburg im Breisgau, Germany), and everomilus under the name Afinitor® (Novartis Pharma Stein AG, Stein, Switzerland) in the Republic of Serbia. In addition to mTOR inhibitors, supportive therapy in the form of bronchodilators and oxygen is recommended, as well as respiratory rehabilitation [3]. Regular immunization against the seasonal flu is necessary, as well as the application of pneumococcal vaccine. As far as lifestyle is concerned, smoking and diving are prohibited [1]. Since our patient was previously diagnosed with TSC, the decision on therapy (everolimus) was made in agreement with a neurologist and immunologist.

Smoking cessation plays a major role in the treatment of PLCH, leading to stabilization and even regression of the disease [14]. However, in one-third of patients, the disease progresses even after smoking cessation. Numerous chemotherapeutic protocols have been tested so far, but with little success [14]. In our case, smoking cessation led to slight radiological regression and ECHO improvement.

For both diseases, pleurodesis is advised after the first episode of pneumothorax, and lung transplantation is indicated in the progressive form of the disease.

These diseases are extremely rare, far less frequently described in the literature compared to numerous other pulmonary diseases and should be distinguished from diseases that mimic lung cysts (emphysema, bronchiectasis, honeycomb lungs). A good cooperation of several specialists is necessary to establish the diagnoses of either LAM or PHLC.

Conflict of interest: None declared.

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Лимфангиолејомиоматоза и Лангерхансова хистиоцитоза – два приказа болесника из наше праксе

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САЖЕТАК

Увод Лимфангиолејомиоматоза и плућна Лангерхансова хистиоцитоза су две најчешће плућне цистичне болести. Премда се разликују у патогенези, имају неколико заједничких карактеристика.

Циљ рада је био описати сличности и разлике између ових болести, као и приказати два случаја из наше праксе.

Прикази болесникâ Болесници са лимфангиолејомиоматозом (43 г.) плућне промене су откривене током редовних контрола основне болести – туберозне склерозе. После четири године лечења еверолимусом она је и даље респираторно асимптоматична, са благом радиолошком прогресијом цистичних промена и падом капацитета дифузије (за 12%). Друга болесница (23 г.) хоспитализована је због обостраних плућних промена и симптома у виду сувог кашља, убрзаног замарања и болова у грудном кошу. Патохистолошким прегледом трансбронхијалне биопсије уочени су бројни хистиоцити, имунохистохемијски позитивни на *CD1a* и *S100*, те је закључено да се ради о Лангерхансовој хистиоцитози. Саветован је престанак пушења. На контролним прегледима болесница је била асимптоматична, налази плућне функције су били уредни, компјутеризована томографија високе резолуције грудног коша указивала је на благу регресију промена. У међувремену болесница је родила здраво дете, трудноћа и пренатално доба су протекли уредно.

Закључак Ове болести су изузетно ретке и у сарадњи са другим специјалностима треба их разликовати од болести које имитирају плућне цисте.

Кључне речи: лимфангиолејомиоматоза; плућна Лангерханосова хистиоцитоза; цистичне плућне болести