Pulmonary Langerhans Cell Histiocytosis

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Introduction

Langerhans' cell was discovered by Paul Langerhans in 1868 and named after him. This cell was first described as an extracellular nerve cell from dendritic morphology.[1] Later, this cell was described as an immune cell as part of the mononuclear phagocyte system in the skin (antigen-presenting cell) and can be found in the other tissue.[2] The unique of Langerhans' cell which different from other dendritic cell are the present of Birbeck granules and CD1a antigen on their cell surface as well as their origin, yolk-sac progenitor cells, and fetal liver-derived monocytes instead of myeloid progenitor cells.[2-3]

Langerhans' cell histiocytosis (LCH) is one of the histiocytosis disorders, abnormal accumulation of monocyte, macrophage, or dendritic cell in organs. It is a rare disease of inconclusive etiology and has a broad spectrum of clinical manifestations and prognosis.[2-4] This disease was firstly described in 1893 and had many synonyms based on organ involvement.[5-6] LCH can affect all age groups and is divided into systemic LCH (Hand-Schuller-Christian disease, Letterer-Siwe disease) and localized LCH. The latter has a better prognosis.[7] Pulmonary Langerhans' cell histiocytosis (PLCH) can be found either in isolated PLCH or systemic LCH.[8]

Epidemiology

The prevalence of PLCH is unknown, but it is estimated at 3-5% of adult diffuse lung diseases[9] This might be underestimated because PLCH could be asymptomatic and spontaneously remitted. Moreover, it is difficult to make a diagnosis in advanced disease based on clinical presentation combined with thoracic imaging and tissue diagnosis in a severe form of cystic lung disease is impracticable.[8, 10-11] PLCH has a peak incidence between the age of 20 and 40. There is no gender predominant however, it tends to develop in older age in female patients. Over 90% of patients are current or ex-smokers.[2,5,7,11] PLCH is almost sporadic. It has been frequently reported in Caucasian and Asian population but not in the African population.[2,7,12-14]

Pathogenesis

Langerhans' cell is one of the subclasses of dendritic cell that found in the skin, under tracheobronchial tree epithelium and function as the first response of defense by a survey of antigen deposition in the airway after inhalation.[15] The immature Langerhans' cell shows a high level of langerin (CD207) which is the lectin necessary for the formation of Birbeck tablets, which was initially considered to be exclusive to Langerhans' cells[16] After the activation, Langerhans' cell migrated through

CCR7-dependent chemokine receptor to the adjacent lymph nodes and induce the inflammatory response.[3,17] However, recent data suggest that Langerhans' cell in PLCH is closely related to myeloid dendritic cell precursor than mature Langerhans' cell.[18] There are 4 aspects of PLCH pathogenesis.[7]

1. The accumulation of CD1a+ cells: this process induces the formation of loose granuloma around the small airways. The accumulation of CD1a+ cell, T-cell, and other inflammatory cells induce local neoangiogenesis, signaling, and cell adhesion molecules.[19] The CD1a+ granuloma in PLCH does not have a marker of proliferation but appears to resist apoptosis.[7,20-22]

2. The destructive behavior of PLCH granuloma: PLCH can destroy and remodel the destructive tissue. The transcription studies of langerin-positive cells in LCH granuloma reveal that these cells have different profiles from epidermal Langerhans' cell and dendritic cell.[7,23] In LCH granuloma, the finding of various metalloproteinases suggests that the cause of PLCH induce tissue injury. Moreover, recent studies suggest the role of IL-17 in the remodeling of environmental tissues. [7, 24,25]

3. PLCH is reactive, clonal, or neoplastic? this topic has been widely speculated and debated. In the past, PLCH was recognized as a reactive disease from smoking since the mitotic feature and recurrent cytogenetic abnormalities were not found in CD1a+ cells of these lesions and the disease remitted spontaneously after smoking cessation.[26-28] Although the aggressiveness in some cases and response to chemotherapy management indicated the neoplastic property. However, the identification of BRAF mutations in LCH development led to significant changes in the concept of disorder.[17] BRAF is a serine/threonine kinase involving in growth signaling within the mitogen-activated protein kinase (MAPK) pathway which is involved in numerous cell functions[3,29]. The *BRAF*V600E mutation results in component activation of BRAF protein and cancer cell proliferation of multiple different tumors.[3,29-30] The *BRAF*V600E mutation also causes the activation of the MAPK pathway which plays a key role in cell differentiation and survival.[3,7] This mutation is found in about 35-60 % of PLCH[31] Other than *BRAF*V600E mutation the mutation in *BRAF* such as in-frame deletion, fusion, and duplication has also been reported.[3] The second most genetic mutation next to *BRAF*V600E is *MAP2K1* mutations (about half of *BRAF*V600E mutation) which affect a kinase downstream of BRAF within MAPK signaling. [29,32-33] Additionally, *NRAS* mutation occurs concurrently with *BRAF*V600E mutation in PLCH, and both mutations are carried by different cell clones[34] and *NRAS* mutation was found only in PLCH. Currently, the clinical importance of MAPK pathway mutation is not well established and needs further evaluation.

4. Role of smoking: PLCH demonstrated a strong association with smoking but the mechanism remains unclear. The previous studies propose that smoking leads to the accumulation of non-neoplastic CD1a + cell in the lung, stimulates the production of cytokines such as TNFα, GM-CSF, TGFβ, CCL20, and promotes the survival of dendritic cell.[35-39] Osteopontin, a glycoprotein with chemokine capacity to induce chemotactic activities of macrophage, monocyte, dendritic cell including Langerhans' cell, support the relationship between smoking and PLCH. The overexpression of osteopontin in the animal model results in the same lesion as PLCH. [5,40] However, the rare prevalence of PLCH relative to the prevalence of smoking suggests that smoking is one of the predisposing causes of PLCH.

Clinical presentation

There are 3 spectra of clinical presentation.[7-8, 41]

1. The respiratory symptoms such as cough, dyspnea on exertion occur in 60% of the patients and 10-20% of patients describe the constitutional symptom (fever, fatigue, night sweat, and weight loss). However, hemoptysis is rare, and if present, further investigation should be performed to rule out the alternative diagnosis.

2. Pneumothorax appears the first presenting symptom in about 10-30% of patients and can occur at any time in the course of the disease (about 30-45% of the case). The pneumothorax can be unilateral, bilateral, or recurrent.

3. Incidental finding of routine chest radiography is revealed in 10-25 % of patients.

Generally, the physical examination could not detect the significant pathological signs except in the advanced stage or presence of another organ involvement. Clubbing of fingers and rales are rare.

Chest imaging [7-8,42-43]

Standard chest radiography: this study has a limitation in the early stage of the disease since most lesions are small and difficult to detect. The finding includes bilateral, and generally symmetric, reticulo-micronodular changes. Cysts might be identified, predominantly the upper and middle lung fields with sparing of the costophrenic angles. Lung volume is either normal or increased. Pneumothorax, the pleural lesion from previous pneumothorax or lytic bone lesion could be presented. The pleural effusion and mediastinal lymphadenopathy are unusual. In the advanced stage, the findings of pulmonary hypertension could be found.

High-resolution computed tomography of chest (HRCT): HRCT has an important role in the diagnostic approach in PLCH. The finding in HRCT is depended on the stage of the disease. In the early stage, the bronchiolocentric nodules, size about 1-10 mm with ground-glass opacity around the lesion represent the granulomatous process. These nodules sometimes have a faint center lesion or cavity, and sometimes could mimic features of RB-ILD. The cystic lesions are initially thick-walled cyst (>2 mm) then progress to the thin-walled cysts. In the advanced stage, cystic lesions become the predominant pattern and form irregular shapes (bizarre cysts) with fibrosis, typically in upper to middle lung zone predilection. The advantage of HRCT is not only to characterize the pattern of PLCH but also to select the site of biopsy, if necessary.

Fluorodeoxyglucose-positron emission tomography (FDG-PET): The role of using PET scan in isolated PLCH has not been well defined. The nodules in PLCH are hypermetabolic which are indistinguishable from the malignancy. In contrast, the finding of an isolated hypermetabolic nodule in PLCH raises a high suspicion of malignancy.

Pulmonary function tests (PFTs)

The abnormalities of PFTs vary on the extent of the destroyed lung and duration of the disease. About 10% of patients have normal PFTs in the early stage.[44] The most common abnormality is a decrease in diffusing capacity of the lungs for carbon monoxide (DLCO), approximately 80-90 % of PLCH.[2,44] The typical PFTs in PLCH illustrate reduced vital capacity (VC), normal or increased residual volume (RV), preserved lung volume (TLC) and, increased or normal RV/TLC.[7-8] The obstructive ventilatory defect occurs in about 30-50% whereas restrictive ventilatory defect appears in less than 20% of patients.[2, 7-8] The mixed ventilatory defect is observed at about 30%. The severity of obstructive defect depends on the extent of the cystic lesion on

HRCT. Some patients could have reversibility after bronchodilator[7,44] The 6-minute walk test may be impaired in the advanced stage of the disease.[2, 8, 17]

Bronchoscopy, BAL, and lung biopsy

On the bronchoscopic examination, the bronchial tree appears normal or non-specific inflammation related to smoking. The diagnostic yield of transbronchial lung biopsy varies about 10-50% due to the natural feature of the focal lesion.[7-8, 17] Cryobiopsy increases diagnostic yield because of the larger size of the specimen collected.[7]

BAL fluid analysis in PLCH usually demonstrates the pattern of smoking exposure such as the non-specific increase of eosinophil, a decrease in the proportion of alveolar lymphocyte, and a decrease in CD4/CD8 ratio.[8] Furthermore, the BAL fluid supports the diagnosis of PLCH if the analysis reveals an increase in CD1a+ cell at least 5% combined with the typical pattern on HRCT. This phenomenon is observed in 10-20% of PLCH cases.[7-8, 17] The elevation of CD1a+ in BAL fluid is not a pathognomonic finding in PLCH since it could be found in COPD, healthy smoker, and pulmonary fibrosis.[20]

The diagnosis of PLCH is routinely established based on clinical presentation and typical findings on HRCT. Nevertheless, tissue examination is required for definitive diagnosis in some cases. Surgical lung biopsy should be considered in a selected case, i.e.- failure to diagnose after performed other less invasive methods or performed during surgical pleurodesis. The specimens should be obtained from the site at which HRCT shows the multiple nodules. In the extensive disease with significantly impaired PFTs, the procedure is high risk and the balance of risk and definitive diagnosis should be concerned.[8,17,42]

Lung pathology

On light microscopy, Langerhans' cell is detected by the relatively large cell, eosinophilic cytoplasm, a pale nucleus with a prominent nuclear groove and a longitudinal crease resembling a coffee-grain[7,42.] In the early stage the poorly formed inflammatory nodules, variables number of Langerhans' cell, lymphocytes, monocytes/macrophages, eosinophils, and rarely giant cells, infiltrate adjacent to small airway and lead to the destruction of the bronchiolar wall and adjacent alveoli. The destruction processes result in cystic lesion forming and make the difficulty to confirm the bronchiolocentric distribution. Organizing pneumonia features might be found at the boundary of the nodules.[7,17,42] With the progression of PLCH, the number of Langerhans' cell decreases while the inflammatory cells persist. The inflammatory nodules become fibrosis with a typical characteristic called "stellate scar" or contiguous and confluent cystic cavities surrounded with the fibrous ring.[7] In the advanced stage (burnout PLCH) Langerhans' cell fade and the cystic and fibrosis pattern become prominent.[17, 42] The background of lung parenchyma of PLCH might show the pattern of smoking-related change similar to respiratory bronchiolitis, desquamative interstitial pneumonia, and/or emphysema.

Immunohistochemistry staining gives significant data and useful in the diagnostic approach in PLCH, especially in the case that limited size and number of tissue sampling. The hallmarks of PLCH is the deposition of a cluster of CD1a+ cells forming loose granuloma[7] In the past S100 protein was the staining of choice for diagnosis. Nowadays, using more specific immunohistochemistry staining such as CD1a and langerin (CD207) provide more accurate results. The less specific S100 protein is falsely positive in various conditions and also found in other cell types such as nerve, myoepithelial, and interfollicular dendritic cells.[17]

According to the histopathological pattern of PLCH, the differential diagnoses are histiocytic/macrocytic lesion and eosinophilic lung diseases such as desquamative interstitial pneumonia, hypersensitivity pneumonitis, Erdheim-Chester disease (ECD), and idiopathic interstitial pneumonia. Though, large clusters and nodules of Langerhans' cell and specific marker of CD1a are not present in these.[7,42]

Treatment

The treatments of LCH depend on organ involvement, the extension of the disease, and degree of destruction.

Smoking cessation: Referred to the relationship between smoking and PLCH, the first and most important treatment is smoking cessation.[7-8,17,28-,29,42,44] A retrospective study reported the smoking cessation in PLCH for at least 6 months slowed the decline of pulmonary function[44] In some patients with severe or progressive disease after smoking cessation, pharmacological treatment should be considered.

Corticosteroid: Oral corticosteroid (Prednisolone 0.5-1 mg/kg/day) with gradual reduction is often prescribed in patients who have disease progression. However, the efficacy of the treatment remains controversial and the duration should not be longer than 6 months. A combination of chemotherapy agents might be considered.[7,17,45] The benefits of inhaled corticosteroid and bronchodilator are seen in some PLCH patients with co-existing reactive airway disease.

Chemotherapy: Due to the lack of well-conducted study, the standard regimens for treatment is unavailable. The treatment regimens in PLCH are based on the treatment of systemic LCH or pediatrics LCH. Vinblastine, the main agent in the treatment of systemic LCH, shows unsatisfied outcomes in PLCH.[8,17,29,45] Cladribine has toxicity to lymphocyte

and monocyte. This synthetic purine analog shows efficacy in selected patients with PLCH i.e. improvement of pulmonary function, reduction of cystic size. The data has been still observed[7,8,17,42]

Targeted therapy: The knowledge of the *BRAF*V600E mutation and the abnormal activation of the MAPK pathway in myeloid precursor lead to finding the appropriate treatment of LCH and PLCH via targeted treatment. The treatment with BRAF inhibitor (Vermurafenib and others) in a recent study demonstrated 86% of the 2-year progression-free survival rate and 96% of the overall survival rate.[46] However, another study reported a high rate of relapse or progression after stopping the medication.[47] Further study is needed for the optimal dose, duration, and safety profile.[3]

Pneumothorax management: About 10-30% of PLCH have pneumothorax as the first presentation and might be recurrent. Pleurodesis is the option of the treatment and does not result in contraindication for lung transplantation[17,45]

Lung transplantation: In patients with advanced PLCH with the deterioration of pulmonary function and/or developing pulmonary hypertension with respiratory failure, lung transplantation is one of the treatment options. The rates in PLCH are relatively good, 76.9% 1-year, 63.6% 2-year, 57.2% 5-year and 53.7% 10-year.[48] The relapse of disease after transplantation has been described, especially in the multisystem LCH and patients resuming smoking after transplantation.[48]

Hypoxemia should be treated with an oxygen supplement. Some patients develop pulmonary hypertension but the role of pulmonary vasodilators is not well established. In PLCH, annual vaccination against influenza and an anti-pneumococcal vaccine are recommended.[8]

Prognosis

The prognosis of PLCH is various and unpredictable. The data revealed PLCH patients have lower mean survival compared to normal subjects.[2] About 50 % have a good prognosis (spontaneous regression, improved or stabilized PFTs) after smoking cessation [2,45] whereas another 30-50% develop the progression. The obstructive ventilatory defect is associated with unfavorable outcomes.[2,44]

PLCH patients are more likely to develop secondary malignancy such as lymphoma, particularly Hodgkin's lymphoma, chronic myeloid leukemia, and lung cancer than the normal population.[2,45]

Follow-up examination

Because of unpredictable outcomes of PLCH, PFTs including DLCO and other diagnostic studies as clinically indicated should be performed in all PLCH patients every 3-4 months interval in the first year. Annually PFTs should be performed after the first year. The role of repeated chest CT imaging during the follow-up has not been well accepted and the use of long-term tracking is a decision that must be made in each case.[7,17]

Conclusion

Pulmonary Langerhans' cell histiocytosis is the diffused lung disease associated with smoking in the adult patient and may associate with multisystem LCH. The analysis sample of PLCH patients has identified the activating mutations of specific mitogen-activated protein kinases (*BRAFV600E* and other). Respiratory symptoms including pneumothorax are often an initial presentation, while up to one-fourth are asymptomatic. The disease prognosis is unpredictable and may be spontaneous resolving after smoking cessation. However, systemic treatment is needed in some patients. The treatment of PLCH should be tailor-made in the case of disease progression or advanced disease, lung transplantation is the treatment option.

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