CASE REPORT

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Pulmonary Langerhans cell histiocytosis in a 26-year-old female: still a diagnostic challenge

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Abstract

Langerhans cell histiocytosis (LCH) is a rare disorder caused by monoclonal Langerhans cells proliferation in bone, skin, lung, lymph nodes, liver, spleen, nervous or hematopoietic system. Pulmonary LCH is a diagnostic trap that is displayed on computed tomography (CT) as an interstitial disorder with honeycomb aspect. In this paper, we present an unusual case of a 26-year-old female that was hospitalized with progressive worsening dyspnea and history of recurrent pneumonia. Lung biopsy showed fibrosis of the interalveolar septa, architectural distortion and large cells with foamy cytoplasm and convoluted nuclei that were marked by CD68, S-100 and the specific antibody CD1a that allowed establishing the diagnosis of pulmonary LCH. The only extrapulmonary manifestations were femoral bone cysts that were radiologically seen 10 years before and were not modified along the years. The therapy consisted on smoking cessation and oral corticosteroids without significant improvement of the clinical symptoms and enlargement of the cystic spaces during six months of follow-up. This case highlights for a rare disorder of the lung that should be taken into account in young patients with progressive pulmonary fibrosis.

Keywords: Langerhans cell histiocytosis, lung, bone, therapy.

Introduction

Langerhans cell histiocytosis (LCH) that is also called histiocytosis X is a very rare disorder (orphan disease) caused by monoclonal Langerhans cells proliferation in different organs like bone, skin, lung, lymph nodes, liver, spleen, central nervous system and hematopoietic system [1]. The real incidence is not well known. It is estimated to be about 3–5‰ in children. More than 2% of all diffuse chronic pulmonary interstitial diseases seem to be pulmonary LCHs [2, 3]. The etiology of LCHs could be related on viral infections, smoking, exposure to environmental factors (hypersensitivity mechanism) and tumors (*e.g.*, lymphomas) but the exact pathomechanism is far to be known [1, 3]. Some authors consider that LCH is an inflammatory myeloid neoplasia caused by a misguided differentiation of the myeloid dendritic cell precursors. *BRAF-V600E* gene mutation is founded in 60–75% of patients and is considered an indicator of severity and increased resistance to chemotherapy [1, 2, 4–6].

Half of the patients diagnosed with LCH present involvement of only one organ/system such bone or lung. The other cases, especially those diagnosed in children, show a multisystemic LCH [7]. The most common affected organs/systems are the hematopoietic system, liver, spleen, lung, central nervous system and bone marrow [1].

In this paper, we present an unusual case of a young female diagnosed with LCH based on lung biopsy. Along with the case presentation, a review of the literature regarding the history of this extremely rare disease (only one case was diagnosed in our university department in the last 20 years) along with the principles of diagnosis and therapy was performed. The signed informed consent of the patient was obtained for publication of this paper.

Case presentation

A 26-year-old female with a body mass index of 26 kg/m^2 was hospitalized in April 2015 with progressively worse dry cough and dyspnea since 2010. The patient declared that she is a current smoker (nine pack-years) and during her childhood and adult period, she presented repeated episodes of pneumonia treated with antibiotics. In the same time, she presented in the puberty a retro-peritoneal inflammatory process (without specific histo-logical findings) that clamed abdominal surgery. In 2005, the radiograph examination revealed for small femoral neck bone cysts without modifications during 10 years of follow-up. Bilateral *coxa vara*, *genu valgum* and *spina bifida* were also noted at that time.

At the admission in the hospital, in 2015, physical examination findings were non-specific and included decreased breath sounds, diffuse crackles, rales, wheezes and rhonchi. A diffuse and bilateral interstitial pattern was revealed at chest X-ray. The lesions were suggestive for interstitial fibrosis of the lung. Respiratory function tests showed a moderate restrictive ventilatory disorder, with decreased of the forced vital capacity (FVC) 68% and forced expiratory volume in the first second (FEV1) 69%

and mild diurnal desaturation (SaO_2) 94%. The transfer factor of the lung for carbon monoxide (TLCO) and the transfer coefficient (K_{CO}) were significantly decreased: TLCO 59%, K_{CO} 67%. Serum analysis revealed neutrophilia (79% – normal range 43.7–77.1%), slight hypercholesterolemia (238 mg/dL), raised inflammatory markers [lactate dehydrogenase (LDH) 780 U/L – normal range 125–220 U/L; erythrocyte sedimentation rate (ESR) 48 mm/h – normal range 5–15 mm/h), and negativity of the following autoimmune antibodies (Ab): antinuclear Ab, rheumatoid factor, anti-neutrophil cytoplasmic Ab (ANCA) and antiphospholipid Ab. Normal values of the serum levels of angiotensin-converting enzyme (20 U/L – normal range 20–70 U/L), alpha-1-antitrypsin (2 g/L – normal range 0.90–2 U/L) and seric immunoglobulins were founded.

Thoracic computed tomography (CT) confirmed the interstitial fibrosis with cystic pattern (Figure 1). Diffuse irregular thin-walled cysts were observed in 60% of the lung surface, predominantly in the upper lobes. The mediastinal lymph nodes were moderately enlarged (13–15 mm in diameter). Magnetic resonance imaging (MRI) exam confirmed the presence of well-defined femoral neck bone cysts and *spina bifida occulta*. No other extrapulmonary lesions were identified.

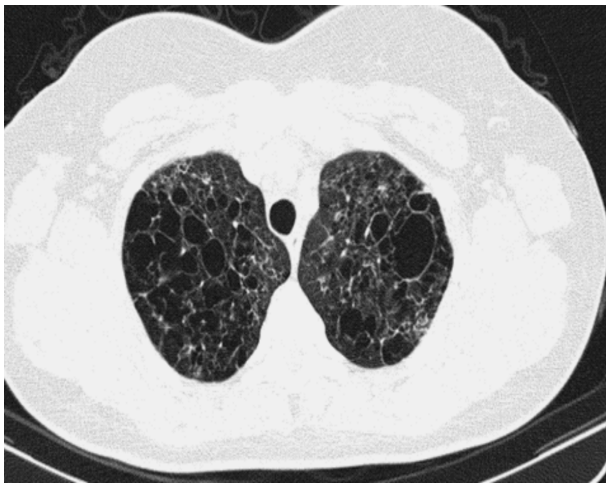

Figure 1 – ***Thoracic computed tomography: lung interstitial fibrosis and multiple thin-walled cysts in the upper lobes.***

The examination of the bronchoalveolar lavage fluid did not reveal tumor cells, bacteria, fungi, Koch bacilli or alveolar proteinosis. For a final diagnosis, pulmonary biopsy was performed through video-thoracoscopy. The bioptic specimens were fixed in 10% neutral buffered formalin and sent for histopathological examination. The microscopic examination, which was performed on paraffin-embedded tissues stained with Hematoxylin–Eosin, showed thick alveolar septa with large areas of fibrosis and distortion of the normal pulmonary architecture (Figure 2, A and B). Within the fibrotic tissue, several lymphocytes and eosinophils and few large histiocytes were observed. Bronchiolitis was associated. The giant foamy cells were characterized by poorly defined cytoplasmic borders, rich cytoplasm with granular aspect and convoluted nuclei with distinct nucleoli (Figure 2, A and B). No histochemical stains were performed. The immunohistochemical (IHC) examination showed that the giant cells were marked by CD68 (mouse anti-human monoclonal antibody, clone KP1, Dako, Glostrup, Denmark, 1:50 dilution), S-100 protein (rabbit anti-human polyclonal antibody, Dako, 1:100 dilution), and CD1a (mouse anti-human monoclonal antibody, CTB6 clone, Dako, 1:100 dilution), and were negative for TTF-1 (rabbit anti-human polyclonal antibody, Dako, 1:100 dilution). This aspect corresponded to the immunoprofile of the Langerhans' cells (Figure 2, C and D).

Based on the clinical-pathological and IHC aspects, the final diagnosis was pulmonary LCH with possible extra-pulmonary (femoral) involvement. The prescribed therapy consisted on smoking cessation, corticosteroids (oral methylprednisolone 48 mg/day for two months, with gradually decrease with 8 mg/week until the stable dose 24 mg/day at least one year) and long-acting bronchodilators. Firstly, the patient refused the therapy with steroids. Repeated episodes of pneumonia occurred and in April 2016, she was re-hospitalized with an episode of pneumonia. Antibiotics were prescribed with favorable outcome.

After this episode, the patient decided for smoking cessation and therapy with corticosteroids was started. At six months of follow-up, worsening dyspnea was noted and the thoracic CT scan revealed the extension of the pulmonary cysts with confluence in the superior lobes. Cardiac involvement was not observed. The increase in severity of the pulmonary lesions during the follow-up period, recommended a step-up treatment with associated vinblastine.

Discussion

In patients with pulmonary LCH, the high-resolution CT scan usually reveals lesions specific for a diffuse interstitial fibrosis of the lung [7, 8]. Except LCH, the differential diagnosis include several chronic interstitial diseases and condition such as idiopathic fibrosis, sarcoidosis, miliary tuberculosis, lymphangiomyomatosis, emphysema, bronchiectasis, multiple myeloma, Hodgkin's disease, malignant histiocytic tumor, metastatic tumors, hypersensitivity pneumonitis, Wegener's granulomatosis, etc. [3, 7, 8].

First case describing an isolated pulmonary LCH was published by Parkinson, in 1949, in a 56-year-old boot-repairer [9]. Since 1987, about 220 cases of pulmonary LCH have been reported, with or without extra-pulmonary involvement [3]. Between 1987 and 2016, more than 850 papers have been published in this field.

Diagnosis of pulmonary LCH that is also called eosinophilic granuloma is based, as in our case, on the histological and IHC examination of the biopsy specimens [7, 8, 10]. The histological pattern is dominated by the interstitial fibrosis and mixed inflammatory infiltrate rich in eosinophils. The main pattern is identification of the Langerhans cells that are large cells with foamy granular cytoplasm and convoluted nuclei with well-defined nucleoli. This cell was firstly described by the German medical student Paul Langerhans, as a dendritic cell of the epidermis and was thought to be a nerve cell [3]. The intracytoplasmic Birbeck's granules that can be observed at electron microscopy were described by Birbeck *et al.*

The IHC profile suggest that the Langerhans cell is a macrophage-like structure that display positivity for CD68, S-100, OKT-6, CD1a and CD207 and are negative for alpha-1 antitrypsin. In contrast, macrophages are not usually marked by OKT-6 and CD1a and display positivity for alpha-1 antitrypsin [1, 3].

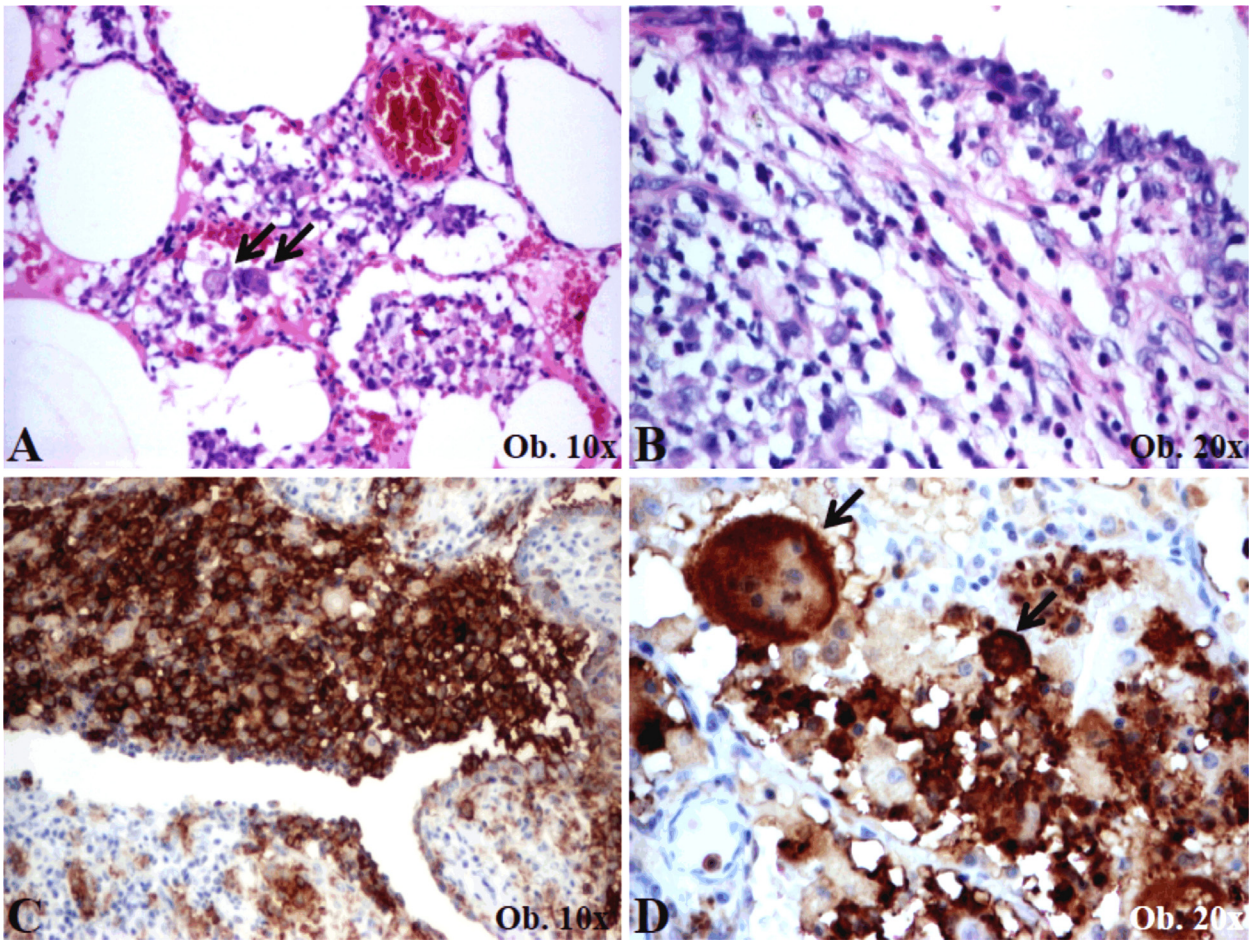

Figure 2 – ***Histopathological findings of Langerhans cell histiocytosis, in Hematoxylin–Eosin staining, consist of thick alveolar septa with foamy cells (A – arrows) admixed with inflammatory infiltrate rich in eosinophils (B). The Langerhans cells are immunohistochemically marked by CD1a (C) and S-100 (D – arrows).***

Most of the LCHs are diagnosed in the childhood period or between 20 and 40 years old, mostly in males [1, 3]. In the present case, although the diagnosis was established at the age of 26, the repeated pneumonia, presence of bone cysts and retroperitoneal inflammatory process at puberty, indicate that the onset was in the late puberty period. However, although extrapulmonary involvement seems to be present, the evolution was relatively slowly without any therapy. In the last six months of follow-up, increasing severity of pulmonary lesions was an indicator of association of vinblastine.

In these patients, the natural evolution consists on increasing severity of respiratory failure, with pulmonary hypertension and installing of chronic *cor pulmonale* [11]. Other complications are spontaneous pneumothorax and pleural or pericardial effusion [1, 3]. In patients with multi-organ involvement orthopedic disabilities, growth retardation, hearing impairment, diabetes *insipidus*, skin scarring, liver cirrhosis and neuropsychological defects can be associated with the increased risk for solid malignant tumors, acute lymphoblastic leukemia or other lymphomas [1].

The therapeutic regimens depend on the severity of the disease and the involvement or not of other organs. Along with smoking cessation, corticosteroids alone or in combination with vinblastine, vincristine, methotrexate or etoposide are indicated. In advanced stages, lung transplantation is the therapy of choice [8, 10, 11].

The patient's response to chemotherapy during the first six weeks of treatment is an indicator of prognosis [1]. The follow-up of patients with pulmonary involvement consists on examination at every six months, to detect the complications and the best period for transplantation. The monitoring includes respiratory functional tests and imagistic methods [CT, MRI, and positron emission tomography (PET)-CT] [12–14]. PET-CT is able to detect the foci of metabolically active LCH (especially in lung, skull, extremities), to point out the therapy and estimate prognosis [12, 13].

The actual lung biopsy with histological and IHC exam was crucial for a disease confirmation and provided a targeted treatment. Chronic smoking rest a risk factor for pulmonary LCH and for this, once more we have to fight against smoking. The lack of patient's compliance to treatment alongside to the extrapulmonary involvement was also risk factor for a mediocre response to the treatment.

Conclusions

The late diagnosis of LCH could be explained by the slow disease evolution and the rarity of the disease that is an exclusion diagnosis. This interstitial disorder of the lung can only be diagnosed based on the lung biopsy and immunoprofile of the Langerhans cell. The last months fast evolution and the poor compliance to steroid therapy categorized the case in the "rapid progressive" group that constrain to a carefully intensive treatment and long term follow-up surveillance by an interdisciplinary team. Lung transplantation should be taken into account in such cases.

Conflict of interests

The authors declare that they have no conflict of interests.

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