

Multisystemic Langerhans Cell Histiocytosis with advanced lung involvement

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ABSTRACT

Langerhans cell histiocytosis is a rare disease of unknown cause, characterized by the proliferation of histiocytic cells (Langerhans cells), that can sometimes be especially difficult to diagnose due to its wide clinical spectrum, ranging from a single lesion to a multisystemic disorder. Appropriate disease staging is fundamental, since treatment depends upon the severity of the disease, and imaging methods play a fundamental role not only in diagnosing and assessing the extent of Langerhans cell histiocytosis, as well as guiding the appropriate treatment for the patient and their monitoring.

CASE REPORT

CASE REPORT

A 54-year old farmer presented with papular lesions on the scalp, ears, underarms, back, abdomen and oral cavity for four years, and an ulcerated lesion in the oral cavity (figure 1). He had a 26 pack year history of smoking, stopped smoking 10 years ago and was otherwise relatively well and asymptomatic and there was no significant past medical history. Physical examination revealed no other abnormality and no lymphadenopathy or organomegaly was detected. Hematologic investigations and biochemical blood tests were unremarkable. Biopsy of the ulcerated lesion of the oral cavity (figure 2) showed Langerhans cell histiocytosis (LCH) and immunohistochemistry was positive for CD1a and S100 protein. Treatment with thalidomide was started with improvement of skin lesions.

Four months after initiation of treatment, the patient developed symptoms of weight loss and dyspnea. Chest x-ray demonstrated a reticular pattern throughout both lungs, mainly in the upper and middle thirds (figure 3). Pulmonary function test (spirometry) showed mild obstructive ventilatory defect with normal forced expiratory vital capacity (FVC). High resolution computed tomography (HRCT) revealed diffuse and bilateral cysts of variable size and shape, predominantly

distributed in the upper and middle lung zones with relative sparing of the lung bases near the costophrenic sulci (figure 4). Multisystemic LCH (MS-LCH) was then confirmed. Chemotherapy treatment was started with two courses of 6-week therapy with vinblastine and prednisone, followed by maintenance therapy consisting of pulses of vinblastine and prednisone every 3 weeks and daily continuous 6-mercaptopurine. Currently, the patient is on maintenance treatment that also includes prednisone (40mg/m²/day) on days 1-5 of week every third week, is asymptomatic and with complete remission of skin lesions.

DISCUSSION

The term LCH is used to include a spectrum of disorders previously designated as histiocytosis X, eosinophilic granuloma, Hand-Schüller-Christian disease, Letterer-Siwe disease and Hashimoto-Pritzker disease. LCH is a rare disease of unknown pathogenesis, characterized by an abnormal nonmalignant proliferation of monoclonal Langerhans cells, a subtype of dendritic cells located in epithelial surfaces [1,2,3]. The pathogenesis of LCH is poorly understood and theories as somatic mutations, viral infections and immunologic factors have all been proposed, but no definitive proof for any of these

mechanisms has been provided [4]. Pulmonary LCH is found almost exclusively in cigarette smokers (90% to 100%), which supports the theory of antigen exposure, and has a peak occurrence at 20-40 years of age, predominantly in white patients. Gender predominance has been debated, but it is believed that men and women are equally affected [1,5]. It is estimated that one to two adult cases of LCH occur per million population [6].

This disease can affect the lungs, usually in isolation, and less commonly, involve more body systems, including bone, pituitary gland, mucous membranes, skin, lymph nodes and liver [1,3,5]. Patients may have skin lesions, with periods of remission and exacerbation, isolated or associated with involvement of other organs, leading to a worse prognosis. In the axillae, inguinal, perianal, neck and retroauricular areas, papules and subcutaneous nodes may ulcerate leading to lesions that are difficult to heal despite treatment. Genital ulcers are more frequent in adults. Oral manifestations may be the first sign of LCH, and on some occasions the oral cavity may be the only area affected, with plaques that tend to ulcerate leading to loss of teeth [3,7].

In this report, we demonstrated a case of MS-LCH with advanced lung involvement. Most patients with pulmonary LCH are symptomatic, and the most frequent presenting complaints include nonproductive cough (50%-70%) and dyspnea (35%-87%). Less common presenting symptoms include fatigue (16%-30%), weight loss (9%-30%), chest pain that is frequently pleuritic (9%-18%) and fever (15%). Approximately 25% of patients with pulmonary LCH are asymptomatic, and the disease is diagnosed because of incidentally discovered radiographic abnormalities [4]. In this case, the patient initially had extensive skin lesions without clinical lung manifestations. Eruptive xanthoma and cutaneous lymphoma were initially included in the differential diagnosis, due to the skin and mucosal lesions.

The diagnosis of LCH is sometimes difficult due to its wide clinical spectrum, ranging from a single lesion to a multisystemic disorder. The most common clinical symptoms include dyspnea, cough, and fatigue, although patients may present with chest pain caused by a pneumothorax [1].

Radiologic findings of pulmonary LCH vary depending on the stage of the disease at diagnosis. Early in the disease, the most common radiographic manifestation is diffuse bilateral and symmetric ill-defined small nodules, which typically range from 1 to 10 mm in diameter, predominantly distributed in the upper and middle lung zones with sparing of the costophrenic angles [1,4,5]. It is thought that these nodules undergo cystic degeneration as the disease progresses, and so a reticular pattern begins to predominate on chest radiographs as the numerous cystic walls are superimposed on one another. The cysts and residual parenchyma can undergo fibrosis over time and eventually lead to changes of honeycombing [4].

The appearance of pulmonary LCH early in the course of the disease on HRCT scans is by multiple nodules that have an upper lung predominance and spare the lung bases. In addition to the nodules, cystic spaces with thin, well-defined

walls are present in most cases [8]. Central necrosis of granulomatous nodules is believed to produce the thin-walled cavities [3]. The diagnostic accuracy of HRCT falls short when only nodules or cysts alone are present. Most of these cases are confirmed by lung biopsy [1]. In end-stage LCH, there may be only diffuse, large and irregular cysts with no nodules. With more extensive and long-standing disease, progressive fibrosis leads to retractile scar emphysema, as well as disruption and remodeling of the elastic fiber network that eventually produces honeycomb lung [8].

Pulmonary LCH must be differentiated from other cystic lung diseases such as bullous emphysema, lymphangioliomyomatosis and bronchiectasis. Lymphangioliomyomatosis affects women almost exclusively and is expressed as diffuse and bilateral cysts. The cystic cavities of emphysema represent foci of destroyed parenchyma and lack definable walls. The cyst like bronchial dilatation seen in bronchiectasis can be distinguished by the communicating branching pattern seen on contiguous CT images [1].

In cases of nodular LCH, other differential diagnoses should be remembered as sarcoidosis, silicosis, metastases, miliary tuberculosis, and other hematogenous infections. Pneumocystis jiroveci pneumonia with formation of cysts or pneumatoceles may not be distinguished from PLCH [1,4].

Diagnosis may be confirmed by Birbeck granules demonstrated on electron microscopy, CD1a and/or Langerin (CD207) positive cells on immunohistochemistry and S100 positive cells with characteristic histopathology [2,9]. In contrast to normal Langerhans cells, the principal histiocytes of LCH are actively proliferating, have a round rather than dendritic shape, and express several contrasting antigenic markers [10].

Cessation of smoking leads to stabilization of symptoms in the majority of patients with pulmonary LCH and may be the only intervention required, but there is no evidence that degree and duration of smoking correlate with severity of disease [4]. According to treatment guidelines of the Histiocyte Society, chemotherapy with prednisone (PRED) and vinblastine (VBL) in combination has been proven to be effective treatment with minimal toxicity and is therefore the standard initial therapy for all patients in whom systemic therapy is indicated. Prophylaxis against Pneumocystis jiroveci should be given in patients who are receiving systemic therapy [2].

More toxic chemotherapeutic agents are reserved for patients who fail to respond. Lung transplantation should be considered for patients with advanced disease and smoking cessation is mandatory in these cases [1,4,5].

The prognosis of LCH is variable, depending on patient age, the extent of disease and treatment. Younger patients tend to have more severe disease [11]. However, LCH generally follows a benign course and in the absence of organ dysfunction, children with either localized or multifocal LCH have an excellent prognosis [12, 13]. Up to one-half will show

clinical and radiographic stability, while up to 25% will demonstrate spontaneous regression. The remaining 25% can have continued cystic replacement of parenchyma that may progress to end-stage lung disease [1,4].

Considering the wide clinical spectrum of LCH and the fact that up to 25% of patients are asymptomatic, imaging methods (specially HRCT) play a fundamental role not only in diagnosing and assessing the extent of LCH, as well as guiding the appropriate treatment for the patient and their monitoring, preventing from incorrect disease staging that can impact on decision making and treatment plans.

TEACHING POINT

Langerhans cell histiocytosis is a rare disease with variable clinical presentations. Radiological evaluation, especially HRCT, is useful to detect lung injury at each stage of pulmonary involvement in LCH, from small centrilobular nodules to diffuse cysts and fibrosis. Differential diagnosis includes lymphangiomyomatosis, bronchiectasis and emphysema when there is lung involvement. Paracoccidioidomycosis, mucocutaneous leishmaniasis and tuberculosis should be considered in endemic areas, in cases of multisystemic disease.

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FIGURES



Figure 1: A 54-year old man with multisystemic Langerhans cell histiocytosis. Multiple papular lesions on the scalp (A), underarms (B) and inguinal region (C), and ulcerated lesion in the oral cavity (D).

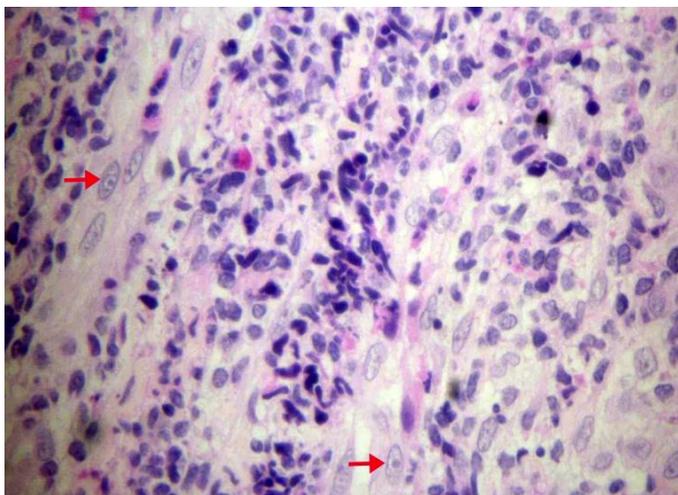


Figure 2 (left): A 54-year old man with multisystemic Langerhans cell histiocytosis. Microscopic histological examination of tissue biopsy of the oral cavity, demonstrating Langerhans cells with abundant cytoplasm (red arrows) and infiltration of inflammatory cells (haematoxylin and eosin stain, magnification: 100x).

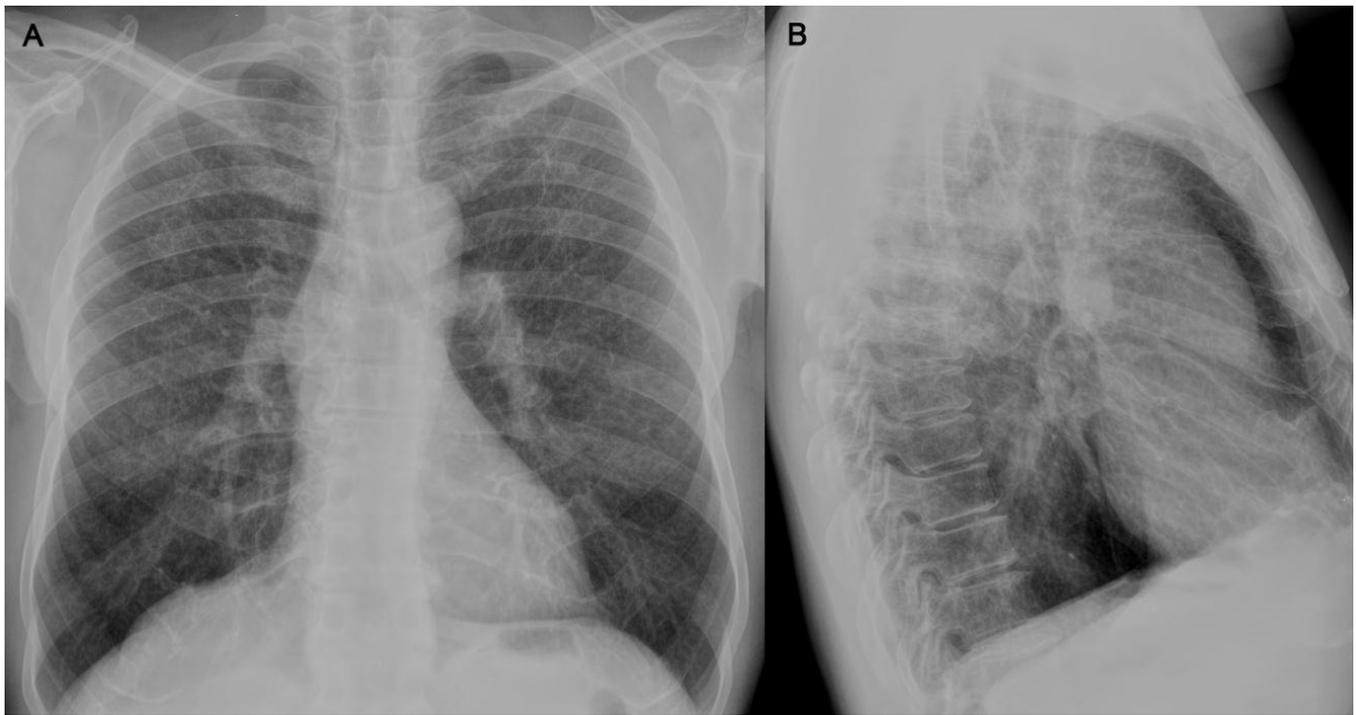


Figure 3: A 54-year old man with multisystemic Langerhans cell histiocytosis. Posteroanterior (a) and lateral (b) chest x-ray demonstrating a reticular pattern throughout both lungs, mainly in the upper and middle thirds.

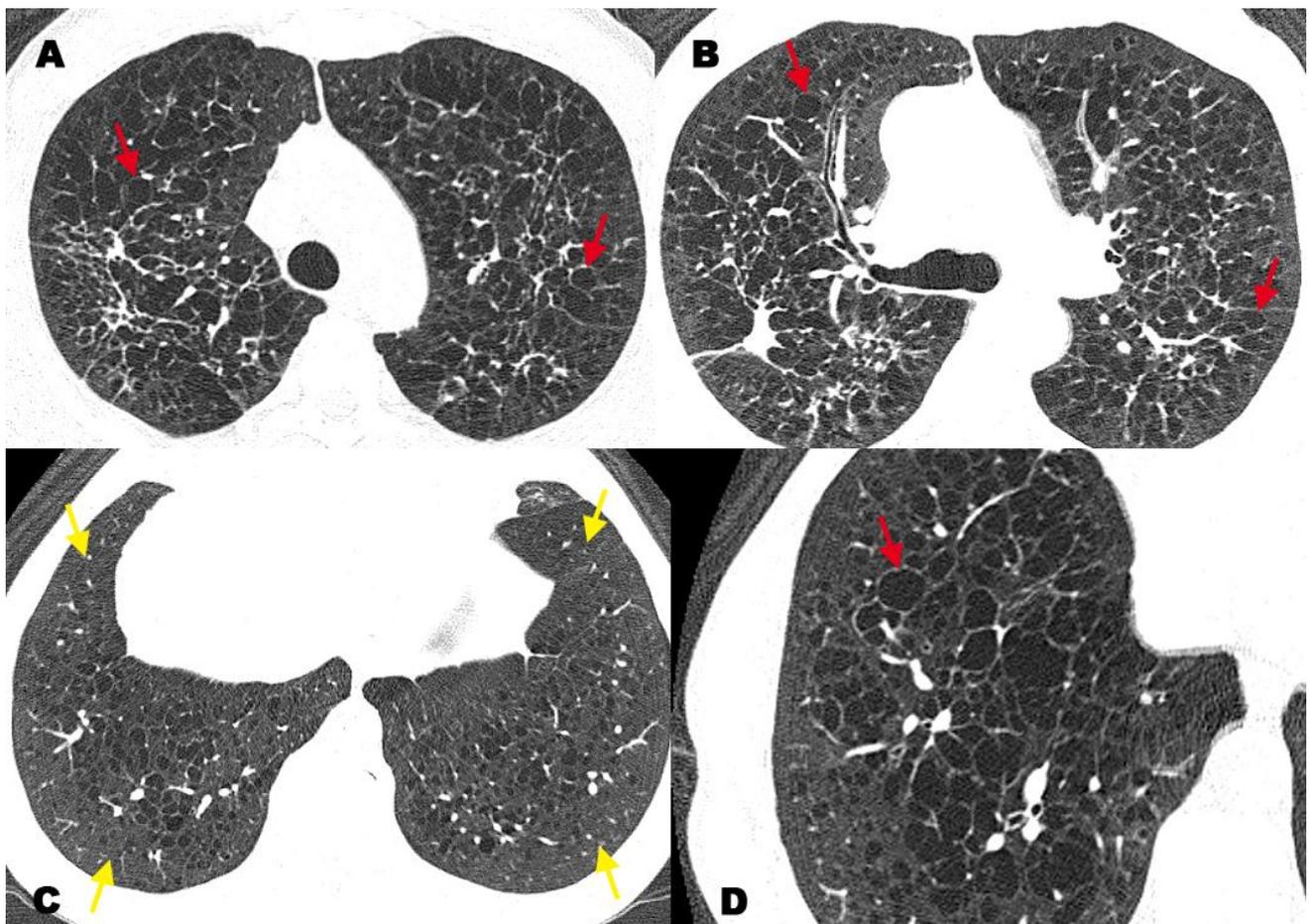


Figure 4: A 54-year old man with multisystemic Langerhans cell histiocytosis. High resolution computed tomography axial images (GE HiSpeed CT, 120 kV, 150 mAs, 1mm slice thickness, without intravenous contrast) from upper lobes to lung bases (a,b,c) and magnified view of the right lower lobe (d), demonstrating diffuse lung cysts of variable size and shape with thin walls (red arrows), predominantly distributed in the upper and middle lung zones and less intensely affecting the lung bases and costophrenic angles (yellow arrows), without evidence of pulmonary nodules.

Etiology	Unknown pathogenesis characterized by an abnormal nonmalignant proliferation of monoclonal Langerhans cells
Incidence	Although specific incidence is unknown, because it is a rare disease, a significant number of patients can be asymptomatic and the disorder may undergo spontaneous resolution, it is estimated that one to two adult cases of LCH occur per million population.
Gender ratio	Gender predominance has been debated, but it is believed that men and women are equally affected
Age predilection	Peak occurrence at 20–40 years of age, predominantly in white patients
Risk factors	LCH is found almost exclusively in cigarette smokers (90% to 100%), which supports the theory of antigen exposure
Main organs involved	Lungs, usually in isolation, and less commonly bone, pituitary gland, mucous membranes, skin, lymph nodes and liver.
Clinical symptoms	Most patients are symptomatic, and the most frequent presenting complaints include nonproductive cough and dyspnea. Less common: fatigue, weight loss, chest pain and fever.
Treatment	First line treatment for MS-LCH patients consists of an initial 6-week course of therapy with prednisone and vinblastine regardless of risk organ involvement. All patients who have complete disease resolution after 6-12 weeks of initial therapy continue with maintenance therapy, that consists of pulses of vinblastine and prednisone every 3 weeks and daily continuous 6-mercaptopurine for a total treatment duration of 12 months. Prophylaxis against <i>Pneumocystis jiroveci</i> should be given in patients who are receiving systemic therapy. Lung transplantation should be considered for patients with advanced disease and smoking cessation is mandatory in these cases.
Prognosis	Variable, depending on patient age, the extent of disease and treatment. Generally follows a benign course and in the absence of organ dysfunction.
Findings on imaging	X-Ray: May appear normal or show multifocal contiguous cysts that measure up to 2–3 cm in diameter. End-stage is characterized by reticular areas of opacity that predominate in the upper and middle lung zones. CT: Early in the course of the disease HRCT scans reveals multiple nodules that have upper lung predominance and spare the lung bases. With long-standing disease, there may be only diffuse, large and irregular cysts, leading to honeycomb lung.

Table 1: Summary table of multisystemic Langerhans cell histiocytosis.

	X-RAY	CT
Pulmonary LCH	May appear normal or show multifocal contiguous cysts that measure up to 2–3 cm in diameter. End-stage is characterized by reticular areas of opacity that predominate in the upper and middle lung zones. Spontaneous pneumothorax may rarely occur.	Early in the course of the disease HRCT scans show multiple nodules that have an upper lung predominance and spare the lung bases. With long-standing disease, there may be only diffuse, large and irregular cysts, leading to honeycomb lung.
Lymphangiomyomatosis	Only females are affected, showing normal to large lung volumes and interstitial reticular opacities that may be subtle. Unilateral pneumothorax and unilateral or bilateral pleural effusions.	Bilateral diffuse thin-walled cysts surrounded by normal lung parenchyma and may also demonstrate associated pleural effusion
Bronchiectasis	Range from linear pulmonary markings and mucus filled bronchi to cystic spaces and honeycombing	Irreversible bronchial dilation which remains in the subsequent images (“railroad track”).
Emphysema	Signs of hyperinflation associated with cystic cavities, honeycombing, reticulations, and in some cases pneumothoraces.	The cystic areas represent foci of lung destruction that typically lack perceptible walls. There are four categories: centrilobular (centriacinar), panacinar (panlobular), paraseptal, and paracicatricial.

Table 2: Differential table of pulmonary Langerhans cell histiocytosis.

ABBREVIATIONS

HRCT = High Resolution Computed Tomography
 LCH = Langerhans cell histiocytosis
 MS-LCH = Multisystemic Langerhans cell histiocytosis

KEYWORDS

Langerhans cell histiocytosis; computed tomography; lung; skin diseases

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