Pol J Pathol 2003, 54, 1, 65-73 PL ISSN 1233-9687

*Bolesław Papla[1], Eugeniusz Malinowski[3], Ewa Niżankowska-Mogilnicka[2], Grażyna Bochenek[2]*

# Pulmonary Langerhans Cell Granulomatosis. A Study of 11 Cases

[1]Chair and Department of Clinical and Experimental Pathomorphology,
[2]II Department of Internal Diseases, Pulmonary Clinic, Collegium Medicum, Jagiellonian University, Kraków
[3]Thoracic Surgery Ward of Specialistic Center of Lung Diseases, Bystra Śląska

**This report based on 11 cases of pulmonary Langerhans cell granulomatosis describes the histological features of this condition and presents results of discours about its character.**

## Introduction

Histiocytosis X or Langerhans cell histiocytosis is a relatively rare disorder covering a spectrum of three diseases:

1. eosinophilic granuloma;
2. Hand-Schüller-Christian disease (exophthalmus, diabetes insipidus, changes in cranial bones);
3. Letterer-Siwe disease (as an acute neoplastic variant in young children).

This classification was first proposed by Lichtenstein in 1953 [29] who regarded Langerhans cell proliferation as a common denominator. Already in 1941 Farber [13] suggested a correlation between these disease entities but he was not heeded much. Even today this correlation is opposed by some investigators. Now it is important to establish which of these disorders is of reactive nature and which is neoplastic and in what way they are interrelated. It is of interest that although changes in the lungs in the generalised disease have been known since the 1920, the most frequent process accounting for up to 85% of cases was described by Parkinson as lately as in 1949 [40].

Langerhans cells, also referred to as dendritic, first described by Langerhans in 1868 [28] originate from the bone marrow and are present mainly in the epidermis in the amount of 500 - 1000 per $mm^2$ and other organs for instance lymph nodes (dendritic cells, interdigitating reticulum cells). In 1961 Birbeck [4] identified by electron microscopy small tennis racket-shaped granules 200 to 400nm in length, of constant diameter 33nm, referred to as X granules or Birbeck's granules or Langerhans granules - the role of these granules being unclear. Upon identification Langerhans believed that dendritic cells were of neural origin. Now it is known that they are associated with the immune response, forming its afferent part and they are antigen-presenting cells. They are not visualised by routine HE staining and they are found mainly in the parabasal section of the epidermis. The cells have a single or several, most frequently two or more processes. The nucleus is oval or kidney-shaped with irregular borders or invaginated, containing a relatively large nucleolus. The cytoplasm is moderately abundant, most frequently clear. Numerous Birbeck's granules are dispersed haphazardly, sometimes more frequently around the Golgi apparatus [19]. The role of Birbeck's granules is unknown but exist two theories about it: they are bound with the cellular membrane as a site of endocytosis and antigen processing; other investigators believe they are secretory granules produced in the Golgi apparatus [19]. Structures resembling Birbeck's granules are sometimes described in hairy-cell leukemias, other lymphatic leukemias and monocytic leukemias.

Immunohistochemically the cells express CD1a(OKT-6), HLA-DR, LCA antigens (in frozen sections), protein S-100 and vimentin, placental alkaline phosphatase and peanut lectin agglutinin. They also show positivity for the presence of catepsin D and E and they are negative for CD30, LN-1 antigens, lysozyme, alpha-1-antitrypsin, EMA and CD15. Precursor Langerhans cells do not contain typical granules and originate from monocytes, but they are S-100 and CD-1a positive. Histochemical studies show that Langerhans cells are positive for adenosine triphosphatase, alpha-naphthylacetic esterase, alpha-naphthylbutyric esterase and acid phosphatase but not for tartrate-resistant acid phosphatase, 5'-nucleotidase, peroxidase, chloroacetate esterase and beta-glucuronidase [23, 53, 54].

Histiocytosis X cells show similar histochemical and immunophenotypic reactions as normal dendritic cells but in frozen sections [30, 53, 54], additionally they are positive for CD2 [16], cytoplasmic CD3 [18], CD4, CD14, HLA-A, HLA-B, HLA-C and HLA-DR but not for other B and T lymphocytic antigens. Histiocytosis X cells are different from normal cells in the expression of adhesion molecules CD54 (ICAM-1) [16], CD58 (LFA-3), CD11c [16], CD49D (VLA-4) [53, 54]. They show a stronger expression for GM-CSF, TNF-alpha, interleukin 1-alpha and beta, interfe-

**TABLE 1**

A series of pulmonary histiocytosis in our study

| No of slides | | Clinic Hospital | Age | Sex | Initial diagnosis | Changes in other organs | Treatment |
|---|---|---|---|---|---|---|---|
| 1269969 | DI | John Paul's II Hosp. | 49 | K | Lesions scattered in the lungs | Skull, skin | Corticoids, metothrexat |
| 1311246 | WR | Bystra Śląska | 26 | M | Lesions scattered in the lungs | | Corticoids |
| 1315766 | JS | Bystra Śląska | 20 | M | Lesions scattered in the lungs | | Corticoids |
| 1375509 | PM | Bystra Śląska | 59 | K | Lesions scattered in the lungs | | Corticoids |
| 1397242 | KM | Bystra Śląska | 25 | K | Lesions scattered in the lungs | | Corticoids |
| 1404317 | PH | Pulmonary Clinic | 40 | K | Sarcoidosis | | No treatment |
| 1414942 | OZ | Bystra Śląska | 29 | M | Sarcoidosis | | Corticoids |
| 1415986 | ZJ | Bystra Śląska | 68 | M | Lesions scattered in the lungs | | Corticoids |
| 1434500 | KM | Bystra Śląska | 28 | M | Histiocytosis X | | Corticoids |
| 1441342 | BK | Pulmonary Clinic | 46 | M | Pulmonary fibrosis | | Corticoids |
| 1452187 | ZJ | John Paul's II Hosp. | 47 | M | Lesions scattered in the lungs | Infiltration in the spine | Corticoids |

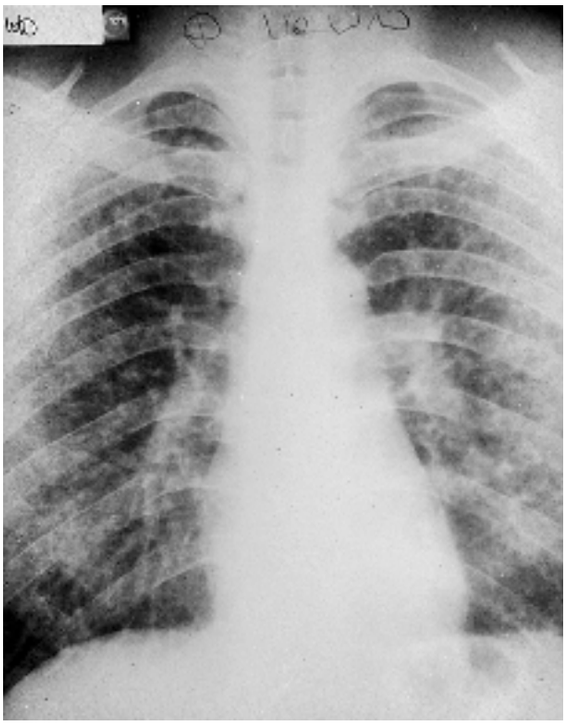

Fig. 1. Anterior chest radiogram with scattered nodular changes in both lungs.

ron gamma and TGF-alpha and beta. They are also positive for fascin, which according to some investigators is localised in normal dendritic cells [41]. In contrast, placental alkaline phosphatase is expressed more strongly than in normal dendritic cells. Some of them showed expression for CD68 antigen and lysozyme [14]. A small proportion of cells also shows proliferative features - PCNA+ and Ki-S1+, Ki67+ [18]. In pulmonary histiocytosis these cells are CD1c+, CD25+, CD4+, CD80+ and CD86+ according to Tazi et al. [47, 48]. Genetic studies reveal diploidy, immunoglobulin heavy chain germ line, immunoglobulin beta, gamma and delta, T-cell receptor chain [53, 54]. Clonal proliferation of these cells has been observed in multiple lesions. It should be remembered that in most studies dendritic cells were obtained from histiocytosis X of other than pulmonary location.

Dendritic cells have no phagocytic abilities typical of macrophages and phagocytes. In patients after bone marrow transplantation a new population of these cells originating from macrophages develops in the skin.

At present Langerhans cell histiocytosis is classified into three variants [52]:

- single-organ involvement, mainly the lungs (over 85% of cases);
- single-organ involvement, other than the lungs: bone, skin, hypophysis, lymph nodes, rarely thyroid, liver, spleen and brain;
- multi-organ involvement with (5 - 15%) and without the lungs.

According to some investigators pulmonary histiocytosis X as a non-neoplastic, reactive process should be discriminated from other neoplastic variants (WHO) [23, 52].

## Material and Methods

From 1994 to 2000 we had diagnosed 11 cases of pulmonary histiocytosis X [38, 39]. There were 4 women and 7 men aged from 20 to 68 years, mean age 39 years (Table 1). The symptoms, mainly cough and dyspnea lasted several months on average. Chest X-rays showed disseminated nodular or infiltrating changes with cystic lesions in the central

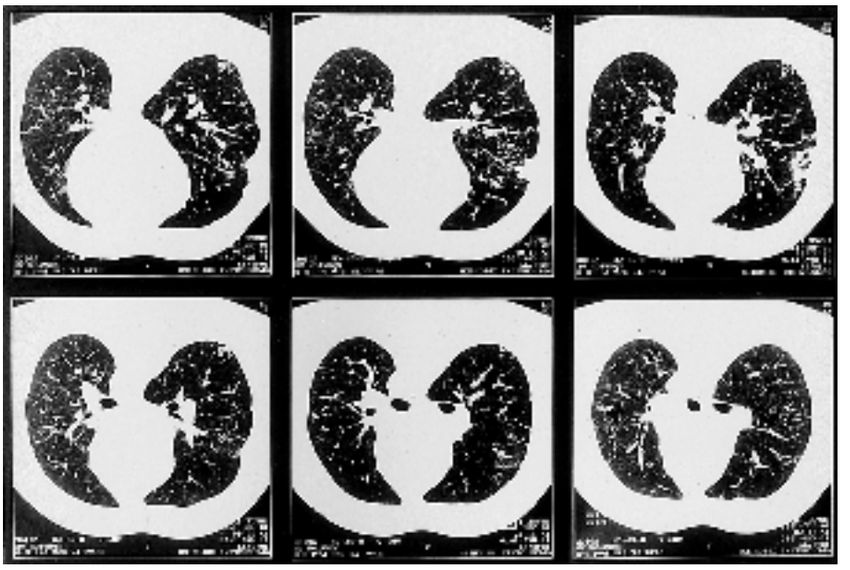

Fig. 2. CT of thoracic region in a patient with histiocytosis X. Scattered nodular changes and small cysts mainly in the peripheral parts of the lungs.

part in both lungs (Fig. 1). The condition was initially diagnosed as sarcoidosis, interstitial fibrosis and other disseminated processes, only in two cases computerised tomography suggested the presence of histiocytosis X (Fig. 2). To establish the final diagnosis explorative thoracotomy was performed in one patient whereas in the remaining ones a thoracic camera was used for subpleural lung tissue sampling.

Tissue was fixed in formalin and embedded in paraffin blocks for routine histopathological and immunohistochemical studies, mainly for the presence of S-100.

## Results

Histological study revealed disseminated stellate or nodular lesions located subpleurally or in the vicinity of bronchi (Fig. 3), occasionally in the central part of the lungs with irregular cystic space (Fig. 4). The lesions were interspersed with normal pulmonary parenchyma containing alveoli with quite numerous phagocytes, frequently with the brown pigment in the cytoplasm. Infiltrates were composed of Langerhans cells with moderately abundant pinkish cytoplasm and distinct nuclear envelope, lying mainly in the lung stroma and occasionally in the lumen of aerial spaces (Fig. 5). Variable numbers of eosinophils, macrophages, lymphocytes, plasma cells and neutrophils were also the components of the infiltrate (Fig. 6). Fibrosis varying in intensity was a concomitant process. Immunohistochemistry for the presence of S-100 protein confirmed the predominant presence of Langerhans cells in the infiltrate (Figs. 7 and 8).

## Discussion

The incidence of pulmonary Langerhans cell histiocytosis is not established yet, but probably it is higher than estimated [49] as a number of patients do not agree to lung sampling by thoracotomy, which is a prerequisite for diagnosis. A possibility of using a thoracic camera in last years supply more biopsies taken from lung.

It is estimated that about 25% of patients are asymptomatic and the process may disappear spontaneously. Knudson et al. [25] in the surgical material identified the disease in 2.6% of 381 patients with disseminated lesions in the lungs, whereas Gaensler et al. [15] in 3.4% of 502 cases. In the USA it is diagnosed in 2 - 5 cases per million children [27]. Nicholson et al. [36] found the disease in 5 cases per million. The disease affects mainly white people. It develops in both sexes with varying frequency: M/F - 3.7:1 [3, 10, 42, 45], equally in men and women [9, 44] or more frequently in women [1, 8, 9, 22, 49, 51]. Pulmonary histiocytosis affects mainly young people in the third and fourth decade [1, 8, 9, 22, 49, 51].

The aetiology is unknown, but one of the main pathogenic factors is cigarette smoking, less frequently marihuana, and probably some immune disorders in patients [19, 23, 52]. Cigarette smoking is observed in over 90 - 95% of patients [3, 8 - 10, 22, 44, 49, 51]. These people usually are heavy smokers, however there is no correlation between the intensity of smoking and the severity of the disease process. It is hardly advisable to relate the disease with smoking in children. Smoking is thought to increase the secretion of bombesin-like peptides by neuroendocrine cells in the lungs. Consequently cytokines are released by macrophages, thus stimulating fibroblast proliferation and fibrosis in the lungs. Glycoprotein present in the tobacco smoke is an immunostimulator, which induces the production of lymphokines by lymphocytes, especially interleukin 2, which normally inhibits the proliferation of histiocytes, but an abnormal, reverse response may occur in histiocytosis [52]. In the literature there is a report on effective treatment of histiocytosis with interleukin in one child in Japan [52].

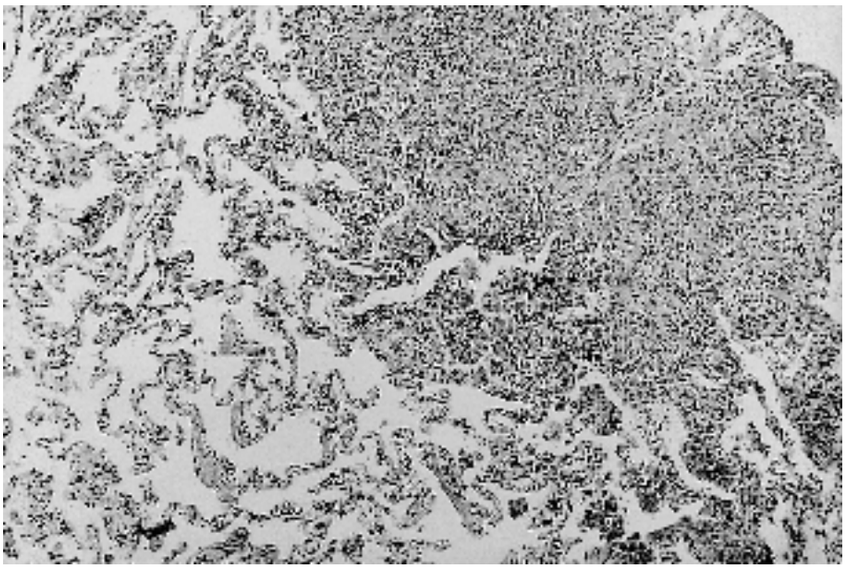

Fig. 3. Subpleural nodular granuloma with partly stellate margins separated from the lung parenchyma. HE.

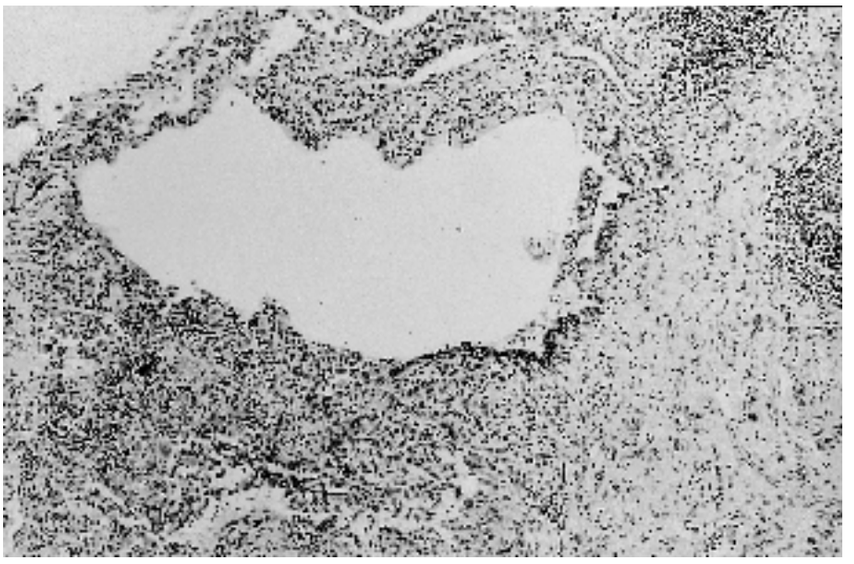

Fig. 4. A larger cystic lesion surrounded by a typical granulomatous tissue. HE.

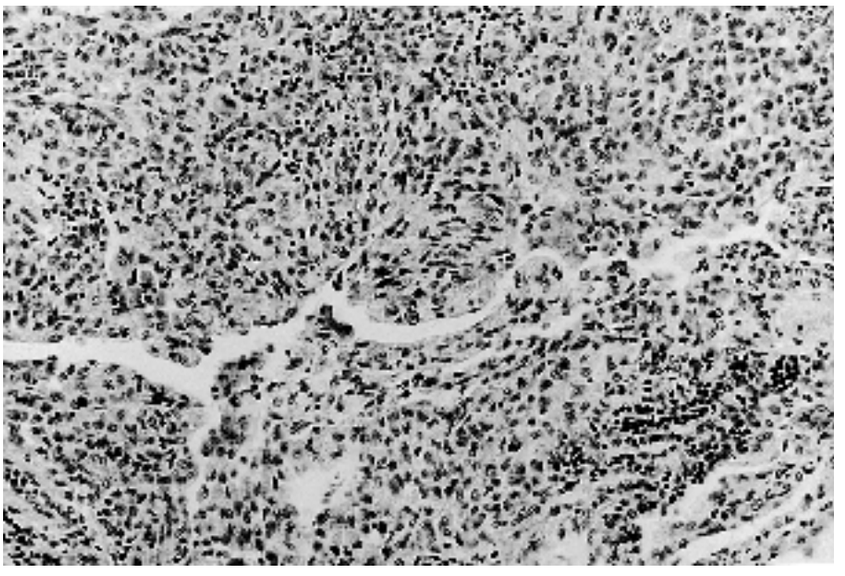

Fig. 5. Langerhans cell granuloma composed of dendritic cells with bright cytoplasm interspersed with lymphocytes and few granulocytes. HE.

Pulmonary histiocytosis is also associated with the macrophage production of TNF-alpha, TGF-beta, GM-CSF, interleukin 1 and 6 and interferon gamma. The role of GM-CSF is especially important as it stimulates the development of Langerhans cells from stem cells (CD-34 positive) [52]. In animal models this factor was associated with pulmonary fibrosis.

Immune complexes, present in the smokers' blood as a result of T-helper stimulation and immunoglobulin production by stimulated B lymphocytes are also believed to play some role [52].

Primary injury to glandular epithelium of small bronchi is also considered as an etiological factor, stimulating the accumulation of Langerhans cells in the form of a granuloma as an immune response. This manner of granuloma development would account for the bronchocentric localisation and relationship with cigarette smoking and other primary factors of epithelial injury [48].

The role of a genetic factor is not well understood, there are however single reports on familial occurrence (for instance father and son) [1, 20]. The correlation with viral processes has not been confirmed [31, 57].

Of note is the occurrence of some neoplastic growths concomitantly with histiocytosis X; they are mainly non-Hodgkin's lymphoma and Hodgkin's lymphoma. Sometimes pulmonary histiocytosis develops in patients receiving chemo- or radiotherapy for Hodgkin's lymphoma [12, 34, 50].

Clinical manifestations of pulmonary histiocytosis X include dry cough and dyspnea in 2/3 of patients. Body weight loss, fever, nocturnal sweating and anorexia occur in 1/3 of cases [51]. Hemoptysis is seen in about 5% and in these cases it is necessary to exclude the neoplastic process. Chest pain is of pleural origin and sometimes is associated with pneumothorax present in 10 - 20% of cases [9, 10, 22, 44, 51]. About 25% of patients are asymptomatic. The duration of clinical symptoms is estimated to be 6 months on average. Functional lung tests reveal the obstructive pattern, and the level of carbon monooxide transfer factor (TLCO) with its decrease in 70 - 100% may be of diagnostic help [8, 9, 51].

Apart from routine radiological examination this relatively rare disease requiring for diagnosis high resolution computerised tomography, and tissue sampling while using a thoracic camera is decisive. Radiological changes in the lungs include initially reticular changes, then scattered small and large nodules progressing into cysts in the advanced stage. The lesions predominate in the middle and upper lung fields, sparing the costophrenic angles, they are usually bilateral and symmetrical in both lungs [6, 7, 33].

There are numerous classifications of the extent and intensity of radiological changes. LaCronique et al. [26] propose a 7-degree classification:

- degree 1 - reticular lesions,
- degree 2 - micronodules up to 2mm in diameter,
- degree 3 - micronodules 2 to 5mm,
- degree 4 - nodules 5 to 10mm,
- degree 5 - nodules over 10mm,
- degree 6 - small cysts up to 10mm in diameter with typically thin walls,
- degree 7 - cysts and caverns over 10mm in diameter.

According to these investigators radiological changes of degree 3 and 6 are most frequent.

Apart from radiology bronchoalveolar lavage (BAL) for the presence of dendritic cells may also be of help. It should however be remembered the dendritic cells, identified by S-100 or CD1a markers are also present in other conditions. Their amount is decisive - over 5% of all cells [2, 48, 49], however histiocytosis X cannot be excluded if it is less than 5% [42, 46]. Examination of skin or bone changes, if present may also help in establishing the diagnosis.

Transbronchial biopsy rarely provides the correct diagnosis. Housini et al. [21] were able to diagnose correctly only 2 out of 12 cases, therefore transbronchial biopsy is of limited value. If material taken during exploratory thoracotomy or videothoracoscopy is adequate in size and obtained from the lesion previously identified by CT, routine HE slides and immunohistochemistry are enough for correct diagnosis.

The histopathological pattern in pulmonary histiocytosis varies and probably changes in the course of the disease: Hammar [19] identifies three stages of the disease:

1. cellular (infiltrates containing Langerhans cells, eosinophils, lymphocytes, plasma cells and neutrophils);
2. proliferative: interstitial and intraalveolar fibrosis with chronic inflammation;
3. recovery and fibrosis stage (recovery with minimal scarring, BOOP, honeycomb fibrosis).

Travis et al. [15] identify four types of changes: cellular, intermediate, fibrotic and cavernous with the following frequencies: 76, 98, 80 and 87%. The first three types are defined on the basis of the amount of Langerhans cells: cellular over 50%, intermediate 50 - 10%, fibrotic below 10%. They estimate the frequency of the three types together to be 57%. They also believe that primary cellular lesions tend to become fibrotic.

Pulmonary lesions are scattered nodules or cyst-like lesions varying in size with regular or stellate margins, interspersed with normal lung parenchyma. The lesions are located in the vicinity of small bronchi in 87%, subpleuraly in 70%, perivascularly in 18% of cases [51]. The central cavity is present in 87% of cases. Tazi et al. [49] believe that at the early stage bronchocentric granulomas are composed exclusively of infiltrating Langerhans cells and T helper lymphocytes and possibly damaged bronchial epithelia. Only at a later stage other infiltrating cells are present as a result of stimulating substances produced by before men-

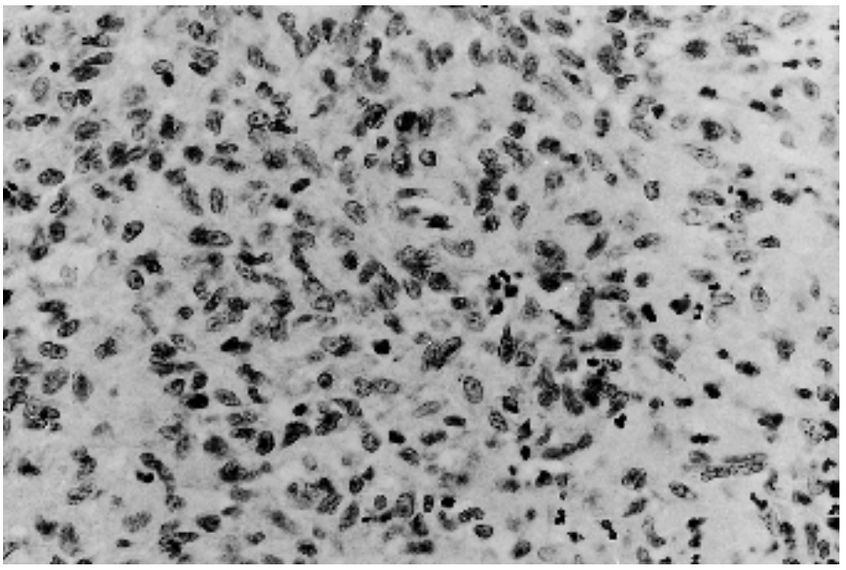

Fig. 6. Gathered dendritic cells with blurred margins and bright cytoplasm and kidney-shaped or invaginated nucleus. Few lymphocytes and eosinophils are visible. HE.

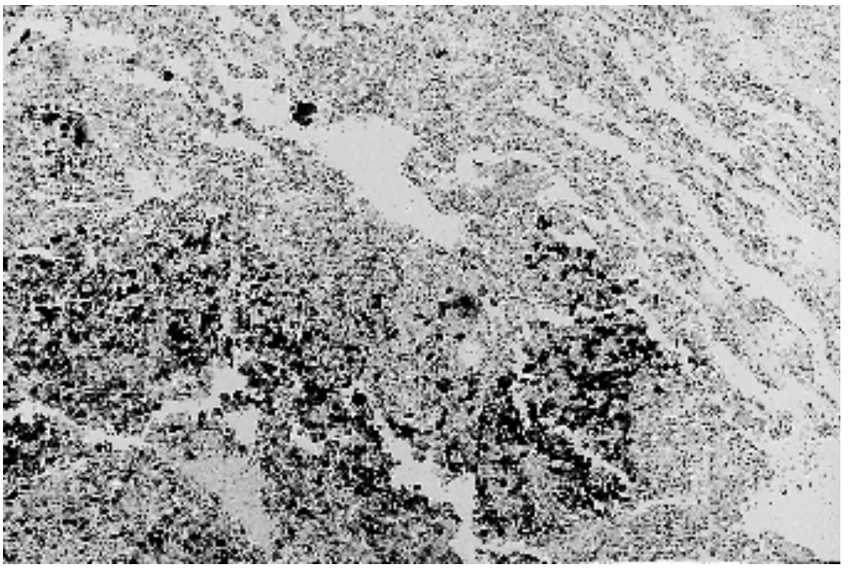

Fig. 7. Multiple S-100 positive dendritic cells within dendritic cells granuloma in the lung.

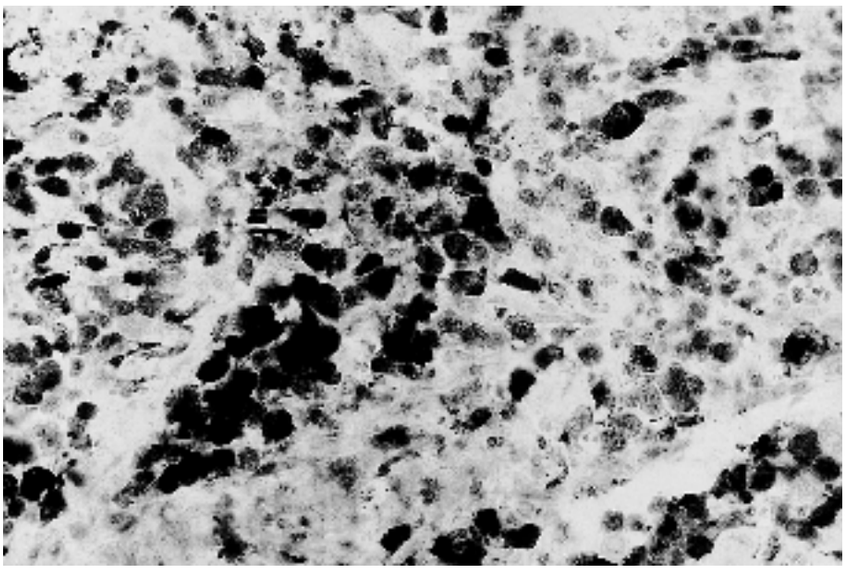

Fig. 8. Strong positive reaction for S-100 protein in dendritic cells.

tioned cells and then fibrosis develops. According to these investigators one sample may contain lesions at various stages of the development.

The identification of Langerhans cells is of key importance. Cell atypia is usually absent and mitoses are rare or absent, which indicates that cells are of inflowing type [5]. Dendritic cells in the lungs are present mainly in the stroma, but sometimes also in the alveolar lumen. The mixed cellular infiltrate may pose some diagnostic difficulties. Some investigators believe that an experienced pathologist may establish the diagnosis upon routine examination of HE sections.

It is also important to determine whether the cells are monoclonal or not. In isolated although multifocal variant it is a controversial problem. Many investigators believe it is a nonneoplastic reversible response to various factors [8, 54]. In histiocytosis X of other localisation, cells are believed to be monoclonal, which creates a possibility of neoplastic interpretation [23]. Dendritic cells according to Tazi et al. [47] are present in close correlation with CD4 lymphocytes, which may confirm the reactive type of the lesion. Electron microscopy in these cases reveals an increased number of Birbeck's granules in dendritic cells [47].

Eosinophils vary in their amount within the lesion and although present, they are not important for the process, in some cases are absent [24], therefore the term eosinophilic granuloma is not recommended any more. Eosinophils are multiple in 25% of cases. Neutrophils are present in 2/3 of cases [51]. Furthermore there are typical phagocytes with brown pigment in 87% of cases, which is probably due to smoking. Necrosis is very rare within the lesion. Fibrosis, frequently interstitial with mature collagen giving the stellate pattern is found in 81% of cases. Fibrosis within the alveoli is even more frequent - 86%.

Infiltrates containing Langerhans cells are frequent in neoplastic and non-neoplastic other than histiocytosis X conditions in the lungs [19] for instance: usual interstitial pneumonia - UIP (IPF), bronchiolitis obliterans organising pneumonia (BOOP), chronic eosinophilic pneumonia, reactive eosinophilic inflammation, idiopathic alveolitis with fibrosis, some nodular granulomatous lesions [24] and rare Erdheim-Chester disease with osteosclerotic changes and foamy histiocyte infiltrates [43, 49]. Lesions in Erdheim-Chester disease involve the bones of skull, hypophysis and brain; in half of these cases pulmonary lesions resemble the morphological pattern of histiocytosis [11, 43, 49]. Neoplastic lesions associated with the presence of Langerhans cells include mainly adenocarcinoma of the lung [37], lymphomas and Hodgkin's disease. The presence of multiple Langerhans cells in lung squamous cell carcinoma and adenocarcinoma associated with HPV infection may be a positive prognostic factor [32].

The number of Langerhans cells is a decisive factor in the diagnosis of Langerhans cell granulomatosis. According to Weber et al. [55] in histiocytosis X their number must exceed 75 per 10 HPF. In other entities they are less abundant, below 35 per 10 HPF. Fibrotic changes with a small number of Langerhans cells may be more difficult to diagnose unequivocally.

Studying whether histiocytosis with dendritic cells is a neoplastic process Willman and Yu demonstrated clonality of proliferations at other sites than the lungs [56, 58] where they have been found in single nodules [56, 57]. Yousem et al. [59] when studying the polymorphic human androgen receptor (HUMARA) associated with the expression of various chromosomes X in 13 women revealed the clonality in 29%, whereas 71% showed no clonality of dendritic cells in pulmonary nodules and concluded that it was a reactive change, not neoplastic in contrast to extrapulmonary variants of histiocytosis X with clonality of proliferations [56, 58]. The presence of clonal proliferations does not indicate only the neoplasm. Yousem et al. [59] find a resemblance with Hp-dependent MALT type gastric lymphoma regressing after eradication of bacteria, clonal lymphoid proliferation in celiac disease or posttransplantation lymphoproliferation. Brabencova et al. [5] did not demonstrate in histiocytosis X increased proliferation of Langerhans cells both in the lungs and skin or bone lesions (mitotic index, AgNOR, Ki-67) in contrast to PCNA results, which could have been biased.

Prognosis in this disease is uncertain. Five types of the disease course are identified [19]:

1. spontaneous complete regression;
2. regression of clinical symptoms and slight regression of radiological changes;
3. clinical and radiological stability;
4. gradual progression of clinical and radiological symptoms and signs;
5. fulminant lethal course.

It is estimated that about 50% have good prognosis, whereas in 10 - 20% the course of the disease is fulminant and unfavourable [49].

The core of the treatment of pulmonary histiocytosis is cessation of smoking. In many cases it is sufficient to quit smoking, frequently corticoids in gradually decreasing doses are added. It is not clear whether this approach is better than smoking cessation only (no randomised trials with groups ceasing to smoke, receiving corticoids and continuing to smoke and both). In serious cases it is recommended to use chemotherapy (cyclophosphamide, metothrexat, etc.) [8, 19, 35, 45, 49] and eventually lung transplantation, which is however associated with a high rate of recurrence [14, 17].

## References

1. *Arico M, Nichols K, Whitlock JA et al:* Familial clustering of Langerhans cell histiocytosis. Br J Haemathol 1999, 107, 883-888.

2. *Averswald V, Barth J, Magnussen H:* Value of CD1 positive cells in bronchoalveolar lavage fluid for the diagnosis of pulmonary histiocytosis X. Lung 1991, 169, 305-309.
3. *Basset F, Corrin B, Spencer H et al:* Pulmonary histiocytosis X. Am Rev Respir Dis 1978, 118, 811-820.
4. *Birbeck MS, Breathnach AD, Everall JD:* An electron microscope study of basal melanocytes and high level clear cells (Langerhans cells) in vitiligo. J Invest Dermatol 1961, 37, 51-64.
5. *Brabebcova E, Tazi A, Lorazeto M et al:* Langerhans cell in Langerhans cell granulomatosis are not actively proliferating cell. Am J Pathol 1998, 152, 1143-1149.
6. *Brauner MW, Grenier P, Moeulhi MM et al:* Pulmonary histiocytosis X: evaluation with high-resolution CT. Radiology 1989, 172, 255-258.
7. *Brauner MW, Grenier P, Tidjani K et al:* CT evolution of pulmonary Langerhans cell histiocytosis. Radiology 1997, 204, 497-502.
8. *Colby TV, Lombard C:* Histiocytosis X in the lung. Hum Pathol 1983, 14, 847-856.
9. *Crausman RS, Jennings CA, Tuder RM et al:* Pulmonary histiocytosis X: pulmonary function and exercise pathophysiology. Am J Resp Cerit Care Med 1996, 153, 426-435.
10. *Delobbe A, Durieu J, Duhamel A et al:* Determinants of survival in pulmonary Lanherhans' cell granulomatosis (histiocytosis X). Eur Respir J 1996, 9, 2002-2006.
11. *Egan AJM, Boardman LA, Tazelaar HD et al:* Erdheim-Chester disease: Clinical, radiologic, and histopathologic findings in five patients with interstitial lung disease. Am J Surg Pathol 1999, 23, 17-26.
12. *Egeler RM, Negilia JP, Puccetti DM, Brennan CA, Nesbit ME:* Association of Langerhans cell histiocytosis with malignant neoplasms. Cancer 1993, 71, 865-873.
13. *Farber S:* The nature of "solitary or eosinophilic granuloma" of bone. Am J Pathol 1941, 17, 625-628.
14. *Gabbay E, Dark JH, Ashcroth T et al:* Reccurence of Langerhans cell granulomatosis following bilateral lung transplantation. Thorax 1998, 53, 326-327.
15. *Gaensler EA, Carrington CB:* Open biopsy for chronic diffuse infiltrative lung disease: clinical, roentgenographic and physiological correlation in 502 patients. Am Thorac Surg 1980, 30, 411-426.
16. *Graaf JH, Tamminga RYJ, Kamps WA, Timens W:* Langerhans cell histiocytosis: expression of leukocyte cellulare adhesion molecules suggests abnormal homing and differentiation. Am J Pathol 1994, 144, 466-472.
17. *Habib SB, Congleton J, Carr D et al:* Recurrence of recipient Langerhans cell histiocytosis following bilateral lung transplantation. Thorax 1998, 53, 323-325.
18. *Hage C, Willman CL, Favara BE, Isaacson PG:* Langerhans cell histiocytosis (histiocytosis X): immunophenotype and growth fraction. Hum Pathol 1993, 24, 840-845.
19. *Hammar SP:* Pulmonary histiocytosis X (pulmonary Langerhans cell granulomatosis). In: Pulmonary Pathology. Dail DH, Hammar SP, eds. Springer Verlag, New York 1993, 567-614.
20. *Hirsch MS, Hong CK:* Familial pulmonary histiocytosis X. Am Rev Respir Dis 1973, 107, 831-835.
21. *Housini I, Tomashefski JF, Cohen A et al:* Transbronchial biopsy in patients with pulmonary eosinophilic granuloma. Comparison with findings of open lung biopsy. Arch Pathol Lab Med 1994, 118, 523-530.
22. *Howarth DM, Gilhrist GS, Mullan BP et al:* Langerhans cell histiocytosis: diagnosis, natural history management and outcome. Cancer 1999, 85, 2278-2290.
23. *Jaffe ES, Harris NL, Stein H, Vardiman JW:* Pathology and Genetics of Tumours of Haematopoietic and Lymphoid tissues. WHO. IARC Press, Lyon 2001, 280-282.
24. *Katzenstein AL:* Miscellaneous specific diseases of uncertein etiology. In: Katzenstein and Askin's Surgical Pathology of Non Neoplastic Lung Diseases. Saunders WB Philadelphia 1997, 395-402.
25. *Knudson RJ, Badger TL, Gaensler EA:* Eosinophilic granuloma of the lung. Med Thorac 1966, 23, 248-262.
26. *LaCronique J, Roth C, Battesti JP et al:* Chest radiological features of pulmonary histiocytosis X. A report based on 50 adult cases. Thorax 1982, 37, 104-109.
27. *Ladisch S, Jaffe ES:* The histiocytoses. In: Principles and Practice of Pediatric Oncology. Pizzo PA, Poplack DG, eds. Lippincot Philadelphia1989, 491-504.
28. *Langerhans P:* Über die Nerven der menschlichen Haut. Virch Archiv 1868, 44, 325.
29. *Lichtenstein L:* Histiocytosis X. Integration of eosinophilic granuloma of bone, "Letterer-Siwe disease" and "Schüller-Christian disease" as related manifestations of a single nosologic entity. Arch Pathol Lab Med 1953, 56, 84-102.
30. *Lieberman PH, Jones CR, Steinman et al:* Langerhans cell granulomatosis. A clinicopathological study encompasing 50 years. Am J Surg Pathol 1996, 20, 519-552.
31. *McClain K, Jin H, Grersik V, Favara B:* Langerhans cell histiocytosis: lack of viral etiology. Am J Hematol 1994, 47, 16-20.
32. *Miyagi J, Kinjo T, Tsuhako K:* Extremely high Langerhans cell infiltration contributes to the favourable prognosis of HPV-infected squamous cell carcinoma and adenocarcinoma of the lung. Histopathology 2001, 38, 355-367.
33. *Moore ADA, Godwin JD, Muller NL et al:* Pulmonary histiocytosis: comparison of radiographic and CT findings. Radiology 1989, 172, 249-254.
34. *Neumann MP, Frizzerea G:* The coexistence of Langerhans cell granulomatosis and malignant lymphoma may take different forms: report of seven cases with a review of literature. Hum Pathol 1986, 17, 1060-1065.
35. *Nezelof Ch, Barbey S:* Histiocytosis: nosology and pathobiology. Pediatric Pathol 1985, 3, 1-41.
36. *Nicholson HS, Egeler RM, Nesbit ME:* The epidemiology of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998, 12, 379-384.
37. *Papla B, Dubiel-Bigaj M, Stachura J:* Dendritic cells in bronchial adenocarcinoma. Folia Histochem Cytobiol 1988, 26, 99-104.
38. *Papla B, Kaczorowska-Polakiewicz K:* Pulmonary Langerhans cell granulomatosis (Histiocytosis X) in an adult woman. A case report. Pat Pol 1994, 45, 313-317.
39. *Papla B, Malinowski E, Niżankowska E:* Pulmonary Langerhans cell granulomatosis. XV Zjazd PTP Kraków 21 - 23 VI 2001. Pol J Pathol 2001, 52, 88(abs).
40. *Parkinson T:* Eosinophilic xanthomatous granuloma with honeycomb lungs. Br Med J 1949, 1, 1029-1030.
41. *Pinkus GS, Pinkus JL, Langhoff E et al:* Fascin, a sensitive new marker for Reed-Sternberg cells of Hodgkin's disease. Evidence for a dendritic od B cell derivation. Am J Pathol 1997, 150, 543-562.
42. *Radzikowska E, Langfort R, Gawryluk D et al:* Postać płucna histiocytozy z komórek Langerhansa - analiza kliniczno-patologiczna 7 przypadków. Pneumonol Alergol Pol 2001, 69, 273-284.
43. *Rush WL, Andriko JA, Galateau-Salle F et al:* Pulmonary pathology of Erdhaim-Chester disease. Mod Pathol 2000, 55, 747-754.
44. *Schonfeld N, Frank W, Wenig S et al:* Clinical and radiological features, lung function and therapeutic results in pulmonary histiocytosis X. Respiration 1993, 60, 38-44.
45. *Sobiecka M, Wesołowski S, Kuś J:* Własne doświadczenia w rozpoznaniu i leczeniu płucnej postaci ziarniniakowatości komórek Langerhansa. Pol Merk Lek 2001, 60, 416-420.
46. *Śledziewska J, Rogińska E, Oblakowski P et al:* Wykorzystanie oznaczenia ekspresji CD1 na powierzchni komórek z popłuczyn

pęcherzykowo-oskrzelowych do rozpoznania histiocytozy X - własne doświadczenia. Pneumonol Alergol Pol 1999, 67, 311-317.

47. *Tazi A, Bonay M, Grandsaigne M et al:* Surface phenotype of Langerhans cells and lymphocytes in granulomatous lesions from patients with pulmonary histiocytosis X. Am Rev Respir Dis 1993, 147, 1531-1536.
48. *Tazi A, Bonay M, Bergeron A et al:* Role of granulocyte-macrophage stimulating factor (GM-CSDF) in the patogenesis of adult pulmonary histiocytosis X. Thorax 1996, 51, 611-614.
49. *Tazi A, Soler P, Hance AJ:* Adult pulmonary Langerhans cell histiocytosis. Thorax 2000, 55, 405-416.
50. *Tomashefski JF, Khiyami A, Klinrman J:* Neoplasms associated with pulmonary eosinophilic granuloma. Arch Pathol Lab Med 1991, 115, 499-506.
51. *Travis WD, Borok Z, Roum JH et al:* Pulmonary Langerhans cell granulomatosis (Histiocytosis X). A clinicopathologic study of 48 cases. Am J Surg Pathol 1993, 17, 971-986.
52. *Vassalo R, Ryu JH, Colby TV et al:* Pulmonary Langerhans-cell histiocytosis. New Eng J Med 2000, 342, 1969-1978.
53. *Weiss LM, Grogan TM, Muller-Hermelink HK et al:* Langerhans cell histiocytosis. In: Tumours of Haematopoetic and Lymphoid Tissues. Jaffe ES, Harris NL, Stein H, Vardiman JM, eds. WHO. IARC Press, Lyon 2001, 280-282.
54. *Weiss LM:* Histiocytic and dendritic cell proliferations. In: Neoplastic Hematopathology. Knowles DM, ed. Lippincot Williams-Wilkins, Philadelphia 2001, 1832-1836.
55. *Webber D, Tron V, Askin F, Churg S:* S-100 staining in the diagnosis of eosinophilic granuloma of lung. Am J Clin Pathol 1985, 84, 447-453.
56. *Willman CL, Busque L, Griffith BB et al:* Langerhans cell histiocytosis (Histiocytosis X) - a clonal proliferative disease. N Engl J Med 1994, 331, 154-160.
57. *Willman CL, McClain KL:* An update on clonality, cytokines and viral etiology in Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998, 12, 407-416.
58. *Yu RC, Chu C, Buluwela L et al:* Clonal prolliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet 1994, 343, 767-768.
59. *Yousem SA, Colby TV, Chen YY et al:* Pulmonary Langerhans cell histiocytosis. Molecular analysis of clonality. Am J Surg Pathol 2001, 25, 630-636.

**Address for correspondence and reprint requests to:**
B. Papla, M.D.
Department of Pathomorphology CMUJ
Grzegórzecka 16, 31-531 Kraków