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Langerhans Cell Histiocytosis in a Non-Smoking Adult Patient: Clinical Considerations in a Rare Presentation

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder characterized by the proliferation of cells of the mononuclear phagocytic system. In addition, they predominantly affect children, with peak incidence between the ages of 1 and 4. However, it is not unusual for them to be diagnosed in adults. In particular, pulmonary involvement occurs in approximately 10% of LCH cases. The diagnosis is confirmed by histology. Treatment is adapted according to the spread of LCH. A 32-year-old female patient presented with a productive cough and exertional dyspnea on June 18, 2023. With a history of Nodular Sclerosis Hodgkin Lymphoma (NSHL) diagnosed on April 28, 2023, without treatment. Family history: mother alive with non-Hodgkin lymphoma treated with chemotherapy. A computed axial tomography (CT) scan was performed, reporting a right lung mass and adenopathy in the bilateral cervical supraclavicular region, bilateral axillary region predominantly on the right, bilateral mediastinal and inguinal regions. Denies a history of smoking and alcoholism. Biopsy and immunohistochemistry result: S100, CD1a, CD68 positive; cytokeratin and EMA negative) confirmed pulmonary LCH. Start treatment with MACOP-B, cytarabine and methotrexate. The patient showed disease progression and died from multiple organ failure. LCH occurs almost exclusively in smokers or former smokers, being considerably less frequent in non-smokers. In addition, it has been associated with Hodgkin's lymphoma and following treatment with chemotherapy and radiotherapy. The definitive diagnosis is established by biopsy of the lesion associated with immunohistochemical techniques (CD1a+ and CD207+). PLCH remains an extremely rare condition in this population, which means that it is rarely considered in the diagnostic workup.

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Introduction

In recent years, medical research has made significant advances in understanding pathologies that fall within the complex spectrum of rare proliferative diseases. In this context, Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder characterized by the proliferation of cells of the mononuclear phagocytic system (monocytes, macrophages, dendritic cells) in different organs and systems [1]. The ubiquitous distribution of these cells explains the wide variety of clinical manifestations observed [2].

In addition, they predominantly affect children, with peak incidence between the ages of 1 and 4. However, it is not unusual for them to be diagnosed in adults, whether they began in adulthood or are the progression of a pediatric form. They are more common in males during childhood, while the gender ratio is more balanced in adults [2].

In particular, pulmonary involvement occurs in approximately 10% of LCH cases. It is much more common in adults and is almost always associated with smoking [3]. Although the etiology is unknown, a possible antigenic cause, somatic mutations, or infectious etiology have been postulated. LCH occurs almost exclusively in smokers or former smokers, which supports the antigenic hypothesis. Much less frequent and known is the occurrence of this disease in non-smokers. Its association with various neoplasms and lymphoproliferative processes has been described, specifically Hodgkin's lymphoma, particularly after chemotherapy and radiotherapy [4].

The disease is also characterized by a variety of manifestations, either single or multiple, with histiocyte infiltration capable of affecting almost all organs, especially the skin, lymph nodes, lungs, thymus, liver, spleen, bone marrow, and central nervous system. Therefore, clinical, histopathological, and immunohistochemical studies must be integrated for timely detection [5].

Therefore, the diagnosis, which is clinically suspected, is confirmed by histology. Treatment is adapted according to the spread of LCH, its evolutionary nature (regressive, stable, or progressive disease), and the presence of organ dysfunction [2]. Given the above, our objective was to describe the clinical, radiological, and histopathological characteristics of a case of pulmonary Langerhans cell histiocytosis in an adult patient diagnosed in Maracaibo, Venezuela, in 2023.

Case Presentation

A 32-year-old female patient presented with a productive cough and exertional dyspnea on June 18, 2023. With a history of Nodular Sclerosis Hodgkin Lymphoma (NSHL) diagnosed on April 28, 2023, without treatment. Surgical history of supraclavicular lymph node excision 1 year ago at the hospital Universitario of Maracaibo. Family history: mother alive with non-Hodgkin lymphoma treated with chemotherapy. She was admitted with a diagnosis of lower respiratory infection: bilateral pneumonia complicated with pleural effusion vs tumor under study. A computed axial tomography (CT) scan was performed, reporting a right lung mass and adenopathy in the bilateral cervical supraclavicular region, bilateral axillary region predominantly on the right, bilateral mediastinal and inguinal regions. Denies a history of smoking and alcoholism.

She was discharged due to clinical improvement, receiving chemotherapy treatment for one year, with no apparent improvement. On July 20, 2024, the following results were obtained from a lung biopsy using immunohistochemistry: 1. Pulmonary parenchyma occupied by granulomatous inflammatory infiltrate of mixed nature, consisting of lymphocytes, both B (CD20+) and T (CD3+), eosinophils, polymorphonuclear cells (CD15*), plasma cells (CD138) and histiocytes (CD68+). 2. Interspersed with these are larger atypical cells with clear or slightly eosinophilic cytoplasm and irregular, folded, and cleft nuclei, these cells were immunoreactive to the S100 protein, CD68 and the CD1A marker. 3. Cytokeratin AE1/AE3 and epithelial membrane antigen (EMA), expressed in carcinomas and adenocarcinomas, were negative. 4. The immunohistopathological findings obtained are compatible with Langerhans cell histiocytosis or histiocytosis X.

Immunohistopathological Report		
Panel for differential diagnosis of tumors		
Immunohistochemical study	**Result 1**	**Interpretation 2**
Broad-Spectrum Cytokeratin	Negative	Carcinoma identification antigen (+) negative in neoplasms of mesenchymal origin
Epithelial Membrane Antigen (EMA)	Negative	High molecular weight (250-400 kDa) membrane glycoprotein present in a wide variety of normal and neoplastic cells of epithelial origin.
Common Leukocyte Antigen (CD45/LCA)	2+	Membrane glycoprotein present in cells of lymphopoietic origin, both normal and reactive. Also useful in the identification of non-Hodgkin lymphomas (+).
CD20/L26	2+ (+ in germ centers)	Immunohistochemical marker for B lymphocytes, both normal and neoplastic. Strongly expressed in the germinal centers of lymphoid follicles. Useful in identifying B-cell lymphomas.
CD45-RO/UCHL-1	2+	Immunohistochemical marker for T lymphocytes, both normal and neoplastic. Useful in the diagnosis of T-cell lymphomas.
CD-68, Macrophage	2+ (+sinusoidal histiocytes)	Glycosylated glycoproteins located in lysosomes, useful in identifying macrophages. Present in sinusoidal histiocytes and germinal centers.
CD30 / KI-1 / BERH-2	Negative	Immunohistochemical markers useful in the diagnosis of Hodgkin's lymphoma. Positive in Reed-Sternberg cells in Hodgkin's lymphomas.
S-100 Protein	3+	Antigen present in glial cells, histiocytes, and melanocytes. Useful in the diagnosis of histiocytosis, schwannomas, and melanomas.
CD 1a	3+	Surface glycoprotein present in cortical thymocytes, Langerhans cells, and dendritic cells. Useful in the diagnosis of histiocytosis X or Langerhans cell histiocytosis.
CD 138	1+ (plasma cells)	Differentiation antigen present in plasma cells and absent in mature lymphocytes. Useful in the diagnosis of plasmacytoma/multiple myeloma.
CD-68, Macrophage	2+ (+sinusoidal histiocytes)	A glycosylated glycoprotein located in lysosomes, useful in identifying macrophages. Present in sinusoidal histiocytes and germinal centers.
CD 15	1+ (+PMN and eosinophils)	Lymphoid differentiation marker strongly expressed in polymorphonuclear cells and eosinophils.
The intensity of cytoplasmic and membrane staining is rated as: +/- (questionable), 1+ (low), 2+ (moderate), 3+ (strong). Nuclear staining is expressed as a percentage (%) of positive cells.		

Figure 1: Report Table

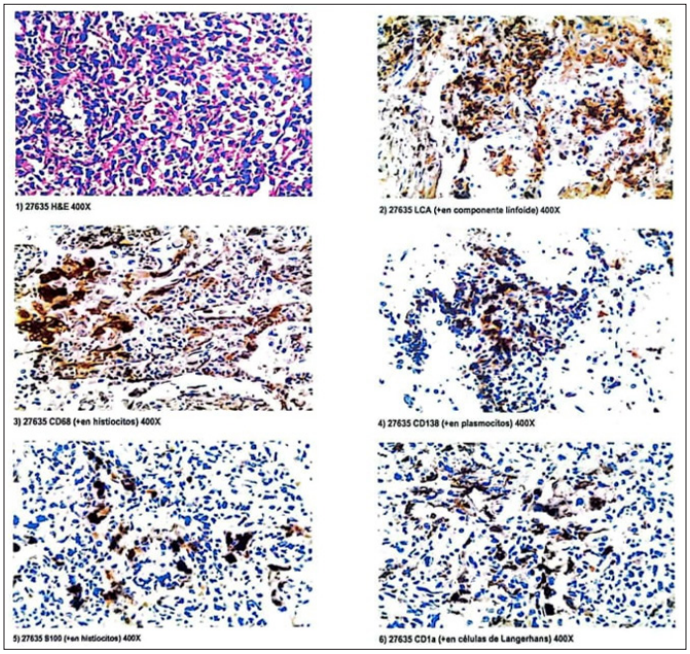

Figure 2: Immunohistochemical Study: Deparaffinized Histological Sections with Antigen Retrieval Were Incubated with Panels of Monoclonal and/or Polyclonal Antibodies, using a Biotin-Free Visualization Technique Based on a Peroxidase-Polymer

complex and DAB as a Chromogen. Parallel Sections of the Corresponding Positive Controls were Processed Simultaneously with the Sample. The photographs show the results presented in the table in the report. (figure 1)

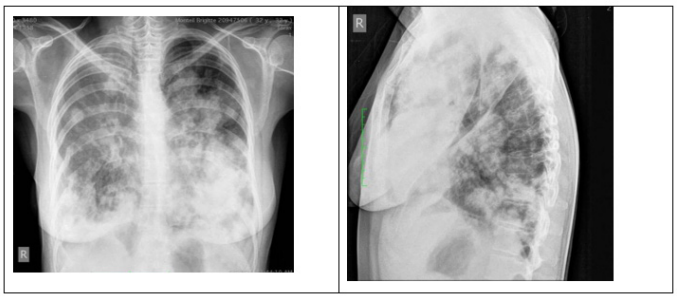

Figure 3: On August 6, 2024, a PA and Lateral Chest X-Ray was Obtained Showing Multiple Radiopaque Images, Nodular in Appearance, with Irregular, Partially Defined Edges, Varying In Size, With Larger Images Observed in the Left Lung Field, Diffusely Distributed Bilaterally, predominantly in the Lower Lobes.

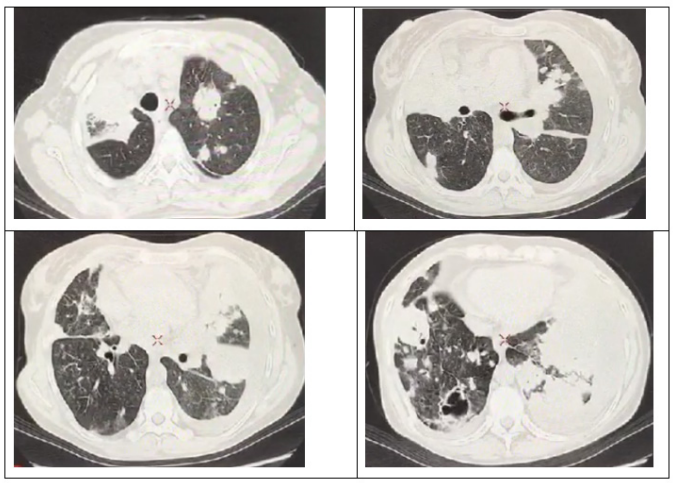

Figure 4: On August 31, 2024, a CT scan Showed Lung Nodules That Were Approximately 50% Larger and More Numerous Than in the Previous Study, Pleural Effusion and Bilateral Fissure, More Pronounced in the Left Lung Field, as Well as Mediastinal Adenopathy's Approximately 30% Larger than in the Previous Study and Pericardial Effusion. The Rest of the Findings Were the Same as Those Described in the Previous Study.

She was admitted again on August 14, 2024, due to asthenia and adynamia, reporting a hypo expandable symmetrical chest on physical examination with supplemental oxygen requirement via nasal cannula decreased vesicular murmur in both lung fields with bilateral crackles. Start treatment with MACOP-B for 17 days with disease progression, therefore, it is changed to CYTARABINE and METHOTREXATE on August 20, 2024, receiving 3 cycles of the protocol without clinical improvement and with worsening of the general condition. The patient died on December 16, 2024, due to multiple organ failure.

Discussion of Findings and Conclusions

LCH is a rare hematological disorder that can affect patients of all ages, although it predominantly occurs in the pediatric population [6]. In adults, the estimated annual incidence is approximately 1 case per million; however, this figure is likely to be underestimated due to the disease being underdiagnosed in this population [7]. Less is known about the differences in underlying biology between children and adults, and it is unclear whether incidence profiles differ between age groups [8]. Velázquez et al. 2025 analyzed data from the US Cancer Statistics System (USCS) between 2001 and 2021, showing significant differences in the incidence of LCH by racial/ethnic group and age range. These disparities could reflect variations in the etiology of the disease according to age. In this context, we present the case of a 32-year-old female adult patient whose clinical presentation is uncommon.

Although its etiology is unknown, hypotheses have been proposed that include antigenic mechanisms, somatic mutations, and infectious agents as possible triggers. LCH occurs almost exclusively in smokers or former smokers, being considerably less frequent in non-smokers [4]. In addition, it has been associated with various neoplasms and lymphoproliferative processes, mainly Hodgkin's lymphoma, and following treatment with chemotherapy and radiotherapy [4]. In the case described, the patient denied a history of smoking and previous exposure to chemotherapy treatments.

The clinical course is heterogeneous, ranging from mesosystemic involvement, localized with isolated involvement, such as a self-limiting indolent lesion (solitary eosinophilic granuloma), to multisystemic involvement, with the potential for progression to multisystemic disease with severe organ dysfunction leading to death [6-9]. It should be noted that in adults, pathological Langerhans cells behave reactively, without presenting neoplastic growth, and the most frequently affected organ, and generally the only one, is the lung, but other locations have been described, such as skeletal structures and the pituitary gland [4, 6].

Pulmonary LCH (PLCH) is a rare diffuse cystic lung disease that usually affects young and middle-aged adults of both sexes. It occurs almost exclusively in smokers (90% of patients) or former smokers [7, 9, 10]. It can manifest as part of a multisystemic histiocytosis or in a monosystemic form, the latter being the most common presentation [6, 11]. It can manifest as part of a multisystemic histiocytosis or in a monosystemic form, the latter being the most common presentation [6, 11].

The clinical presentation may include dyspnea, chest pain, fatigue, chronic cough, or spontaneous pneumothorax; however, a quarter of patients are asymptomatic [4]. In this case, the patient presented with typical symptoms. Recurrent pneumothorax is one of the most specific manifestations of this pathology, although not the most frequent [4, 6]. Pulmonary hypertension is associated with a worse prognosis [4].

The diagnosis of LCH can be complex in patients with a history of neoplasia, since, particularly in its nodular form, radiological findings can mimic metastatic disease or opportunistic infections. Therefore, LCH should be included in the differential diagnosis of diffuse nodular lung disease in the context of Hodgkin lymphoma [4]. In the reported case, the patient had a previous diagnosis of scleronodular variant Hodgkin lymphoma, as well as a maternal family history of cancer. Other differentials to consider are miliary tuberculosis, sarcoidosis, and silicosis [4].

The diagnostic approach should include a thorough interview and detailed physical examination, as this disease can affect any system. The definitive diagnosis is established by biopsy of the lesion associated with immunohistochemical techniques (CD1a+ and CD207+) [6,7]. Histological examination may show aggregates of intermediate-sized cells with reniform nuclei,

dispersed chromatin, and abundant eosinophilic cytoplasm [6]. Immunohistochemistry reveals positivity for CD68, S100, surface CD1a, cytoplasmic langerin antigen (CD207), and cyclin D1, findings that were conclusive in confirming the diagnosis in this patient [4,6,7]. Likewise, a complete laboratory workup is recommended, including a complete blood count, ionogram, liver function tests, C-reactive protein (CRP), thyroid profile, and imaging studies [7].

Radiographic findings are typical of the presence of a reticulonodular pattern with cystic formation, which was present in this patient's radiograph, which showed multiple radiopaque images with a nodular appearance [7]. The literature also establishes that lung volume is preserved or increased, unlike in other interstitial diseases. Fibrosis adjacent to the cysts is sometimes observed, and coexistence with emphysema is common [4].

Computed tomography (CT) usually reveals characteristic patterns, such as cystic changes, nodular lesions, enlargement of the pulmonary arteries, ground-glass opacities, emphysematous changes, reticular patterns, honeycomb patterns, and the presence of pneumothorax [4, 6]. The CT scan performed reported similar findings, such as pulmonary nodules and mediastinal adenopathy's, as well as pericardial effusion.

Existing paradigms for the management of CLD in adults are largely based on evidence from the pediatric literature. Therefore, the therapeutic approach must be individualized, taking into account the degree of involvement of the affected organ [7, 11]. In many cases, additional measures are required, such as corticosteroid therapy or chemotherapy. In patients with advanced LCH, lung transplantation may be considered a therapeutic option [4]. In this case, despite the initiation of appropriate treatment, its application was delayed as a result of a delayed diagnosis.

PLCH remains an extremely rare condition in this population, which means that it is rarely considered in the diagnostic workup. Nevertheless, it should be suspected in patients with a history of Hodgkin lymphoma who present with respiratory symptoms. It should be noted that the available data on cases in older adults remain limited.

Conflicts of Interest

It is declared that there is no conflict of interest.

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