

Special Article - Radiology Case Reports

Pulmonary Langerhans Cell Histiocytosis: Trapped Case

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Abstract

Langerhans Cell Histiocytosis (LCH) is a rarely seen disease and has a very large spectrum varying between solitary bone lesions and involvement of many organs or systems. Pulmonary involvement in LCH may be a component of a multisystem disease or it may affect only lungs. Herein, we are presenting a 35-year-old male patient with LCH confined to lungs which progressed with the development of spontaneous pneumothorax that might be overlooked during histopathological evaluation because of its development in the interstitial space without nodular formation.

Keywords: Langerhans cell histiocytosis; pulmonary

Introduction

Langerhans Cell Histiocytosis (LCH) is a rarely seen disease characterized by nodules consisting of cells having the phenotype of Langerhans cells, and various inflammatory cells. It has a very large spectrum varying between solitary bone lesions and involvement of many organs or systems [1].

Pulmonary involvement in LCH may be a component of a multisystem disease or it may affect only lungs. Pulmonary Langerhans Cell Histiocytosis (PLCH) is generally confined to lungs. Basically PLCH is a form of interstitial pulmonary disease, and it is accepted as a disease different from systemic LCH. The symptoms of this disease are very variable and may include dyspnea, chest pain, hemoptysis, and spontaneous pneumothorax [2].

Herein, we are presenting a 35-year-old male patient with LCH confined to lungs which progressed with the development of spontaneous pneumothorax that might be overlooked during histopathological evaluation because of its development in the interstitial space without nodular formation.

Case Report

A 35-year-old male. Smoking stories are available for 10 years. He has quit smoking for the last 5 years. On 05.12.2016, the patient came to the emergency service. There was an increased chest pain in battle style with movement. Except for a reduction in respiratory sounds in the left lung, physical examination was unusual in the patient with COPD. Imaging findings with pneumothorax pre-diagnosis revealed that the lower lobes of both lungs were preserved (Figure 1). Due to the developing pneumothorax, wedge resection of the lower left superior segment was performed.

Pathological Findings

Macroscopically, a slight outward bulging with its greatest dimension being 1.2 cm was detected in pulmonary wedge resection material whose end was occluded with a stapler attracted attention. The surface of the slices cut from this area had a spongy structure containing very small cystic formations. All of the tissue was sampled. Microscopically, under small magnification marked congestion,

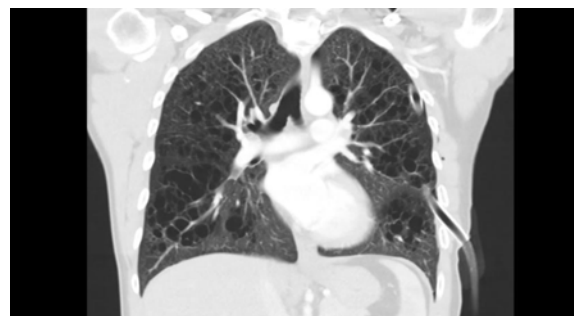


Figure 1: High-resolution computed tomography image in coronal plane shows numerous bizarre shaped cysts of varying size in both lungs. Note that only the lower zones were spared.

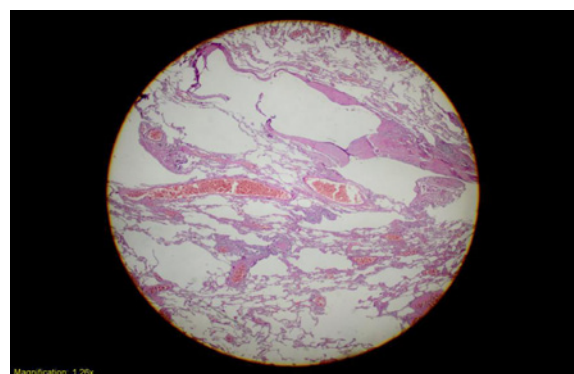


Figure 2: Low power magnification; marked congestion, emphysematous changes and slightly fibrotic alveolar septa adjacent to enlarged airways (H&E x20).

and emphysematous changes, and slightly fibrotic alveolar septa adjacent to enlarged airways in-between were more prominent (Figure 2). At only a few areas nodular formations enlarged, and extended into alveolar structures attracted our attention (Figure 3a). More attentive examination of these nodular structures revealed their bronchiolocentric characteristics (Figure 3b). Under greater magnification, these nodular formations were infiltrated with histiocytic cells with round-oval shaped, pale nuclei, and moderately

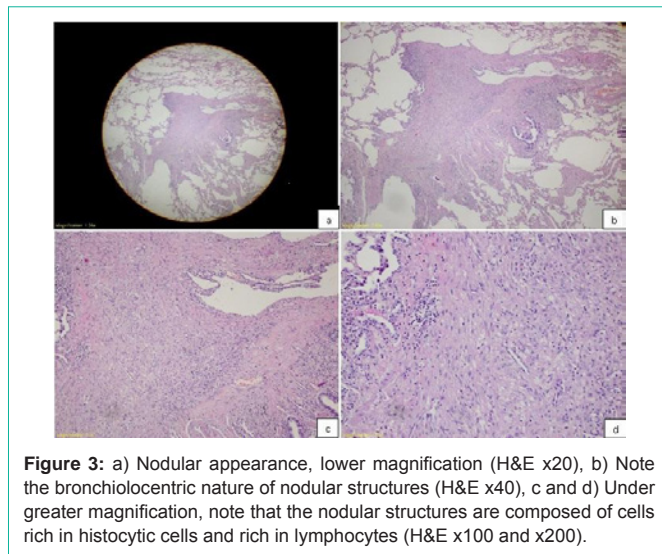


Figure 3: a) Nodular appearance, lower magnification (H&E x20), b) Note the bronchiocentric nature of nodular structures (H&E x40), c and d) Under greater magnification, note that the nodular structures are composed of cells rich in histiocytic cells and rich in lymphocytes (H&E x100 and x200).

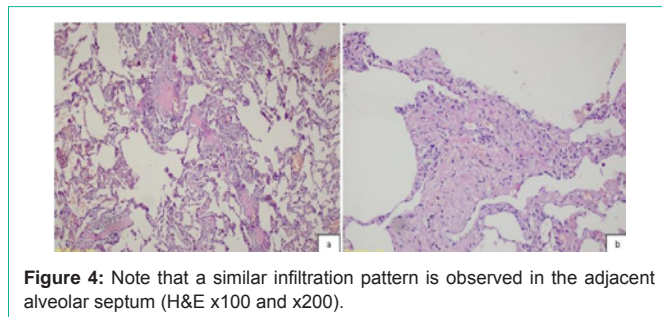


Figure 4: Note that a similar infiltration pattern is observed in the adjacent alveolar septum (H&E x100 and x200).

enlarged acidophilic cytoplasm, and mixed type inflammatory cells relatively rich in lymphocytes (Figure 3c and 3d). More detailed examination revealed cells with similar formation which indistinctly infiltrated entire length of alveolar septa (Figure 4a and 4b). Patchy areas of fibrosis were detected. Immunohistochemical staining with CD1a, S-100 demonstrated marked uptake of dye by histiocytic cells (Figure 5). Not only scarce number of cells contained in nodules, but also, cells in the adjacent interstitial space were stained.

Based on these findings, the final diagnosis was pulmonary LCH.

Discussion

Langerhans cells are a subtype of dendritic cells. Dendritic cells involve in the mononuclear phagocytic system, and they fulfill their functions by presenting antigen to T-lymphocytes. These cells are found in the skin, and mucosa, and normally they are scattered all along the airways. PLCH are the most important dendritic cell proliferation affecting the lungs. This condition is generally known as a form of interstitial pulmonary disease which is only confined to lungs, and it is accepted as a distinct entity from systemic LCH [3]. PLCH is generally an adult disease, and it is almost always seen in active smokers or quitters. Any risk factor is not known for the systemic form, and it is very frequently observed in small children [4].

PLCH has miscellaneous clinical presentations. Only 25% of the patients are asymptomatic, and they demonstrate characteristic signs in incidentally performed imaging modalities. In 15-25% of the cases the disease is complicated by spontaneous pneumothorax [5]. Our

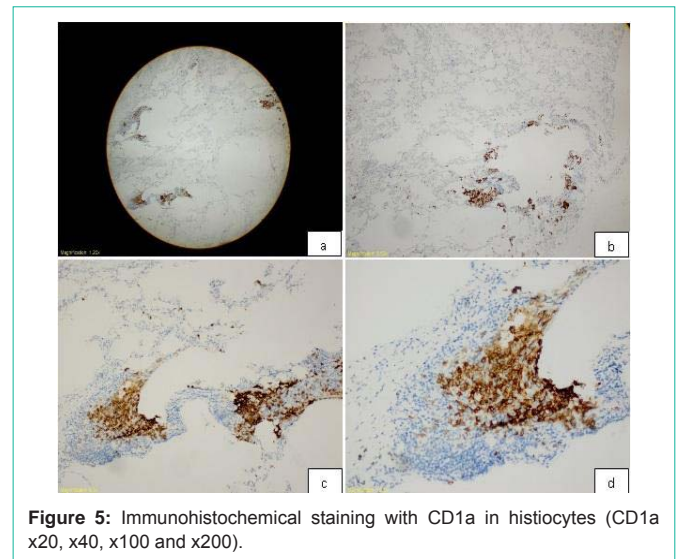


Figure 5: Immunohistochemical staining with CD1a in histiocytes (CD1a x20, x40, x100 and x200).

case has been followed up since 2014, and underwent open lung biopsy two years later because of development of pneumothorax. In the presence of typical radiological findings on HRCT scan (involvement of upper and middle pulmonary lobes, and relatively intact basal regions), and consistent clinical data (middle age, smoking history in a male patient) very frequently, the diagnosis of PLCH is successfully made [3]. Lung biopsy may not be required. However in cases with atypical radiological findings, and clinical presentation tissue biopsy may be required for definitive diagnosis. Open lung biopsy is more frequently regarded as a diagnostic tool for PLCH. These types of biopsies should be performed with the aid of CT (if possible), and biopsy materials should be obtained from multiple lobes. Biopsy material resected from only left inferosuperior segment was sent to us. If a marked nodular infiltrate can be macroscopically identified in an open pulmonary biopsy material obtained during wedge resection, the pathologist is lucky. Because the nodules are generally small in size, occasionally large nodules can be seen. In our case, macroscopically a prominent nodular formation was not seen, and very minute, cystic spongy pinhead-sized areas were observed. Microscopically, a conspicuous nodular structure was not found. Only, in addition to clinical follow-up, and imaging findings, very attentive microscopic evaluation allowed us to arrive at an accurate diagnosis.

In the early stage PLCH, cellular infiltration is marked, and typically forms loose cellular nodular structures scattered all over lung tissue, and spaces adjacent to small airways. At this stage, since bronchiolar wall, and neighbouring alveolar structures were exposed to destructive changes, small airways are subjected to progressive dilatation. With time, small airways are surrounded by hypocellular tissue rich in fibrotic tissue. Star-shaped scar, and irregular parenchymal cystic lesions become conspicuous. Later Langerhans cells can not be detected in the lesion, and such lesions are defined as "burnt-out" PLCH.

Though rarely seen honeycomb changes are still observed in end-stage disease. Since the patients with PLCH have a history of smoking, smoking-related changes in pulmonary parenchyma as respiratory bronchiolitis, Desquamative Interstitial Pneumonia (DIP), and/or emphysema are seen. These conditions are considered in the

histological differential diagnosis of PLCH. Detection of clusters of Langerhans cells with characteristic findings of morphology, and immunohistochemical staining allows exclusion of many disease states included in the differential diagnosis of PCHL. In the detection of PLCH, bronchiolocentric characteristic of the disease, enlargement of cystic airways, and presence of mixed inflammation are also very important markers. In the differential diagnosis spectrum of PLCH histiocytic/macrocyclic lesions [DIP, respiratory bronchiolitis, Erdheim-Chester Disease (ECD), and hypersensitivity pneumonitis], and eosinophilic diseases (eosinophilic pneumonia) are taken into consideration. In all these diseases large groups and nodules of Langerhans cells are not seen. However in interstitium, and bronchiolar mucosa a few scattered Langerhans cells can be found. Besides, in all pulmonary diseases excepting PLCH histiocytes do not stain with CD1a, and langerin (CD207), they may only be stained with S-100 dye. Lets analyse disease states considered in the differential diagnosis one by one. DIP is a completely diffuse process, rather than a nodular formation. Besides, cellular infiltration in DIP does not resemble to that seen in PLCH, and predominantly infiltration rich in macrophages is observed. In our case, we detected very minute indistinct nodular formations during very careful microscopic examination. This nodule was infiltrated with conspicuous lymphocytes, while in all other interstitial spaces faintly seen lymphocytes were observed. Apparent macrophage dominance was not noted. In Eosinophilic Pneumonia (EP) presence of multiple number of eosinophils together with macrophages in airspace nodules is remarkable. Clusters of Langerhans cells are not seen. In ECD infiltration and/or nodules of histiocytes have/has a characteristic appearance. In ECD, histiocytes have a foamy cytoplasm, typical nuclear characteristics of Langerhans cells are not observed. Similar to PLCH, peribronchiolar space may contain histiocytes. However histiocytes demonstrate a lymphangitic distribution, and they are most frequently found in subpleural, interlobular septa, and perivascular areas. Advanced fibrotic stage of PLCH may be similar to the Usual manifestation of Interstitial Pneumonia (UIP). Contrary to UIP, PLCH has a predilection for subpleural space rather than centrilobular areas. Besides, star-shaped pattern of fibrotic nodules is a descriptive feature of PLCH, rather than UIP.

The most important treatment for PLCH is cessation of smoking. However still some cases progress or become stable despite continuation of smoking. Nowadays, any predictive biomarker which can fully foresee progression of PLCH is not available. In some studies beneficial effects of corticosteroids, and chemotherapeutic agents in the management of severe or progressive disease have been reported. Cladribine (2-chlorodeoxyadenosine), an agent cytotoxic to lymphocytes and monocytes, has been used in LCH and recently has also been tried for a few patients with PLCH. However, these medications seem to be of limited value additional data are also needed to assess the efficacy of these agents [6]. Lung transplant might be considered for patients with advanced, progressive disease. But, PLCH can recur after lung transplantation.

It is debatable whether PLCH is a reactive or a neoplastic condition. Since in most of the patients it is associated with smoking, it was thought to be a non-neoplastic disease. However in systemic LCH,

any provocative agent has not been clearly defined. The presence of clonality in systemic LCH was demonstrated in a study by Willman et al. performed on 10 patients in the year 1994 [7]. Further studies have also provided additional support for the clonality of LCH [8,9]. More recently, in two studies the presence of BRAF V600E expression has been described which will substantiate the assertion that systemic LCH might be a type of myeloid neoplasm [10,11].

Two different studies performed by Yousem et al. have also supported the presence of clonality in PLCH [12,13]. Later on Roden et al. defined BRAF V600E expression in 28% of PLCH, and 35 % of systemic LCH patients [14].

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