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March 2021 Pulmonary Case of the Month: Transfer for ECMO Evaluation

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History of Present Illness

A 31-year-old male fire fighter with a history of recurrent “atypical pneumonia,” environmental and drug allergies, nasal polyps, asthma, and Crohn's disease (not on immunosuppressants) was transferred from an outside hospital for management of acute hypoxic respiratory failure with peripheral eosinophilia. Prior to admission he reported a 2-week history of worsening dyspnea, productive cough and wheezing, prompting an urgent care visit where he was prescribed amoxicillin-clavulanate for suspected community acquired pneumonia. Despite multiple days on this medication, his symptoms significantly worsened until he was unable to lie flat without coughing or wheezing. He was ultimately admitted to an outside hospital where his labs were notable for a leukocytosis to 22,000 and peripheral eosinophilia with an absolute eosinophil count of 9700 cells/microL. His blood

cultures and urine cultures were negative, and a radiograph of the chest demonstrated bilateral nodular infiltrates. With these imaging findings combined with the peripheral eosinophilia there was a concern for *Coccidioidomycosis* infection and he was subsequently started on empirical fluconazole in addition to ceftriaxone and azithromycin. Bronchoalveolar lavage (BAL) was performed revealing 80% eosinophils, 14% polymorphic nuclear cells (PMNs), 4% monocytes and 2% lymphocytes, no pathogens were identified. The patient's clinical status continued to decline despite antimicrobial therapy, and he was intubated for refractory hypoxia. At this point, the patient was transferred to our hospital for further care.

Key Words: *eosinophilic pneumonia, acute eosinophilic pneumonia, differential diagnosis, bronchoalveolar lavage, eosinophilia, Valley Fever, coccidioidomycosis, causes, drug-induced, chest x-ray.*

What is the *most likely* diagnosis in this patient?

1. Acute asthma exacerbation
2. Bacterial pneumonia
3. Coccidioidomycosis pneumonia
4. Eosinophilic pneumonia
5. Rocky Mountain Spotted Fever

Correct!

4. Eosinophilic pneumonia

Eosinophilic pneumonia (EP) and pulmonary eosinophilia are terms that are used to broadly classify the infectious and non-infectious etiologies that cause an accumulation of eosinophils in the lungs (1). Normally less than 2% of cells counted on bronchoalveolar lavage (BAL) are eosinophils. In EP, the BAL fluid sample should have a minimum of 25% eosinophils but often contains more than 40%. In addition to eosinophilic infiltration of the lungs, EP is often accompanied by peripheral blood eosinophilia, with severe peripheral eosinophilia defined as absolute eosinophilic count (AEC) greater than 5000 (2). Bacterial pneumonia is less likely given the peripheral eosinophilia and lack of improvement with antibiotic therapy. Mild peripheral eosinophilia has been seen in patients with acute asthma exacerbation but would not explain the chest x ray findings that are more consistent with pneumonia. Coccidioidomycosis and Rocky Mountain Spotted Fever are considerations, but less likely given the clinical presentation.

Physical exam

On admission, the patient was found to be febrile with temperature of 38.9° C, tachycardic to 132 beats per minute and had a blood pressure of 111/70 mm Hg without vasopressor support. While mechanically ventilated, the patient was saturating at 95% with an FiO₂ of 100% and positive end expiratory pressure (PEEP) of 9. Diffuse wheezing was present in all lung fields. The skin exam was notable for a confluent, erythematous, nonpapular rash covering the torso, bilateral flanks and posterior thighs. The remainder of the exam was unremarkable.

Laboratory and radiology

CBC on admission was significant for a leukocytosis of 51,000 (previously 22,000) with an absolute eosinophil count of 22.9. Coagulation studies were notable for an elevated PT/INR, fibrinogen, and D-dimer. Antithrombin III was decreased. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were slightly elevated. Lactate was normal. Ferritin was elevated at 1,661 ng/ml. Chest x-ray redemonstrated diffuse patchy opacifications and appropriate placement of the endotracheal tube.



Figure 1. Chest X ray remonstrating diffuse patchy opacities.

What is the ***best next step*** in management of this patient?

1. Broaden antimicrobial coverage and consult infectious disease
2. Specific IgE allergen testing
3. Perform punch biopsy of patient's skin rash
4. Start patient on high dose steroids
5. All of the above

Correct!

4. Start patient on high dose steroids

Given the current etiology of the EP is unknown and the patient remains unstable with an uptrending WBC despite the current antibiotic regimen. The patient's antimicrobials should be broadened, and ID consulted for recommendations on infectious workup. The patient can also be started on high dose steroids given they meet the criteria for eosinophilic pneumonia as previously stated. Specific IgE allergen testing, CT scan of chest and a punch biopsy of the skin can be performed but will not change the clinic picture and thus are not immediately indicated.

Hospital course

The patient was started on amphotericin 5mg/kg, doxycycline 100mg PO and ivermectin 200 mcg/kg in addition to fluconazole, levofloxacin and vancomycin after consulting with infectious disease. An extensive infectious and autoimmune workup was completed, and patient was started on IV methylprednisolone. Complete viral respiratory PCR panel and bacterial workups were unremarkable aside from an indeterminate QuantiFERON. The patient tested negative for aspergillus, cryptococcus, coccidioides, Strongyloides, histoplasma, blastomyces, pneumocystis, and Toxoplasma gondii. Additional laboratory tests were significant for low C3 but normal C4. Quantitative serum immunoglobulin tests were ordered and detected a low level of IgM, normal levels of IgG/IgA, and elevated levels of IgE. ANA was negative. Given the elevated IgE on serology, he underwent specific IgE allergen testing which showed low levels of serum *Ascaris* IgE.

CT imaging was performed and showed multiple peripheral and peribronchovascular

areas of consolidation. (Note: This patient's presentation was in the pre-COVID-19 era.)

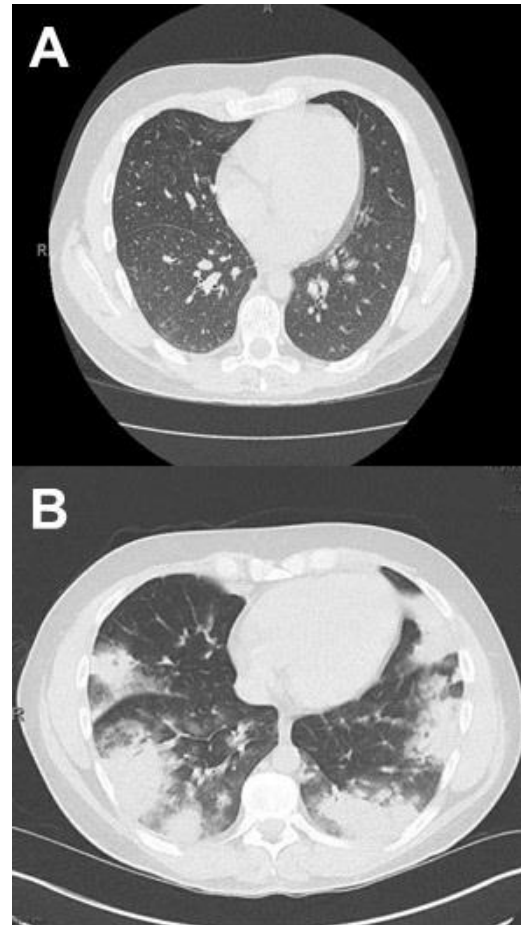


Figure 2. Representative axial images in lung windows from thoracic CT scan.

A punch biopsy of the patient's skin rash showed edema, vascular dilatation, neutrophils, lymphocytes and eosinophils with some inflammatory cells within the interstitium consistent with urticarial dermatitis. After completing high dose intravenous methylprednisolone, patient was transitioned to prednisone 80 mg daily with a taper. He was extubated four days later with complete resolution of skin symptoms and was downgraded to the general medical floors with no oxygen requirement. Follow up pulmonary function tests (PFTs) three months later were normal.

Which of the following is the most likely cause of this patient's Eosinophilic Pneumonia (EP)?

1. Drug induced
2. Eosinophilic granulomatosis with polyangiitis (EGPA), previously Churg-Strauss syndrome
3. Loeffler syndrome
4. *Strongyloides* larvae
5. None of the above

Correct!
1. Drug-induced

The most common causes of secondary EP are toxins and drugs. Nearly every class of medication has been implicated in EP but it is more often seen in those taking antibiotics (3). There have been 196 case reports of drug induced eosinophilic pneumonia documented between the years 1990 and 2017. Of the 196 cases, 26 patients required mechanical ventilation. Less common etiologies of EP include fungal and parasitic infections. The term Löffler's syndrome is generally used when referring to an EP secondary to parasitic infection (1). Helminth larvae, most commonly the *Ascaris* species, can migrate from the small intestines into the lungs where they mature causing destruction to the capillary and alveolar walls. This process of larvae migration is typically asymptomatic, but can present with cough, low grade fever, dyspnea, and asthma with wheezing (4).

In our case, the patient's medical history, drug allergies, and IgE specific antigen testing makes determining the etiology of his EP more difficult. His worsening symptoms after antibiotic exposure combined with the skin biopsy results were most consistent with drug induced acute eosinophilic pneumonia. However, this does not rule out an underlying chronic condition. After an extensive chart review, it was found that the patient's history of chronic sinusitis, cough, and dyspnea on exertion were documented 1 year prior to his admission for EP. At that time, his pulmonologist stated the patient had a normal physical exam, normal imaging, and PFTs. He was unclear of the cause of patient's persistent dyspnea on exertion that was unrelated to environmental triggers. Additionally, the patient had very low levels of *Ascaris* specific IgE. The clinical relevance of allergens in that quantity are undetermined and it is unlikely that a helminth infection was

the underlying cause of the patient's acute episode of EP. However, IgE sensitization to *Ascaris* has been documented to be a clinical indicator of asthma severity (5). It is unclear whether allergic sensitization to *Ascaris* played a role in this patient underlying illness.

Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome cannot be ruled out in our patient. Per the American College of Radiology, a diagnosis of EGPA can be made with a sensitivity of 85% and specificity of 99.7% if four out of six criteria are met: history of asthma, paranasal abnormalities, peripheral eosinophilia of greater than 10%, pulmonary infiltrates, neuropathy, and extravascular eosinophilia on biopsy (6). Our patient's history of asthma, chronic sinusitis with nasal polyps, peripheral eosinophilia >50% and pulmonary infiltrates meet these criteria. Given this information, serum anti-neutrophil cytoplasmic antibody (ANCA) was ordered at a follow up visit three months after the patient's discharge as ANCA is positive in 40% of EGPA cases. This was negative, placing a diagnosis of EGPA lower on the differential but not entirely ruled out.

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