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## **Langerhans cell sarcoma with pulmonary manifestation, mediastinum involvement and bronchoesophageal fistula. A rare location and difficulties in histopathological diagnosis**

### **Abstract**

Langerhans cell sarcoma, a neoplastic proliferation of Langerhans cells with malignant cytologic features, is a very rare disease. Only a few cases have been documented in the English-language literature. Special methods, like immunohistochemistry and/or ultrastructural examination, are indispensable for appropriate diagnosis. Correct diagnosis is difficult. In fact, the disease is often misdiagnosed.

We present the case of a 47 year-old man with a large mass in the middle lobe of the lung, infiltrating anterior mediastinum, with multiple pulmonary round lesions and enlargement of local lymph nodes, and with bronchoesophageal fistula. Clinical examination indicated the possibility of advanced primary lung cancer.

However, the first histological diagnosis was Langerhans cell histiocytosis.

In spite of treatment, the progression of pulmonary lesions was observed. Therefore, upper- and middle-lobectomy was performed. The diagnosis of Langerhans histiocytosis was confirmed microscopically again. Nevertheless, the patient's condition deteriorated progressively and he was admitted to the National Tuberculosis and Lung Diseases Research Institute in order to establish a final diagnosis. Revision of earlier resected specimens, as well as an immunohistochemical and ultrastructural examination of samples, taken once again from a bronchial tumor, led to the establishment of a diagnosis of a unique form of Langerhans cell sarcoma with rare pulmonary manifestation.

**Key words:** Langerhans cell histiocytosis, lung, sarcoma, malignant histiocytosis X, Langerhans cell sarcoma

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### **Introduction**

Neoplastic proliferation of dendritic or histiocytic cells is exceedingly rare. Neoplasms derived from dendritic or histiocytic cells represent less than 1% of tumors occurring in lymph nodes [1]. They can appear at any age (the median age is 41 years). A fe-

male predominance has been described [2]. Correct diagnosis is often difficult. Unfortunately, the neoplasms are often recognized as benign reactive proliferation of these cells or other malignant processes, like lymphomas, melanoma and carcinomas.

Nowadays, special methods, like immunohistochemistry (IHC) reactions and/or ultrastructu-

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**Table 1. Classification of histiocytic and dendritic cell neoplasms (WHO 2008)**

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumour
- Indeterminate dendritic cell tumour
- Disseminated juvenile xanthogranuloma

ral examination, are indispensable for appropriate diagnosis. A variety of antibodies that react with monocytes, lymphoid cells and macrophages are derived. These include in particular CD21, CD35, S-100, CD68, CD1a, CD205 (langerin), CD20, CD3, CD4 and lysozyme [2, 3]. On occasion, it is necessary to extend the panel of antibodies by more IHC markers to exclude the possibility of other malignant neoplasms.

The classification of these malignant tumors remains controversial. The controversy is due to their extreme rarity and the variable terminology used in different publications.

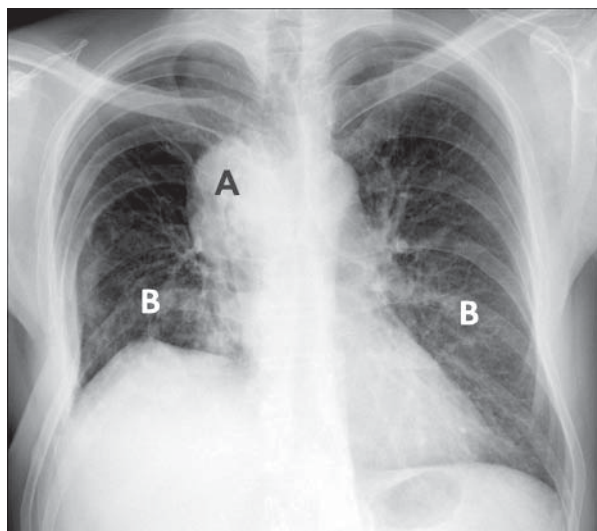
In the 'World Health Organization Classification of Tumours of Lymphoid Tissues' from 2008, several types of neoplastic proliferations are recognized (Tab. 1) [4]. The clinical course of neoplasms deriving from histiocytic and dendritic cells varies widely and is often difficult to predict. The prognosis for both histiocytic and interdigitating dendritic cell sarcomas is usually poor, characterized by an aggressive clinical course and sometimes generalized spread. However, follicular dendritic cell sarcoma is usually localized, with a tendency to local invasion and recurrence, but infrequent distant metastases [1, 3]. Neoplastic proliferation of Langerhans cells exhibits a wide spectrum of clinical course depending on the type of the process. Langerhans cell histiocytosis (LCH), especially a localized form of the disease, usually has a good prognosis [1, 5]. However, the neoplastic proliferation of Langerhans cells with overtly malignant cytologic features is classified as a sarcomatous variant, called the Langerhans cell sarcoma (LCS) [1, 3]. LCS is a very rare and usually aggressive neoplasm, with a poor response to therapy.

We present a rare case of LCS, clinically resembling lung cancer, invading mediastinum and pericardium, with multiple pulmonary round lesions and enlargement of local lymph nodes, and with bronchoesophageal fistula.

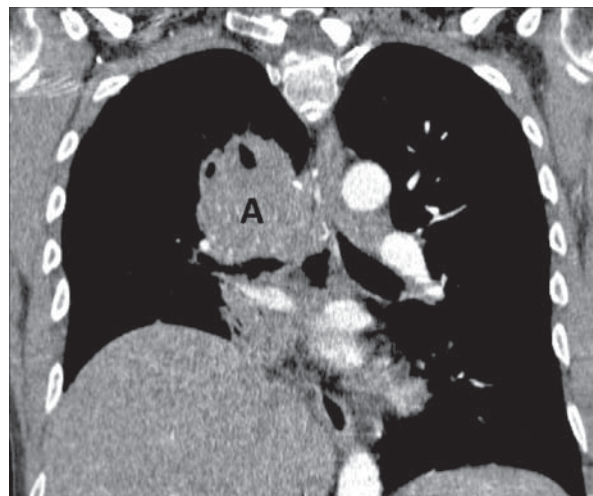
## Case report

A 47 year-old man, a smoker (30 pack-years) was admitted to the National Tuberculosis and Lung Diseases Research Institute (NTLDRI) in order to confirm the diagnosis of LCH and to plan the correct treatment.

The first symptoms appeared in August 2006 with productive cough and hemoptysis. At that time, the patient was taken to a district hospital because of a large tumor in the middle lobe with enlargement of hilar, paratracheal and periaortical lymph nodes, as disclosed on thorax CT examination. Bronchoscopy revealed a tumor obstructing the intermediate bronchus. A bronchoscopic biopsy of the tumor was performed for histological examination. Malignant mesenchymal neoplasm was initially suspected. However, after further consultation, the diagnosis of LCH was established. Prednisone in a dose of 1 mg/kg b.m./d was administered. Despite this therapy, the progression of pulmonary changes was noted, and in November 2006 cyclophosphamide in a dose of 100 mg/d p.o. was additionally administered. The immunosuppressive therapy proved ineffective. Therefore in February 2007 upper- and middle-lobectomy was performed. The diagnosis of LCH was confirmed microscopically again. Nevertheless, the patient's condition deteriorated, with concomitant pulmonary infections, a progression of tumor in the right hilum, and round opacities in the left lung being observed. Subsequently, in May 2007 he was admitted to the NTLDR. On admission he was in poor condition (performance status -3 in ECOG scale) and cachectic. Fever, loss of weight (more than 20% of his initial weight) and expectoration of a large amount of purulent sputum were noted. Laboratory examination revealed an elevated sedimentation rate (100 mm/h), CRP (62.7 mg/l), leucocytosis ( $24.6 \times 10^9/l$ ) with granulocytosis ( $22 \times 10^9/l$ ). Radiological examination showed a large tumor mass with central cavity in the right lung. The process extended into the mediastinum, constricting the trachea and caval vein superior, invading the great vessels of the chest and pericardium, involving the right main bronchus. Bilateral mediastinal and hilar lymphadenopathy as well as multiple pulmonary round lesions with cavities were revealed (Figs. 1 and 2). Bronchoscopy showed a narrowing of the main right bronchus communicating with a large cavity filled by exophytic masses. Inflammation of the left bronchus and a large amount of purulent discharge in the bronchial lumen were also seen. Gastroscopy disclosed infiltration of the lower part of the esophagus, with



**Figure 1.** The large tumor mass in the right lung (A) connecting with widened mediastinum. Multiple round lesions in both lungs (B) are visible



**Figure 2.** Chest CT , mediastinum window, coronal plane. The large cavitating tumor mass in the upper right area (A), infiltrating the mediastinum, constricting the trachea and vena cava superior, invading the great vessels, pericardium, and involving the right main bronchus

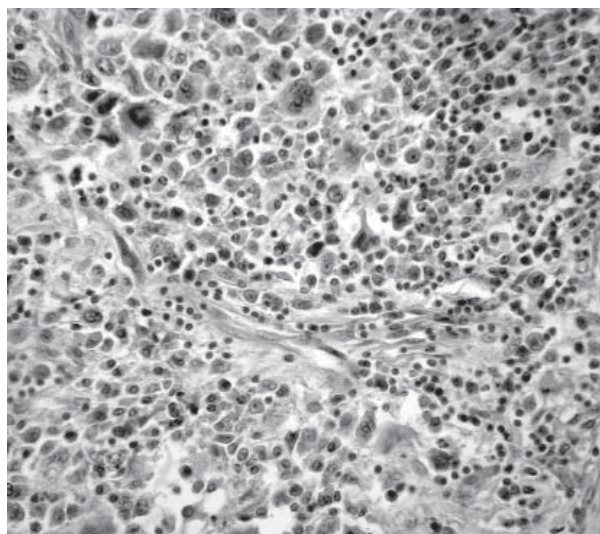
**Tabela 2. Panel of antibodies used for immunohistochemical study**

Antibody specificity	Marker	Clone	Dilution	Pretreatment	Source
Cytokeratin AE1/AE3	Epithelial cells	AE1, AE3	1:100	Microwave	Novocastra*
Cytokeratin	Epithelial cells	CAM5.2	Predilution	Microwave	Becton Dickinson**
Vimentin	Stroma cells	V9	1:100	Microwave	DAKO***
LCA	Leucocyte antigen	2B11+PD7/26	1:50	Microwave	DAKO
CD1a	Langerhans cells	MTB-1	1:40	Microwave	DAKO
S-100	Dendritic cells	Polyclonal	1:200	Microwave	DAKO
CD68	Pan-macrophage	KP-1	1:100	Microwave	DAKO
CD20	Lymphocytes (B type)	L-26	1:50	Microwave	DAKO
CD3	Lymphocytes (T type)	PS1	1:100	Microwave	Novocastra
CD30	Activated lymphocytes	BerH2	1:20	Microwave	DAKO
CD15	Activated lymphocytes	C3D-1	1:20	Microwave	DAKO
CD246	Chimeric NPM-Alk proteins	Alk-1	1:40	Microwave	DAKO
CD56/NCAM	Neuroendocrine cells	ERIC-1	1:100	Microwave	Novocastra
HMB45	Melanoma	HMB45	1:50	Microwave	DAKO
EMA	Epithelial cells	E29	1:50	Microwave	DAKO

\*Novocastra, Newcastle upon Tyne, UK; \*\*Becton Dickinson, San Jose, CA, USA; \*\*\*DAKO Glostrup, Denmark

fistula to the bronchus. A revision of previously estimated microscopic bronchial samples and resected specimen was performed. Further bronchoscopic biopsy from the main right bronchus was taken for histological, histochemical, immunohistochemical and ultrastructural examination. The extensive panel of antibodies for IHC study was used (Tab. 2). For all histologic slides, the microscopic examinations demonstrated diffuse, highly

cellular neoplastic infiltrate, composed of large, round, epithelioid cells with abundant pale eosinophilic cytoplasm, and oval to irregular or folded nuclei with vesicular chromatin pattern and prominent nucleoli. Many tumor cells showed frankly malignant cytologic features such as pleomorphic or hyperchromatic nuclei. Multinucleated giant cells were also seen. Some of the atypical cells had occasional delicate longitudinal nuclear gro-



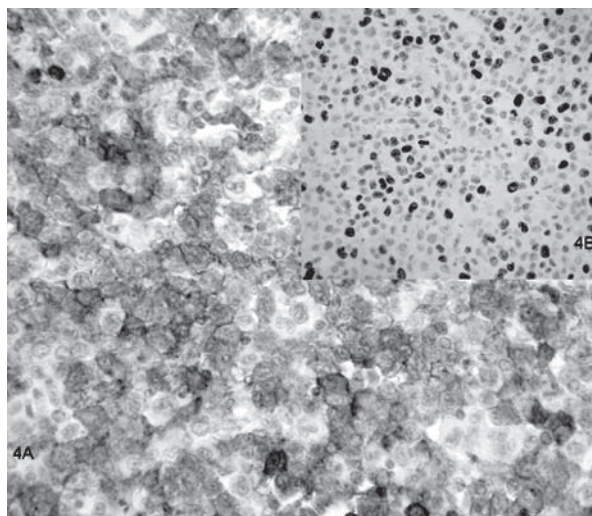
**Figure 3.** Microscopic appearance of the neoplastic infiltration. Pleomorphic and large, epithelioid cells with abundant eosinophilic cytoplasm, eccentric vesicular nuclei and prominent nucleoli are seen. Scattered multinuclear giant cells intermingled with lymphocytic infiltration and eosinophils are visible (hematoxylin–eosin, high magnification  $\times 100$ )

oves, which gave the cells a characteristic ‘coffee bean’ appearance, reminiscent of LCH. There were numerous mitotic figures, greater than 35 per 10 high power fields. Some of them were abnormal. Small foci of necrosis intermingled with neutrophils were identified. Occasionally, a few eosinophils and plasma cells, and small mature lymphocytes were dispersed throughout the neoplastic cells. Neoplastic infiltrate involved bronchial mucosa, lung parenchyma, pericardium and adipose tissue of mediastinum (Fig. 3). IHC studies showed that tumor cells strongly expressed CD1a, S-100 protein, vimentin and LCA. The cells were also focally weakly positive for CD68, but negative for cytokeratins (AE1/AE3, CAM 5.2), epithelial membrane antigen (EMA), HMB45, CD56, CD20, CD3, CD30, CD15 and ALK1. The Ki-67 proliferation index reached 70% (Fig. 4).

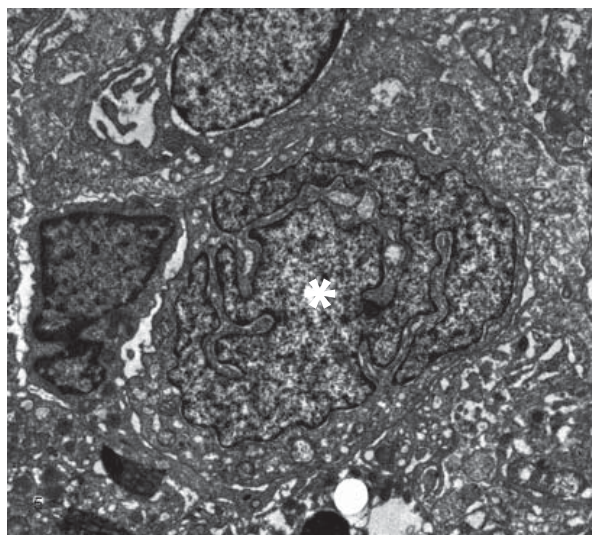
The ultrastructural analysis demonstrated Langerhans cells, characterized by a highly convoluted nucleus and numerous smooth vesicles in cytoplasm, and Golgi apparatus, as well as few rough endoplasmic profiles. The single Birbeck granules were found (Figs. 5 and 6).

On the basis of the microscopic picture and IHC reactions, as well as ultrastructural examination, the diagnosis of Langerhans cell sarcoma was established.

Antibiotics and antifungal treatment were administered and gastrostomy was performed. As a result, the status of the patient improved slightly and he was moved to the district hospital for supportive care.



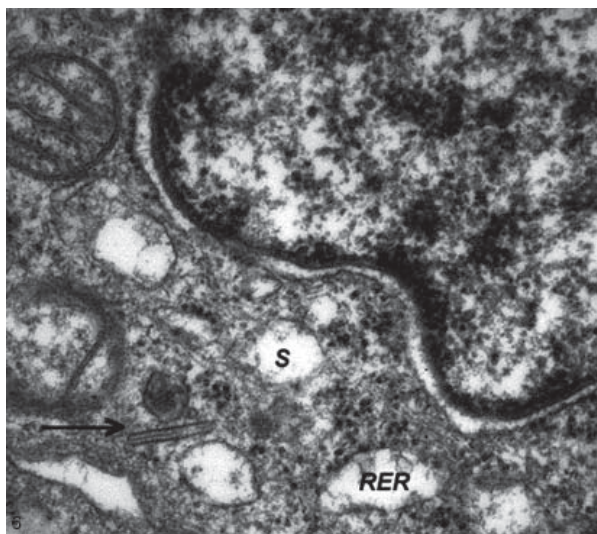
**Figure 4A.** Tumor cells are strongly positive for CD1a (immunohistochemical stain, high magnification  $\times 100$ ); **B.** A Ki-67 stain disclosed a high proliferative fraction of tumor cells (inset, immunohistochemical stain, high magnification  $\times 100$ )



**Figure 5.** Langerhans cell (\*) in the lung specimen tissue (electron micrograph, magnification  $\times 10\,000$ )

## Discussion

Langerhans cell sarcoma is an extremely rare malignant neoplastic proliferation of Langerhans cells. Few cases (about 23) have been reported in English-language literature [6–14]. The first case of LCS was published by Wood et al. in 1984. They described a 71 year-old patient with diffuse pulmonary infiltration and multiple nodules of the skin, each with an infiltration by Langerhans cells in histological specimens [14]. In 1991, Ben-Ezra et al. reported the results of a large study of 31 patients with neoplastic proliferations of Langer-



**Figure 6.** Langerhans cell with Birbeck granule (↑), disk-shaped, with a dilated rim along its periphery and smooth vesicles (S), and dilated rough endoplasmic reticulum (RER) (electron micrograph, magnification  $\times 75\ 000$ )

hans cells, including seven cases characterized by atypical and malignant-appearing Langerhans cells and a more aggressive clinical course. The authors concluded that some of the patients suffered from a malignant variant of LCH, which they named 'malignant histiocytosis X' [6].

The disease may develop *de novo* or by progression from pre-existing LCH [1, 11]. Recently, the case of LCS in a patient who underwent liver transplantation was reported [8]. Typically, LCS is characterized by multi-organ involvement, mainly of lymph nodes, spleen, liver, skin, bone marrow, thymus, lung and kidney [1, 6]. However, cases of the unifocal form of the disease have also been described, in which LCS appears as a single tumor with subsequent regional lymph nodes involved, resembling other malignant neoplastic processes [2]. The disease may occur at any age, with a small female predominance (1:1.5). The average age of patients was 48 (range from newborn to 81 years) [2]. The course of LCS has been very aggressive, frequently with a rapid dissemination, poor prognosis and high-grade mortality. Overall survival was approximately 50% [6, 14]. Morphologically, the sarcomatous variant of Langerhans histiocytosis  $\times$  is characterized by proliferation of intermediate to large size cells, with markedly malignant cytologic features. Occasionally, longitudinal nuclear grooves in atypical cells are seen and multinucleated forms appear. Mitotic figures are easily found, usually more than 50 figures per 10 high power fields. Rare infiltration by eosinophils and small foci of necrosis surrounded by

neutrophils can be identified [2, 6, 10, 14]. The neoplastic cells generally demonstrate immunophenotypic features similar to those of LCH, such as a consistent expression of S-100 protein and CD1a, lysozyme, and a positive reaction with CD68, CD45 and vimentin. They are negative for markers of follicular dendritic cells (CD21, CD 35), specific B-cell and T-cell associated antigens, CD30, EMA, and cytokeratins. Ki-67 labelling ranges from 10 to 60% with a mean value of 22% [6, 10].

Ultrastructurally, characteristic Birbeck granules in cytoplasm of tumor cells are usually identified. Theoretically, Birbeck granules should be found in all cases of LCS which have been properly examined [6, 15]. According to the WHO classification, tumors with microscopic features resembling LCS, and with expression of CD1a and S-100 protein but without evidence of Birbeck granules, should be classified as 'indeterminate dendritic cell tumors' [4, 10].

Tani et al. put forward a proposal for diagnosis of malignant neoplasm of Langerhans cells on the basis of two criteria: (a) malignant cytological features as atypia and frequent mitotic figures, and (b) proliferation of tumor cells containing Birbeck granules [16]. Nevertheless, immunohistochemical or ultrastructural examinations are necessary in each suspected LCS case.

Primary pulmonary localization of LCS is extremely rare. Recently, two cases of LCS in this location have been described [10, 11]. One of them was an 81 year-old man with a large tumor occupying the right lower lobe of the lung and mediastinum with enlargement of regional lymph nodes [10]. The second case was detected in the left lower lobe of the lung of a 34 year-old man. LCS arose from an antecedent pulmonary LCH [11]. In both cases, the tumor cells were strongly positive for S-100 protein and CD1a. They were also focally positive for CD68. Unfortunately, ultrastructural examination failed to demonstrate any Birbeck granules in the cytoplasm of tumor cells in either case. The absence of Birbeck granules was explained, in the former case, by the fact that fresh tissue was unavailable for examination, and, in the latter case, by the fact that neoplastic cells may lose their ultrastructural characteristics or their immunophenotype as they become less differentiated and more atypical. Nevertheless, the diagnosis of LCS was established in both cases. Overtly malignant cytological features of tumor cells and a very high proliferation rate, and especially IHC analysis, favored the diagnosis of LCS [10, 11].

In our case we confirmed LCS of the lung not only via IHC but also by ultrastructural examination. On electron microscopy, Birbeck granules and lysosomes were found in the cytoplasm of neoplastic cells.

A pathologic diagnosis of LCS is difficult, especially because of the rarity of the disease and morphological resemblance to other neoplasms. Before the development and widespread use of IHC techniques, LCS was diagnosed very infrequently. Most cases were misdiagnosed, often as other lymphoproliferative disorders, either as benign reactive or malignant processes, especially diffuse large B-cell lymphoma (mainly anaplastic large cell lymphoma) and peripheral T-cell lymphoma associated with haemophagocytosis. Other tumors, such as undifferentiated large-cell carcinomas, malignant melanoma and soft tissue sarcomas with epithelioid differentiation, primary or metastatic, have also been confused with LCS [6, 15]. Nowadays, the application of immunohistochemistry has improved the diagnosis of LCS.

Generally, using a broad panel of antibodies is an invaluable tool for diagnosis of LCS. IHC panel should include markers reactive with histiocytes and dendritic cells (CD56, LYS, CD1a, Langerin-CD207, CD21, CD35) as well as S-100 protein and other antibodies making it possible to distinguish between LCS, on the one hand, and more common tumors such as carcinomas, malignant melanoma and epithelioid soft tissue sarcomas [2]. Both CD1a and S-100 protein expression are needed for the diagnosis of LCH/LCS. However, LCS is identified by overtly malignant cytologic features and high proliferation index [1, 2].

Recently, the use of CD56 (NCAM-neural adhesion molecule) marker in the diagnosis of LCS has been recommended. A report by Kawase et al. describes four cases of LCS arising in lymph nodes and at various visceral sites, in which they showed CD56 expression on the tumor cells, in addition to a positive reaction with CD1a, S-100, and langerin (CD207). For control, they also examined CD56 in cases of LCH. The results of the staining of the LCH cells were negative. In the authors' opinion, CD56 marker could be a clinically relevant biologic marker for predicting an intractable course of Langerhans cell neoplasm, and very helpful in differentiating between LCH and LCS, particularly when definite morphologically-based distinction is difficult [17]. Unfortunately, we could not confirm this observation because IHC reaction with CD56 was negative in our case. However, given the small number of cases reported by Kawase et al., further investigation is necessary to establish whether CD56 is a good marker for diagnosis of LCS.

The usefulness of fine needle aspiration cytology for diagnosing LCS is also limited. However, cytology may be a helpful means of correc-

tly classifying LCS as a primary, non-metastatic lymph node neoplasm, as well as estimating the stage of the disease and follow-up of recurrences [12].

The course of LCS is very aggressive, as is that of other malignant neoplasms showing rapid dissemination and distant metastasis, and usually short survival times. Unfortunately, due to LCS's rarity, no curative methods have been developed to date. It seems that chemotherapy including steroids may help slow, or even stop, the progression of the disease [10, 13].

## Conclusions

Langerhans cell sarcoma is a very rare neoplasm and characterized by multi-organ involvement. Diagnosis is very difficult because of the rarity of these tumors and depends on an array of histologic, ultrastructural and most importantly immunohistochemical studies.

We present a rare case of LCS with an unusual pulmonary manifestation and with enlargement of hilar and mediastinal lymph nodes. The first microscopic diagnosis was LCH. But the clinical course of the disease and a revision of microscopic slides established a diagnosis of LCS. Our case is an example of the diagnostic difficulty arising from the rarity of LCS. To the best of our knowledge, this is the first case of LCS affecting the lung and with bronchoesophageal fistula, confirmed not only by immunohistochemical studies but also by ultrastructural examination. We believe the presented case of LCS with pulmonary manifestation is also the first published case in Polish literature.

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