Original Research Paper

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General Medicine

A CASE OF PULMONARY LANGERHANS CELL HISTIOCYTOSIS IN A NON-SMOKER FEMALE

Dr. Darshan Pandya	3rd Year Resident, Department of General Medicine, Smt. NHL Municipal Medical College, Ahmedabad.
Dr. Vishal Parmar*	3rd Year Resident, Department of General Medicine, Smt. NHL Municipal Medical College, Ahmedabad. *Corresponding Author
Dr. Dhaval Chaudhary	3rd Year Resident, Department of General Medicine, Smt. NHL Municipal Medical College, Ahmedabad.

ABSTRACT Langerhans cell histiocytosis (LCH) is a rare disorder caused by monoclonal Langerhans cells proliferation in bone, skin, lung, lymph nodes, liver, spleen, nervous or hematopoietic system.Pulmonary LCH is proliferation of monoclonal Langerhans cells in lung interstitium and airspaces. Etiology is unknown, but cigarette smoking plays an important role. Symptoms are dyspnea, cough, fatigue, and pleuritic chest pain. Diagnosis is based on history and imaging tests and sometimes on bronchoalveolar lavage and biopsy findings. Corticosteroids are given in many cases, but efficacy is unknown. Lung transplantation is usually curative when combined with smoking cessation.

KEYWORDS : Pulmonary LCH, Langerhans' cells, cigarette smoking, bronchoalveolar lavage and biopsy findings. Corticosteroids

INTRODUCTION

Langerhans' cell (LC) histiocytosis (LCH) encompasses a group of disorders of unknown origin with widely diverse clinical presentations and outcomes, characterised by infiltration of the involved tissues by large numbers of LCs, often organised into granulomas. Pulmonary involvement in patients with multisystemic disease is rarely at the forefront of the clinical picture, yet may be of adverse prognostic significance. Isolated or predominant pulmonary involvement is the pattern encountered by pulmonologists in adults and has a number of specific epidemiological and clinical features that warrant its individualisation as a separate entity.

CASE PRESENTATION

A 20 year old female coming from middle socio-economical class presented with

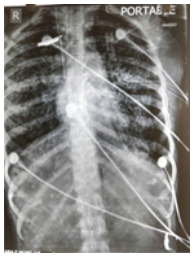
- Nonproductive cough since 5 days
- Fever without chills since 2 days
- Dyspnea since 2 days
- Patient was relatively asymptomatic before 5 days, then she developed acute onset of dry cough 5 days back without sputum . The cough was not associated with whoop , wheeze or barking. She also developed mild grade fever since 2 days not associated with chills and rigors. Fever was intermittent and would spike at least once every day. Patient had developed breathelessness on exertion since 2 days which was present even at rest.
- Past History: No p/h/o pulmo Koch's.
- Family History: NAD
- Personal History: no addiction history and no significant drug allergy history.

ON EXAMINATION:

- On examination Tachycardia and tachypnea was evident. Occasional fever spikes were present.
- Chest Auscultation revealed Bilateral Inspiratory crepts and expiratory rhonchi present.

INVESTIGATIONS:

- Total counts were high on complete blood count . LFTs and RFTs were normal except raised alkaline phosphatase . Arterial blood gas analysis showed type 1 respiratory failure.
- At first , Patient was su spected of having H1N1 Pneumonitis, But the throat swab sample turned out to be negative.
- Sputum AFB was negative. Serum Pneumo-panel was done which was normal.
- HRCT thorax showed extensive cystic changes noted in bilateral lung field sparing the postero-basal segments of the lower lobes. Multiple Nodular opacities with surrounding ground glass opacity and septal thickening are seen in postero-basal segment of bilateral lower lobe.
- CT findings suggestive of bilateral diffuse cystic lung disease-changes consistent with Langerhans' cell Histiocytosis.



DIAGNOSIS:

- 20 year old Non-smoking female Bilateral diffuse cystic lung disease-Pulmonary Langerhans cell Histiocytosis.

LANGERHANS CELL HISTIOCYTOSIS

- LCH is a disorder characterized by the accumulation of LCs in Various organs and tissues. LCs are bone-marrow derived dendritic cells(DCs) whose normal physiological function is processing and presentation of skin derived antigens. In LCH aberrant accumulation of LCs often results in granuloma formation with eosinophilic infiltration.
- Essentially any part of the body can be affected. The course of the disease ranges from that spontaneously regresses to those that have a rapidly progressive course.

TYPES:

1. Eosinophilic Granuloma:

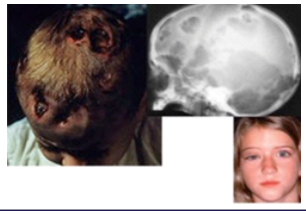
- Single site disease which usually occurs in young adults, typically affects bone(70%), brain or lungs.
- Best prognosis as lesions confined to one organ system.

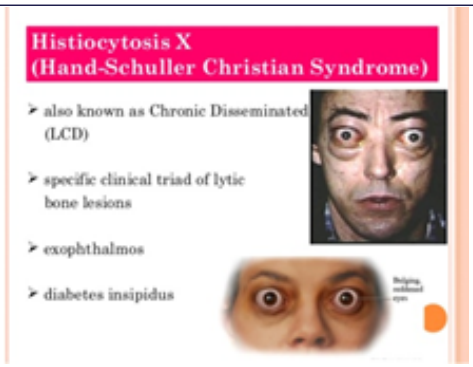
2. Letterer-Siwe Disease:

- Acute onset diffuse LCH involving multiple organ systems occurs typically in young children and infants.
- Fulminant course with poor prognosis.

3. Hand-Schuller-Christian Disease:

- Between the two extremities multifocal LCH, typically occurs in older children and adolescents and has intermediate prognosis.
- Classical Triad(25%):Multiple "punched out" calvarial bone defects,unilateral or bilateral exophthalmos,Diabetes Insipidus





PULMONARY LANGERHANS CELL HISTIOCYTOSIS

- PLCH is a disease in which monoclonal CD-1A positive Langerhans cells(a type of histiocyte) infiltrate the bronchioles and alveolar interstitium , accompanied by lymphocytes , plasma cells , neutrophils and eosinophils.
- PLCH can occur as an isolated disorder or a component of multisystem illness. In the latter setting, the pulmonary disease does not usually dominate the clinical picture at presentation, but contribute to morbidity and mortality.
- Patient presenting with isolated PLCH have extrapulmonary involvement in approximately 15% cases.
- In adults, Isolated PLCH is more common.

ETIOLOGY AND EPIDEMIOLOGY:

- The etiology of PLCH is unknown , but Smoking is strongly associated with PLCH.H/O current or previous smoking is identified in 95% cases.
- PLCH is usually identified in young adults(20-40years) population.
- Rare disorder, No gender predilection, More common in Caucasian population.

CLINICAL FEATURES:

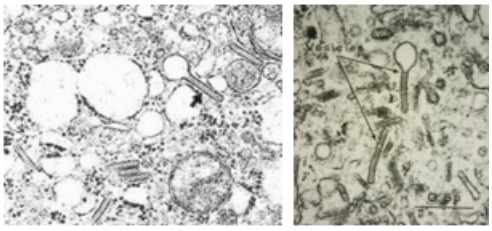
- Dyspnea or Non-Productive cough often insidious in onset and patient may contribute it to smoking.
- Up to quarter of the patients are entirely asymptomatic and present only with abnormal chest radiograph.
- It can present as spontaneous pneumothorax, which tends to recur and may be bilateral.
- Fever, weight loss Malaise like constitutional symptoms in minority of patients.
- Chest pain due to either rib involvement or pneumothorax.
- Clubbing is rare and advanced PLCH is associated with signs of Pulmonary Artery Hypertension and Cor Pulmonale.
- Extra-Pulmonary Features in PLCH I 15%pts: cystic bone lesions, diabetes insipidus from posterior pituitary involvement(polyuria) and skin lesions.

PHYSICAL EXAMINATION:

- Usually Unremarkable unless there is pneumothorax and findings suggestive of systemic involvement.
- Fine Crackles and Digital clubbing may be present.

PATHOPHYSIOLOGY:

- Recruitment and proliferation of Langerhans cells in bronchiolar and bronchial epithelium in response to cytokines and macrophages secreted by alveolar macrophages in response to cigarette smoke.
- Granuloma evolve, Peripheral fibrosis forms resulting in traction on the central bronchiole which become cyst like.
- Electron Microscopy reveal characteristic Birbeck Granules.
- Associations with haematopoetic neoplasm like ALL and AML.



Birbeck Granules found on electron microscopy

BIRBECK GRANULES:

- They are rod shaped or "Tennis-Racket" cytoplasmic organelles with a central linear density and a striated appearance, found solely in Langerhans cells. Formation is induced by langerin.
- They provide a mechanism to differentiate LCH from proliferative disorders caused by other cell lines.

DIAGNOSIS

- 1. Chest X-ray and HRCT
- 2.PFTs
- 3.Bronchoscopy and Biopsy

PLCH is suspected based on history and chest x-ray and is confirmed by HRCT and bronchoscopy with biopsy and bronchoalveolar lavage.

1. **Chest X-ray:** Bilateral symmetrical nodular opacities seen in upper and middle zone with cystic changes and normal or increased lung volumes. The Lung bases are often spared. The Nodules are upto 1 cm in size and irregular in appearance . The costophrenic angles are typically spared in all but the most severe cases. Advanced PLCH progress to Honeycombing and fibrotic changes.
2. **HRCT Thorax:** Diagnostic test in PLCH particularly when cysts and/or nodules in characteristic upper and middle zone distribution with interstitial thickening . If this pattern with typical history, Lung Biopsy is frequently not required. Though typical pattern is less common, Most patients have cysts or nodules alone.
3. **PFTs:** Pulmonary Function Test findings are usually normal, restrictive, obstructive depending on when the test is done during the course of the disease . Most commonly, the diffuse capacity for carbon monoxide(DLco) is reduced and exercise ie impaired.
4. **Bronchoscopy and Biopsy:** are indicated when imaging and PFTs are inconclusive. Finding >5%of CD1a cells in BAL is highly suggestive of the disease . Biopsy show proliferation of Langerhans cells with occasional clustering of eosinophils in the midst of cellular and fibrotic nodules that may take on stellate configuration.

- Immuno-histological staining is positive for CD1a,S-100 Protein, and HLA-DR antigens.

PROGNOSIS

- Spontaneous resolution of symptoms occur in some patients with minimally symptomatic PLCH.
- 5 year survival is about 75% and median survival is 12 years.

Cause of death is generally respiratory failure due to progressive disease or malignancy. PLCH is associated with increased risk of both lung cancer and haematological malignancies with continued smoking a major risk factor.

TREATMENT

- Smoking Cessation-most important step in management of the disease.
- Corticosteroids-frequently used despite limited evidence of benefit. Experts suggest that it should be reserved to symptomatic patients with predominantly nodular lesions on HRCT scans rather than when fibrotic lesions are present . Typical corticosteroid dose in PLCH is 0.5 mg/kg/day to 1 mg/kg /day tapered over six to twelve months.
- Cytotoxic Drugs-best reserved for patients with multisystem LCH. Drugs like vinblastine , cyclophosphamide, methotrexate, cladribine, etoposide has been used.
- Pleurodesis and Lung Transplantation-pneumothorax due to PLCH is believed to result from rupture of cystic lesion. Pleurodesis involves adhesion of the two pleura so pleural space is artificially obliterated. It is recommended in PLCH when pneumothorax occurs as recurrence rate is very high.
- Lung Transplantation for PLCH is performed when severe respiratory failure develops . Frequently severe pulmonary hypertension is an indication of lung transplantation as it is associated with higher risk of death.
- Either single or double lung transplantation is performed, but the disorder may recur in transplanted lung if patient resumes smoking.

CONCLUSION :

Although some of the steps in the disease process that leads to pulmonary Langerhans' cell histiocytosis are beginning to come to light, further work is needed to explain the different aspects of the

Langerhans' cell granuloma. A key goal is determination of the mechanisms involved according to the location and clinical expression of the disease. Improved understanding of the pathogenesis of Langerhans' cell histiocytosis and, in particular, of the role of Langerhans' cells should ultimately lead to the development of rational treatments for this orphan disease.

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