

A 55-Year-Old Non-Smoker with Severe Airway Obstruction Requiring Bilateral Lung Transplantation

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Received: September 02, 2015; **Accepted:** October 05, 2015; **Published:** October 08, 2015

Keywords: Hypersensitivity pneumonitis, Pigeon breeder, Lung cirrhosis, Emphysema, Cystic pneumonia

History

A 55 year-old non-smoker Caucasian man with history of hypertension presented to the pulmonary clinic with six months of progressive shortness of breath on exertion and productive cough. The patient endorsed occasional exacerbations of his symptoms characterized by flu-like symptoms, subjective fever and worsening productive cough of purulent sputum. He noted progression of his dyspnea with no return to his previous baseline following these exacerbations.

He denied past diagnosis of asthma or chronic obstructive pulmonary disease (COPD). His family history was unremarkable. He was not taking any medication and denied alcohol or drug abuse. He reported that for 17 years, he took care of many birds including cockatiels, parrots, and ring neck doves which were housed in a screened cage room inside his house. He denied second hand smoking or exposure to any wood burning fumes. The patient was given a clinical diagnosis of COPD with emphysema. He was initially started on inhaled long-acting bronchodilators and required home oxygen supplementation. Over the next few months, he suffered progressive clinical decline in his condition with rapidly worsening airflow limitation and increased oxygen needs (**Table 1**). The patient's condition required further maximization of therapies including the addition of systemic steroids. Because of the presence of fibrosis on his lung biopsy a diagnosis of interstitial lung disease was also considered and he was subsequently initiated on azathioprine and N-acetyl cysteine. However, the patient failed all treatment attempts.

Physical Examination

On presentation, vital signs were remarkable for mild hypertension,

tachycardia and tachypnea. He was hypoxemic upon ambulation with oxygen desaturation to 86%. Digital cyanosis and clubbing were present. His lung exam revealed generalized decreased breath sounds, prolonged expiratory phase, occasional wheezing, and dry "velcro-like" crackles mainly heard at the left lung base.

Table 1 progressive clinical decline with rapidly worsening airflow limitation and increased oxygen needs.

	Initial Eval.	3 Months	12 Months	24 Months	36 Months
FEV1 (% of predicted)	60%	48.6%	41.2%	40%	Lung Transplant
O2 Needs	2 L/m by nasal canula on exertion	2 L/m at rest	2-2.5 L/m at rest	3 L/m at rest	Lung Transplant

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Citation: Renzo AB, Jose T, Hanania NA, et al. Formal and Informal Sector Workers Care in Cameroon-Need for Equitable Protection Approach based on Rational Assessment of Risks and Exposures through Carpenter's Respiratory System Assessment. *Insights Allergy Asthma Bronchitis*. 2015, 1:1.

He had a mild increase in the pulmonary component of the second heart sound. No murmurs, rubs or gallops. No jugular venous distention or lower extremity edema were noted. The rest of his physical exam was unremarkable.

Diagnostic Studies

On initial presentation, his complete white blood count, basic metabolic panel, liver function panel and electrolytes were normal. His HIV test was negative. His initial pulmonary function tests were consistent with a moderate obstructive ventilatory defect. His FEV1 was 2.11 liters (60% predicted), forced vital capacity was 4.26 liters (98% predicted) and his FEV1/FVC ratio was 50%. His lung volumes showed a residual volume at 141% of predicted value and DLCO at 5.6 ml/min/mmHg (25% predicted). His chest radiograph was only remarkable for bilateral lung hyperinflation. A high-resolution CT scan demonstrated severe diffuse emphysema, air trapping, and peripheral lower lobe interlobular septal thickening without ground-glass opacities or honeycombing (**Figure 1**). All his microbiologic studies were negative including mycobacterial and fungal sputum cultures. His anti-nuclear antibodies were negative as well as the rest of the rheumatologic workup. A hypersensitivity pneumonitis (HP) panel was positive for serum precipitins to pigeon. Alpha-1-antitrypsin level was normal. After six month of initial presentation, transbronchial biopsies revealed patchy interstitial thickening and fibrosis with fibrin deposition in the inter-alveolar spaces with nodular peribronchiolar lymphoplasmacytic inflammation in association with foamy macrophages and rare multinucleated giant cells containing cholesterol clefts. No granulomas were seen. Three years following his initial presentation, he underwent successful bilateral lung transplantation. His explanted lungs were sent for histopathological examination.

What is the Diagnosis?

Cystic fibrous interstitial pneumonia with diffuse muscular hyperplasia (CFIP/DMH) secondary to chronic hypersensitivity pneumonitis (Chronic Bird Fancier's Lung).

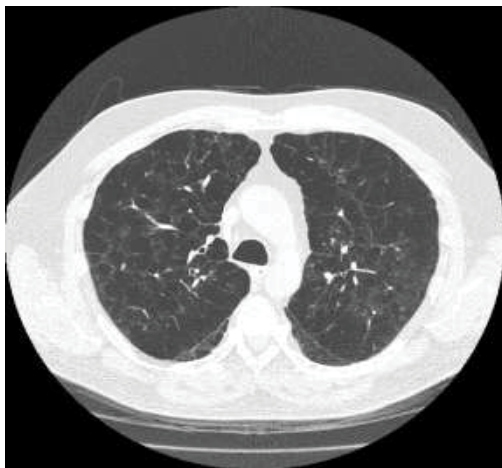


Figure 1 Chest high-resolution computed tomography. High-resolution computed tomography demonstrated severe and diffuse emphysema with upper lobe predominance.

Discussion

We report a case of chronic HP secondary to chronic bird antigen exposure which presents with clinical features of COPD. The severity of bronchiolocentric interstitial lung disease with massive smooth muscle hyperplasia in association with diffuse cystic emphysema-like lesions generated a paradoxical clinical, functional and radiological presentation of progressive obstruction resembling a picture of COPD with severe emphysema.

Chronic Bird Fancier's Lung (BFL) is caused by a T cell-mediated type IV delayed hypersensitivity reaction to chronic inhalation of bird-related antigens. Chronic BFL patients typically present with interstitial lung disease with restrictive physiology mimicking idiopathic interstitial pneumonia. While patients with HP may have a component of airflow obstruction, most of the available histologic information regarding airway involvement in the setting of HP comes from farmer's lung disease. Although radiological evidence of emphysema and functional evidence of airflow limitation within the context of bird antigen exposure have been previously described, the specific histological pattern of emphysema after chronic bird antigen exposure has not been well characterized in the literature.

In our patient, the explanted lung tissue revealed diffuse bronchiolocentric interstitial fibrosis with patchy interstitial

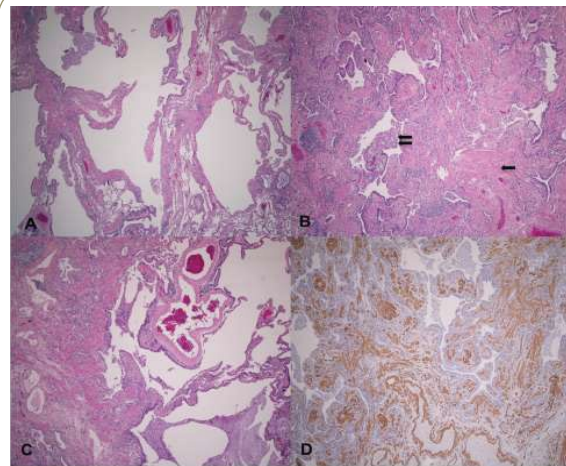


Figure 2 A, H/E, 100X, A low magnification of lung parenchyma with cystically dilated spaces (emphysema-like) surrounded by interstitial fibrosis and mild chronic interstitial inflammation. No honeycombing is seen.

B, H/E, 200X, Dense and diffuse interstitial fibrosis with marked proliferation of interstitial smooth muscle cells (single arrows), mild chronic inflammation and focal respiratory bronchiolitis (double arrows).

C, H/E, 200X, Lung parenchyma with higher magnification of cystic spaces next to dense interstitial fibrosis consistent with Cystic Fibrous Interstitial Pneumonia.

D, Immunohistochemistry for smooth muscle actin (SMA), 200X, There is a dense and diffuse proliferation of interstitial smooth muscle (lung cirrhosis) highlighted by antibodies against SMA.

mononuclear inflammation and cystic dilated air spaces (**Figure 2A and 2C**). Furthermore, the interstitium showed prominent and diffuse proliferation of smooth muscle cell actin (SMA) positive smooth muscle cells (SMC) (**Figure 2B and 2D**). These cells were negative for HMB-45 (a marker of lymphangioleiomyomatosis (LAM) cells). Rare fibroblastic foci, focal honeycombing, and patches of hyalinized fibrosis were also present. Focal, mild respiratory bronchiolitis was seen.

CFIP/DMH was formerly named as "Lung Cirrhosis" and was initially described as an atypical histological manifestation of chronic fibrosing alveolitis almost exclusively due to chronic inhalation injury. It represents the end-stage of a chronic interstitial pneumonia characterized at a histological level by massive proliferation of smooth muscle in the lung interstitium associated with cystic dilation of the terminal airways and emphysema-like lesions. Although it is not well understood why some patients develop interstitial smooth muscle hyperplasia in the lung when exposed to chronic interstitial inflammation, this could be due to the fact that smooth muscle lacks the capacity to regenerate following injury.

Other diagnoses which may mimic the above histological findings are smoke-related interstitial fibrosis (SRIF), LAM, idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) and desquamative interstitial pneumonia (DIP). SRIF is seen in heavy smokers and characterized by patchy hyalinized fibrosis, smooth muscle cell hyperplasia, emphysema and respiratory bronchiolitis. Our patient never smoked or was exposed to second-hand smoking, and the fibrosis noted didn't have the hyalinized features described in SRIF. Because of the smooth muscle hyperplasia, LAM was also entertained, however the

patient is male and the smooth muscle cells were positive for SMA and negative for HMB45, a marker that highlights LAM cells and perivascular epithelioid cell tumors. Furthermore, the fibrosis in this case did not show the predominance of lower lobe and sub-pleural distribution of UIP, and fibroblastic foci and honeycombing were not prominent features. Finally, DIP usually shows diffuse and prominent intra-alveolar proliferation of pigmented macrophages and it is a disease of smokers, both of which were not present in our patient.

Clinical Course

After the lung transplantation, the patient had an uncomplicated clinical course.

Clinical Pearls

1. Clinicians should obtain a detailed history for occupational and environmental exposures in all patients presenting with chronic airflow limitation or emphysema but particularly in those with minimal or no smoking history.
2. Clinicians should recognize the role of chronic bronchiolocentric inflammation in the pathogenesis of a primary obstructive lesion. While this effect has been well documented in different types of HP it is especially prominent in farmer's lung disease. This effect is also enhanced by concomitant tobacco abuse.
3. At the histologic level, chronic HP can present as CFIP/DMH. This histologic lesion can result in a paradoxical clinical, functional and radiologic presentation resembling COPD with emphysema.

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