

Airway-centered Interstitial Fibrosis: An Unusual Presentation

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Abstract

Airway-centered interstitial fibrosis (ACIF) is described as one of the interstitial lung diseases (ILDs) with rare histologic patterns. It is characterised by predominant airway involvement with centrilobular fibrosis, peribronchiolar metaplasia and bronchiolocentric inflammatory changes. We report the case of a female who presented with pneumothorax and central diabetes insipidus, diagnosed as ACIF on lung biopsy.

[Indian J Chest Dis Allied Sci 2016;58:139-141]

Key words: Airway-centered interstitial fibrosis, Pneumothorax, Diabetes insipidus.

Introduction

Airway-centered interstitial fibrosis (ACIF) is an entity that has recently been described in the literature. Its pathological characteristics include a combination of interstitial lung disease (ILD) and airway fibrosis. The exact aetiology of this entity has not been determined; however, it has been associated with a variety of substances, organic and inorganic dust exposures and fumes. Whether it is a variant of existing idiopathic interstitial pneumonias (IIPs) or exists only in association with other conditions, such as hypersensitive pneumonitis or collagen vascular disease is uncertain.¹ Lack of granulomas, minimal inflammation on histology and paucity of lymphocytes on bronchoalveolar lavage (BAL) differentiates it from hypersensitive pneumonitis. We report a case of ACIF with unusual manifestations.

Case Report

A 20-year-old female, non-smoker was referred to our centre for further evaluation and management of a left-sided pneumothorax. She was symptomatic for the past one year with complaints of dry cough and progressive shortness of breath. She also had a history of polydipsia, polyuria and secondary amenorrhea. She did not give any history of exposure to any organic or inorganic dust, indoor pollution exposure, recent travel or change of residence. There was a past history of right-sided pneumothorax managed with intercostal drainage.

On clinical evaluation, she has a short stature, desaturation at rest and bilateral fine basal crackles with decreased breath sounds on the left side.

Haematological and biochemical investigations were within normal limits. The chest radiograph showed a left-sided pneumothorax and bilateral reticulonodular opacities (Figure 1). High resolution computed tomography (HRCT) was suggestive of interstitial fibrosis without significant bullous or cystic disease and a left pneumothorax with small right-sided residual pneumothorax of the previous episode (Figure 2).

The pneumothorax was managed with a pigtail catheter insertion. A detailed endocrine work-up, including magnetic resonance imaging (MRI) of brain and water deprivation with vasopressin challenge test was done. MRI brain showed pituitary gland

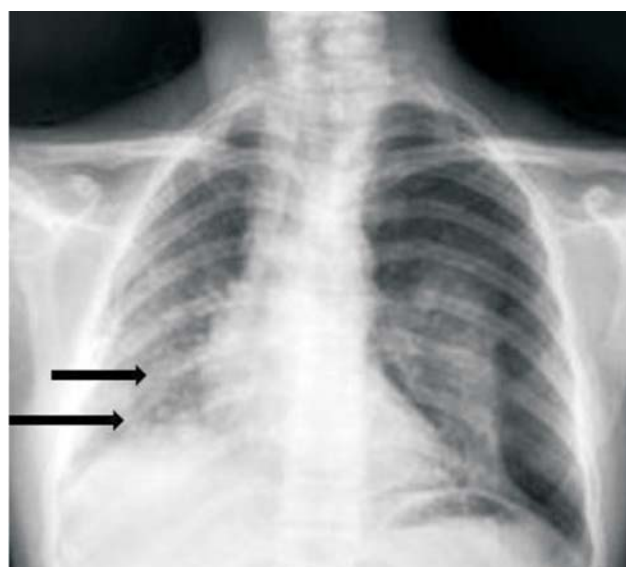


Figure 1. Chest radiograph (postero-anterior view) showing bilateral reticulonodular opacities (arrows) with left-sided pneumothorax.

[Received: March 24, 2014; accepted after revision: August 31, 2015]

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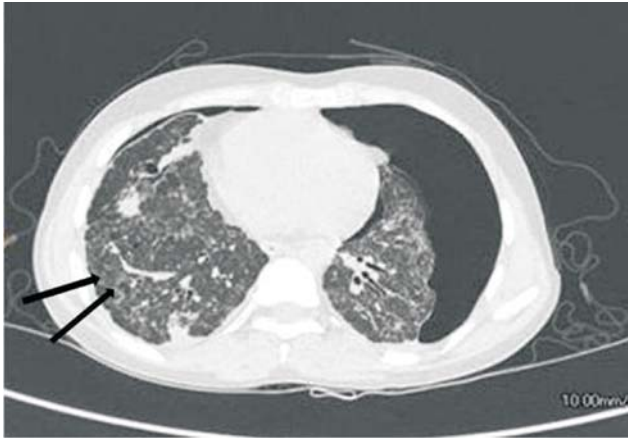


Figure 2. High resolution computed tomography of thorax showing interstitial fibrosis (arrows) without significant bullous or cystic disease and a left-sided pneumothorax with small right-sided residual pneumothorax.

that was small for her age with absent posterior pituitary bright spot. Vasopressin challenge test showed increased serum osmolality (318mos/kg) and decreased urine osmolality (92mos/kg) which increased after vasopressin challenge test (212mos/kg), based on which a diagnosis of central diabetes insipidus was made. She was managed with oral desmopressin 50mcg and her urine output decreased.

Spirometry done after resolution of pneumothorax showed a forced vital capacity (FVC) 0.45L (18% predicted), forced expiratory volume in 1 second (FEV_1) 0.45L (21% predicted) and FEV_1/FVC ratio of 100, suggesting restrictive abnormality. Diffusion carrying capacity (DLCO) estimation was not possible due to poor lung functions. Arterial blood gas showed mild hypoxaemia with pH-7.37, $PaCO_2$ -39.4, PaO_2 -74.7, HCO_3 -22.5, SpO_2 -94.3% and alveolar arterial gradient of 26. Serum angiotensin converting enzyme (ACE) was 54IU/L (8-52IU/l). Mantoux test was negative.

Open lung biopsy was performed to establish the diagnosis. It showed marked fibrosis around bronchioles with moderate lymphohistiocytic inflammatory infiltrates (Figure 3). Few alveoli lined by type II pneumocytes showed emphysematous changes. There were no granulomas or atypia seen. Polarising microscopy showed no refractile crystals. Immunohistochemistry (IHC) for CD1a and S100 was negative that ruled out pulmonary Langerhans cell histiocytosis (PLCH), besides the fact that the patient was a non-smoker female. Diagnosis of ACIF with left-sided pneumothorax and diabetes insipidus was made and the patient was started on triple drug therapy with azathioprine 100mg daily, prednisolone 20mg alternate day and N- acetyl cysteine 600mg thrice daily. This was an empirical approach as no treatment guidelines are available for ACIF. However, she continued to deteriorate and died two months later.

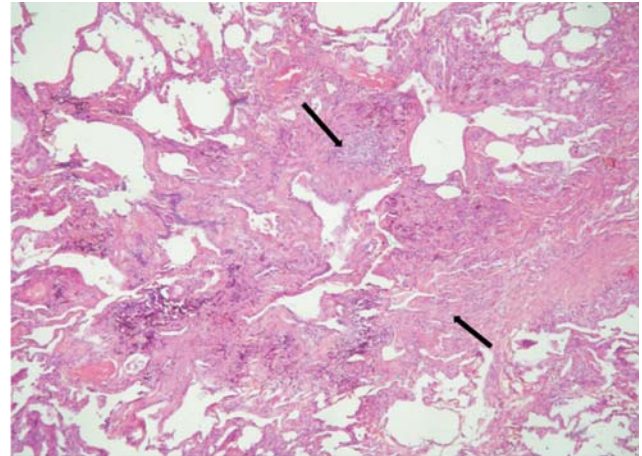


Figure 3. Histopathological photograph showing marked fibrosis around bronchioles with moderate lymphohistiocytic inflammation (arrows) (Haematoxylin and Eosin x100).

Discussion

Airway-centered interstitial fibrosis is a newly described pattern of ILD with associated airway involvement. It is now included in the group of rare histologic patterns of IIPs called bronchiolocentric patterns of interstitial pneumonia.¹ It has a female preponderance with the mean age of onset being 46 years. The term "airway-centered interstitial fibrosis" was coined by Churg *et al*² in 2004 and described in a middle-aged woman with dyspnoea and chronic cough. The aetiopathogenesis of ACIF is still unclear. Yousem and Dacic³ in 2002 proposed it to be a manifestation of a burnt-out phase or an unusual type of hypersensitivity pneumonitis. Spillane in 1952,⁴ presented four cases who had an association of diabetes insipidus and diffuse pulmonary disease of which one case had a classical presentation of sarcoidosis. In two of his cases the diagnosis could not be established, questioning the aetiology of this association.

High resolution computed tomography findings in patients of ACIF show peribronchovascular fibrosis and interstitial thickening. Our patient had HRCT findings of interstitial fibrosis without significant bullous or cystic disease and a left-sided pneumothorax. IPF, sarcoidosis, hypersensitivity pneumonitis, PLCH, lymphangioleiomyomatosis are some common ILDs that may get complicated with pneumothorax. Histopathology in our case showed marked fibrosis around the bronchioles with moderate lymphohistiocytic inflammatory infiltrates. There were no granulomas or atypia seen. Absence of granuloma ruled out diagnosis of sarcoidosis. PLCH rarely presents with ILD. Central nervous system involvement with diabetes insipidus is seen in 30% of PLCH cases and has a poor prognosis.⁵ Immunohistochemistry for CD1a and S100 which are gold standard markers for the diagnosis of PLCH

were negative which excluded PLCH.⁶ Literature mentions hypersensitivity pneumonitis as the main differential diagnosis of ACIF.⁷ In our case, there was no history of exposure to substances known to cause hypersensitivity pneumonitis. Absence of granulomas on histopathology further excluded the diagnosis of hypersensitivity pneumonitis.

As there is no clear understanding of the entity; there are no guidelines for specific therapy. Patients have generally shown no improvement with corticosteroid and bronchodilator therapy and have a poor prognosis with 40% mortality within a 10-year follow-up period. Recently, there are reports regarding clarithromycin therapy that has been shown to retained the decline in lung functions of ACIF patients.⁸ The effectiveness of macrolides may be similar to that seen in other chronic inflammatory diseases through their immunomodulatory effects.⁹ Our patient continued to deteriorate on triple drug therapy with azathioprine, low dose prednisolone and N-acetyl cysteine. Churg *et al*² associated the disease with exposure to various agents, and noted a poor prognosis despite glucocorticoid therapy. Good clinical, radiologic and pathological correlation is essential for the diagnosis of ACIF.

It is yet to be determined whether these conditions characterised by peribronchiolar fibrosis are well-differentiated diseases, pulmonary fibrotic responses secondary to various aetiologies, or different stages of the same disease.¹⁰

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