Langerhans Cell Histiocytosis and Other Histiocytic Diseases of the Lung

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KEYWORDS

• Histiocyte • Langerhans cell • Macrophage • Cigarette smoking • Lung • Interstitial • BRAF

KEY POINTS

- Several of the primary histiocytic disorders may affect the lung in varying ways: among the histiocytic disorders occurring in adult patients, Langerhans cell histiocytosis is the most commonly encountered and usually is associated with cigarette smoking.
- The histiocytic disorders are rare, and all manifest variable clinical courses that may range from benign disease with spontaneous regression to life-threatening aggressive disorders associated with high morbidity and mortality.
- Definitive diagnosis of these rare clinical entities requires histopathologic confirmation.
- Activating mutations associated with specific cell regulatory pathways have been described in Langerhans cell histiocytosis and Erdheim-Chester disease and provide information about the natural biology of these diseases as well as potential for specific targeted treatment using inhibitors of these pathways.
- Management includes specific treatment of the underlying histiocytic disorder, avoidance of exacerbating factors like cigarette smoking or second-hand smoke exposure, management of complications (such as pneumothorax or pulmonary hypertension), and lung transplantation in selected instances.

INTRODUCTION

The histiocytic syndromes are a diverse collection of diseases caused by proliferative abnormalities in the macrophage and dendritic cell lineage, but resulting in strikingly varied clinical behavior. Although some syndromes are life-threatening, others follow an indolent course and require minimal therapeutic intervention. The Langerhans cell histiocytoses (LCH) are a subclassification of these syndromes caused by infiltration of specialized dendritic cells (Langerhans cells) into the lung as a single disease site, or multiple organs.[1] These infiltrating cells trigger an inflammatory cascade and varying degrees of organ dysfunction.[2,3] Other, less common, histiocytic syndromes that can involve the lung include Erdheim-Chester disease (ECD) and Rosai-Dorfman disease (RDD). Key aspects of these histiocytic entities are summarized in **Table 1**. Pulmonary LCH (PLCH) is reviewed in detail in the current review, because it is the predominant

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Table 1
Summary of certain contrasting features between pulmonary Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease

	Pulmonary LCH	Erdheim-Chester Disease	Rosai-Dorfman Disease
Association with cigarette smoking	Yes	No	No
Key histopathologic findings	Bronchiolocentric lesions with Langerhans cells, eosinophils, and other inflammatory cells forming loosely formed nodular lesions	Tissue infiltration by foamy histiocytes with interspersed inflammatory cells and multinucleate giant cells in a background of variable fibrosis	Tissue infiltration by histiocytic cells with mixed inflammatory infiltrates. Emperipolesis (histiocytic cells engulfing leukocytes) is a cardinal feature
Immunostaining profile of lung biopsy	S-100+, CD1a+, Langerin+ Factor XIIIa−	CD68+, CD163+, Factor XIIIa+ CD1a−, S-100−, Langerin−	S100+, CD14+, CD68+, and CD11c+ CD1a−, Langerin−, Factor XIIIa−
Birbeck granules on electron microscopy	Present	Absent	Absent
Detection of BRAF-V600E mutation	Approximately 30% of cases	At least 50%	Usually negative
Predominant chest CT findings	Cysts and lung nodules distributed mainly in the mid and upper lung fields with sparing of the lung base.	Mediastinal infiltration, pleural thickening/effusion, interlobular septal thickening, centrilobular nodular opacities, ground-glass opacities, and lung cysts	Mediastinal and hilar adenopathy most common feature. Cystic change, parenchymal infiltrates, and airway disease are less common

histiocytic disorder encountered by pulmonary specialists, while key features of ECD and RDD will also be outlined.

EPIDEMIOLOGY AND DEMOGRAPHICS

Although considered an uncommon disease, the exact prevalence and incidence of LCH are unknown. One study described greater than 500 patients with lung diseases who underwent surgical lung biopsy; PLCH was identified in 3.4% of cases.[3] PLCH can affect all ethnic groups and all ages, although most often patients are diagnosed between the ages of 20 and 40 years.[4,5] Heritable genetic factors do not appear to play a prominent role in pathogenesis.[6] Isolated PLCH is primarily a disease of young adult smokers, with greater than 90% of patients endorsing a smoking history in several series.[4,7,8] In multisystem LCH, the smoking connection is less clear. Although multisystem LCH is 3 times more prevalent in the pediatric population than adults, isolated PLCH is exceedingly rare in children.[9,10] Case reports of PLCH recurrence in adolescents who smoke with childhood multisystem LCH in remission support the hypothesis that tobacco smoke exposure plays a critical role in the pathogenesis of PLCH.[11]

PATHOLOGY AND PATHOPHYSIOLOGY

In cases of advanced PLCH, gross pathologic inspection may reveal cysts on the pleural surface and palpable nodules of various sizes.[12] Although most nodules are between 1 and 5 mm in size, they can grow to sizes of up to 15 mm. In late disease, nodules are replaced by advanced bullous and cystic lesions, often in association with hyperinflation and late-stage fibrosis with honeycombing.[13] PLCH affects the bronchiolar, interstitial, alveolar, and vascular compartments of the lung to variable degrees in different patients. Although traditionally considered an interstitial lung disease, it is arguably more appropriate to consider PLCH as an inflammatory bronchiolitis with loosely formed nodules of dendritic cells aggregating around small airways,[8,12,14] resulting in varying degrees of interstitial inflammation, alveolar macrophage infiltration,[13] and proliferative vasculopathy of both arteries and veins.[8,15,16]