June 2013 Pulmonary Case of the Month: Diagnosis Makes a Difference

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History of Present Illness

A 64 year old man from Southern Arizona was referred for a second opinion on a diagnosis of chronic eosinophilic pneumonia that was poorly responsive to corticosteroid therapy. The patient first became ill February 2012 with cough and congestion. His wife was ill at the same time. Both were treated with antibiotics. His wife improved but he never fully recovered with ongoing symptoms of cough and some dyspnea.

He was admitted to another hospital in August 2012 due to worsening shortness of breath and pulmonary infiltrates on chest x-ray. During this admission he underwent bronchoscopy with bronchoalveolar lavage (BAL) that demonstrated 78% eosinophils. A video-assisted thorascopic (VATs) lung biopsy was done and the patient was diagnosed with chronic eosinophilic pneumonia. He was begun on therapy with high dose prednisone (80 mg/day) but had only slight improvement in symptoms.

He was followed by a pulmonologist and continued on prednisone who questioned the possible development of pulmonary fibrosis. Earlier this year he was started on mycophenolate mofetil and the dose was increased to 1000 mg bid while the prednisone was tapered to 5 mg every other day. He was also being treated with fluticasone/salmeterol 250/50 twice a day. The patient continues to have dyspnea with limited activity. His last pulmonary function testing was done in December 2012. At that time his forced vital capacity (FVC) was 51% of predicted and his diffusing capacity for carbon monoxide (DLco) was 40% of predicted.

PMH, SH, FH

He had a history of obstructive sleep apnea (OSA) and had undergone an uvulopharyngoplasty (UPPP). There was also a history of gastroesophageal reflux disease (GERD) and he had a prior Nissen fundoplication. He had a history of osteoarthritis and had undergone a right shoulder replacement.

He had a remote smoking history, a history of modest alcohol use, but no history of using recreational drugs. He worked as an airline pilot.

His present medications included mycophenolate mofetil 1000 mg twice a day, prednisone 5 mg every other day, voriconazole 200 mg daily (started after BAL showed a few colonies of Aspergillus), and fluticasone/salmeterol 250/50 twice a day.

Physical Examination

Blood pressure 134/88 mm Hg. Resting oxygen saturation 96%.
Chest: bibasilar crackles but no wheezes.
Cardiovascular: the heart had a regular rhythm but no murmur.
Extremities: no clubbing or edema.
The remainder of the physical examination was unremarkable.

Chest Radiography

His chest x-ray is shown in figure 1.

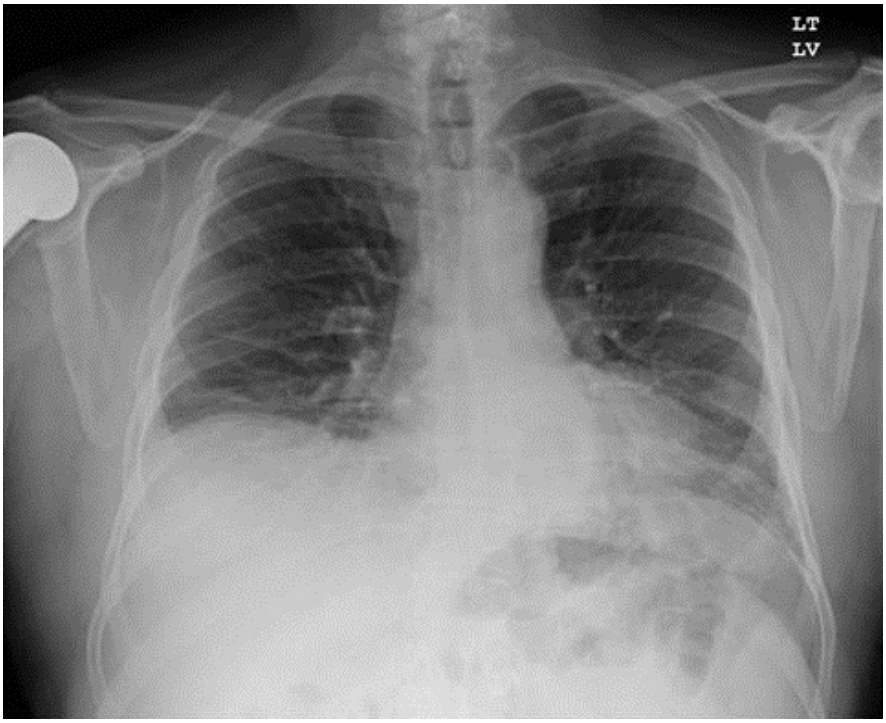

Figure 1. Initial chest x-ray.

Which of the following diseases has/have been ***associated with increased eosinophils*** in bronchoalveolar lavage fluid?

1. Interstitial lung diseases
2. Acquired immunodeficiency syndrome (AIDS)-associated pneumonia
3. Idiopathic eosinophilic pneumonia
4. Drug-induced lung disease
5. All of the above

Correct!
5. All of the above

Allen et al. (1) reviewed 1,059 consecutive patients undergoing bronchoscopy with BAL. Forty-eight patients were found to have 5% or more BAL eosinophils. The most common causes for increased BAL eosinophils were interstitial lung diseases (40% of patients), acquired immunodeficiency syndrome (AIDS)-associated pneumonia (17% of patients), idiopathic eosinophilic pneumonia (15% of patients), and drug-induced lung disease (12% of patients). In contrast, eosinophils were uncommon in the BAL of patients with the adult respiratory distress syndrome, lung cancer, community-acquired pneumonia, or immunocompromising diseases other than AIDS. The authors concluded that although the finding of an increased percentage of BAL eosinophils is uncommon, when present it is relatively specific for a limited number of diseases

Which of the following ***is/are true*** regarding our patient?

1. Chronic eosinophilic pneumonia usually responds to corticosteroids
2. He likely has asthma from bronchopulmonary aspergillosis
3. He likely has a drug-induced lung disease
4. A thoracic CT scan is not indicated because the chest x-ray is normal
5. All of the above

Correct!

1. Chronic eosinophilic pneumonia usually responds to corticosteroids

Corticosteroids are usually effective in chronic eosinophilic pneumonia raising the possibility that the diagnosis is incorrect (2). His course does not fit well with asthma. He does not have episodic shortness of breath accompanied by wheezing and his pulmonary function tests show restriction rather than reversible obstruction. Furthermore, asthma usually responds to corticosteroids. He is not taking drugs usually associated with drug-induced lung disease. His chest x-ray is not normal with increased interstitial markings at the bases. A thoracic CT may better characterize and define the extent of the interstitial changes and is shown in Figure 2.

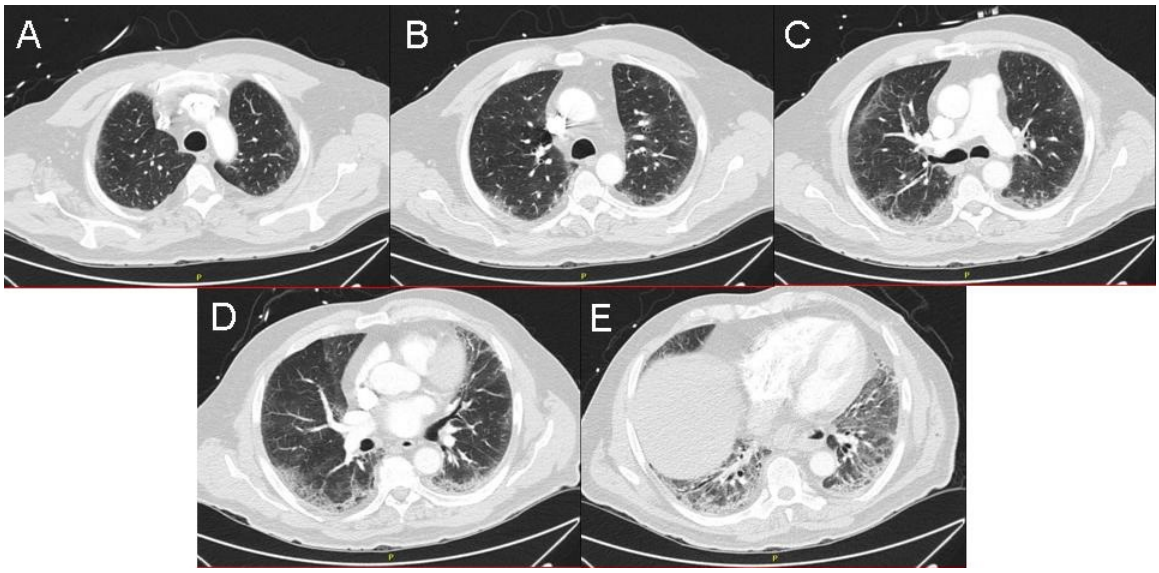

Figure 2. Selected images from thoracic CT scan.

The CT scan is ***most compatible*** with which of the following diseases?

1. Acute eosinophilic pneumonia
2. Chronic eosinophilic pneumonia
3. Pulmonary edema
4. Coccidiomycosis
5. Pulmonary fibrosis

Correct!
5. Pulmonary fibrosis

The thoracic CT scan shows peripheral reticular opacities with predominance at the lung bases. There is also subpleural fibrosis with a suggestion of honeycombing, lower lobe volume loss and traction bronchiectasis. These findings are most compatible with idiopathic pulmonary fibrosis (3). The other diseases usually show ground glass opacities, and although ground glass opacities can be seen in pulmonary fibrosis, the degree of fibrosis usually exceeds the degree of ground glass opacities.

Which of the following is the ***best next step*** in evaluating the patient?

1. Review the VATS lung biopsy
2. Repeat the bronchoscopy with bronchoalveolar lavage
3. Perform a CT/PET scan
4. Increase the corticosteroid therapy
5. Begin tacrolimus

Correct!
1. Review the VATS lung biopsy

The patient's course, CT scan, and response to corticosteroids are not very compatible with his diagnosis of chronic eosinophilic pneumonia. The VATS biopsy was obtained (Figure 3).

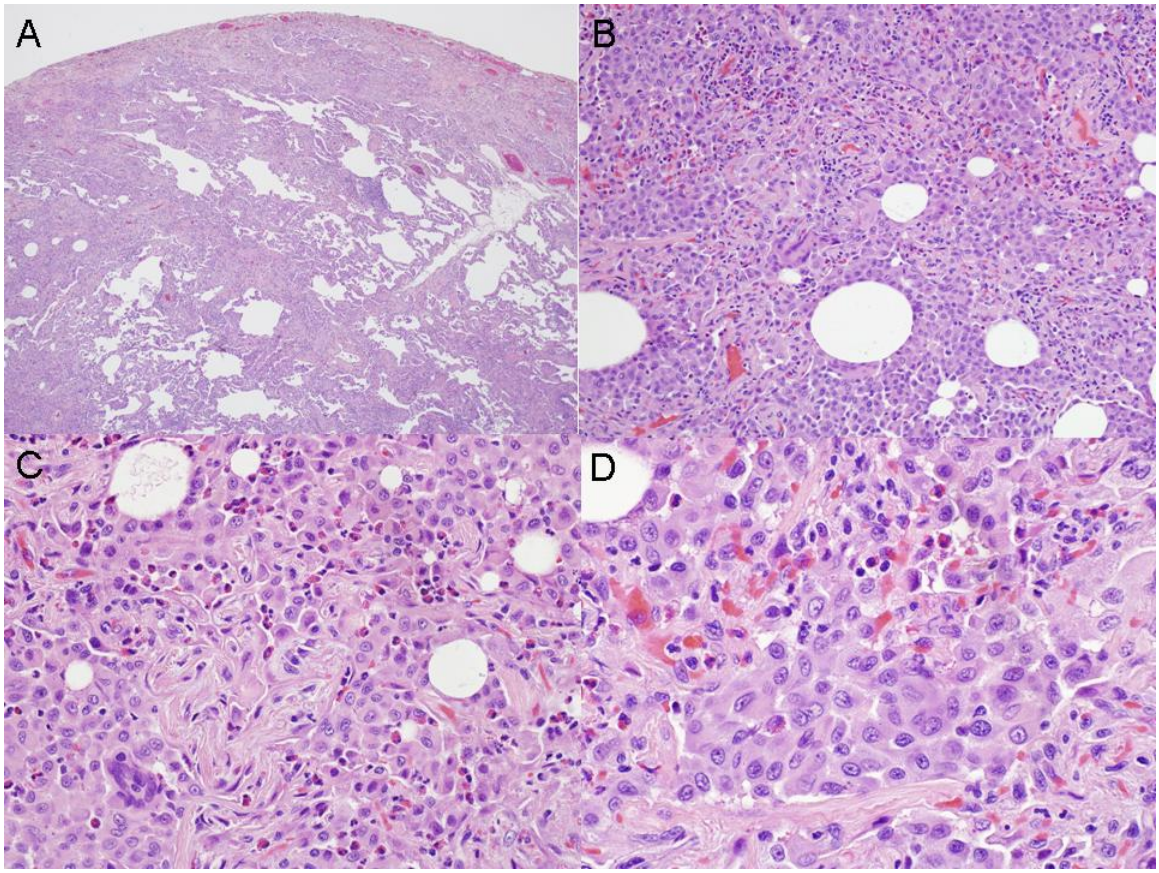

Figure 3. Progressively higher power views of the patient's VATS lung biopsy.

The biopsy showed predominantly airspace disease, which was relatively homogeneous at low power (Figure 3A). Alveoli were filled with macrophages (Figure 3B) which had slightly granular cytoplasm. Occasional giant cells (Figure 3C) were present as were foci containing moderate numbers of eosinophils (Figure 3D). The biopsy lacked airspace edema, fibrin or significant acute lung injury as would be more typical of chronic eosinophilic pneumonia. These findings were thought to be most consistent with desquamative interstitial pneumonitis (DIP) rather than chronic eosinophilic pneumonia (3). There was no significant fibrosis histologically.

Chronic eosinophilic pneumonia is characterized histologically by the presence of a diffuse infiltrate of eosinophils within the alveolar spaces and the interstitium, typically associated with airspace edema, fibrin (Figure 4A) and in about 50% of

cases, prominent foci of organizing pneumonia. The eosinophils are typically admixed with variable numbers of macrophages, from few to many (Figure 4B), and a mixed interstitial infiltrate of lymphocytes and plasma cells (Figure 4) (4). Variable findings include the presence of eosinophils within vascular walls (Figure 4C), eosinophilic microabscesses (Figure 4D), rare scattered multinucleated giant cells or granulomas, and scattered neutrophils.

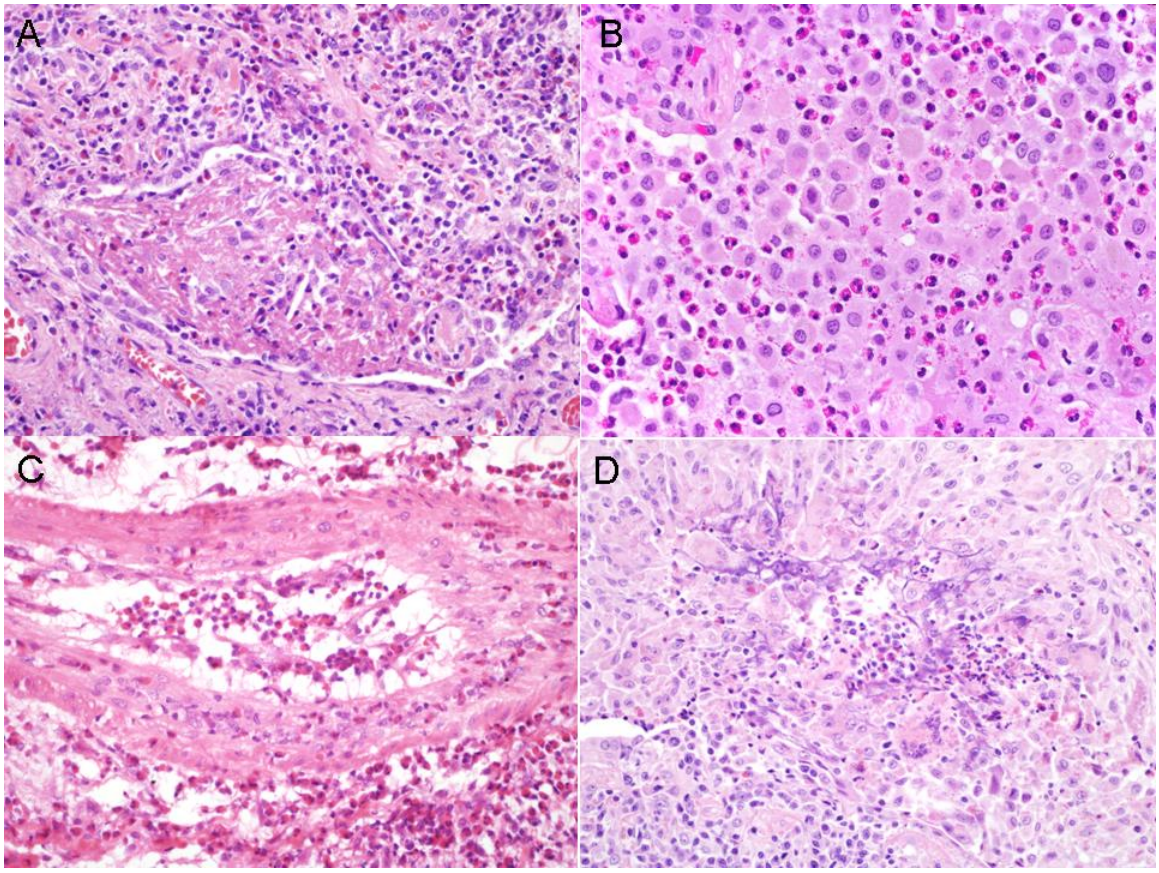

Figure 4. Lung biopsy typical of chronic eosinophilic pneumonia.

DIP usually presents in the fourth-fifth decade with symptoms of dyspnea and cough and restrictive findings on pulmonary function testing. Furthermore, BAL findings in DIP often contain high numbers of eosinophils (3,5). Based on the clinical findings and the biopsy, both the clinician and the pathologist favored a diagnosis of DIP.

Which of the following has/have been reported to be ***beneficial for corticosteroid resistant DIP***?

1. Mycophenolate
2. Tacrolimus
3. Thalidomide
4. Macrolide antibiotics
5. All of the above

Correct!
4. Macrolide antibiotics

Macrolide antibiotics have a number of anti-inflammatory properties and have been used in multiple pulmonary inflammatory diseases (6). Recently, macrolides have been reported to help a patient with corticosteroid-refractory DIP. The patient was begun on daily therapy with clarithromycin and his FVC has improved from 51% to 68% predicted.

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