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Similar to Past Flareups Pulmonary Eosinophilia: Putting the Pieces Together

Urgent message: Pulmonary eosinophilia is a generic term for a heterogeneous group of disorders that result in increased eosinophils within the pulmonary parenchyma. Ultimately, the patient here was treated with an extended course of glucocorticoids to treat his chronic eosinophilic pneumonia until he could follow up with his hematologist/pulmonologist.

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Case Presentation

The patient is a 29-year-old male with history of pulmonary eosinophilia, degenerative disc disease, and asthma who presents to an urgent care center with increased shortness of breath, nonproductive cough, and dyspnea on exertion. He states his symptoms are, "similar to my past flareups I have had over the last year." He reports his asthma was well controlled until these episodes started, and he was recently diagnosed with "a lung condition." When asked about pulmonary eosinophilia listed in his chart he replies, "That sounds right." He was prescribed a pocket pulse oximeter by his pulmonologist, and he noted a reading of 87% while at work earlier today. The patient was receiving injections of mepolizumab (Nucala) until 6 months ago, but he had to discontinue the course secondary to an insurance lapse.

The patient was seen 18 days ago at the same urgent care by another provider and given a breathing treatment with ipratropium bromide and albuterol sulfate (DuoNeb). His $Sp0_2$ improved from 90% to 93%. At that time, he was referred to the emergency department, where he received another breathing treatment. He was discharged home with a 12-day taper of glucocorticoids.

He states symptoms initially improved after the first few days of taking the steroid, but the dyspnea and cough returned after tapering down to 20 mg.

The patient works in construction and reports exposure to heavy particles during demolition. He is intermittently compliant with his respiratory mask while on the job site. He self-reports a 3-year pack history of smoking cigarettes (quit 8 years ago).

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Physical Exam

Vitals

Temperature: 98.6° Fahrenheit

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Blood pressure: 136/86
Heart rate: 89 bpm
SpO_2: 93% on room air

General: Sitting on exam table in NAD
HENT: TMs without bulging, erythema, or effusion. Posterior OP clear.
Cardiac: HR 90 bpm, no murmurs, rubs, or gallops.
Pulmonary: Course and diffuse wheezing bilaterally with bibasilar crackles.
Abdomen: Soft, nontender, no guarding or masses
Musculoskeletal: Moving bilateral upper and lower extremities through FROM without difficulty.

Shortness of Breath: A Few Things to Consider

The differential diagnoses for shortness of breath is wide and includes both acute illness (eg, viral bronchitis) and chronic conditions such as chronic obstructive pulmonary disease (COPD) and pulmonary eosinophilia. COVID-19 has also added a new diagnostic difficulty. The majority of patients with underlying chronic conditions will be aware of their diagnosis as well as their baseline status. For those patients who are stable and presenting with risk factors and symptoms for chronic disease, appropriate outpatient follow-up with either a primary care physician or referral to pulmonology should be made to ensure further testing and evaluation.

Viral bronchitis is characterized by acute onset of persistent cough lasting between 1 and 3 weeks in the absence of COPD. This cough can be accompanied by sputum production, and a productive cough does not necessarily correlate with bacterial etiology.[1] Wheezing and rhonchi can be present as well; however, rales should raise suspicion for bacterial pneumonia and a chest x-ray should be obtained. Currently, any patient presenting with a respiratory tract infection should be tested for COVID-19, but the Infectious Diseases Society of America has also set priorities where testing is limited which include hospitalized patients and those at high risk, like healthcare workers and first responders.[2]

Patients with increased shortness of breath in the setting of COPD need to be risk stratified. If the patient is maintaining their O_2 saturation without an increase in oxygen requirement or does not have red flag symptoms such as cyanosis, altered mental status, or edematous extremities, they can safely be treated outpatient. However, those with significant comorbidities, like heart failure and diabetes mellitus, or previous hospitalization should be considered for further evaluation and treatment in the emergency department.[3]

In short, do not ignore abnormal vital signs and overall clinical picture.

Overview of Pulmonary Eosinophilia

Eosinophils are white blood cells that participate in both innate and acquired immunity. They produce proinflammatory cytokines and other proteins that contribute to vascular permeability and contraction of smooth muscles. They also present antigens to T helper cells, leading to their activation and migration to sites of inflammation.[4] *Pulmonary eosinophilia* is a generic term for a heterogeneous group of disorders that result in increased eosinophils within the pulmonary parenchyma. The condition is defined by one of the following findings: peripheral blood eosinophilia (absolute eosinophil count ≥500 eosinophils/mcL) with abnormal imaging, increased eosinophils on bronchoalveolar lavage (BAL), or lung biopsy with lung tissue eosinophilia.[5] A list of these disorders is discussed in further detail later in this article, and two were ultimately considered as the most likely cause of the patient's presentation and helped determine management.

"Common symptoms of idiopathic acute eosinophilic pneumonia include nonproductive cough, dyspnea, and fever with other nonspecific symptoms such as myalgias, pleuritic chest pain, and fatigue. Auscultation of the lungs reveals bibasilar inspiratory crackles and occasional rhonchi."

Idiopathic Acute Eosinophilic Pneumonia

First described by Badesch, et al, idiopathic acute eosinophilic pneumonia (AEP) typically presents with a febrile illness and associated hypoxemia.[6] AEP usually occurs in young healthy males (average age 30 years). Common symptoms include nonproductive cough, dyspnea, and fever with other nonspecific symptoms such as myalgias, pleuritic chest pain, and fatigue.[7] Auscultation of the lungs reveals bibasilar inspiratory crackles and occasional rhonchi.[7] Alveolar damage results from fibroblast proliferation leading to collagen production and widening of the alveolar septae that ulti-

mately weakens and leads to alveolar collapse.

The disease has a strong association with smoking tobacco.[8] Water pipe use, including with tobacco and marijuana, has been associated with the disease secondary to the increased volume of smoke inhaled and concentration of particles.[9] It is also known to develop after environmental exposures to inhaled contaminants such as sand and dust. Chest x-ray may show reticular or ground-glass opacities. With disease progression, bilateral diffuse mixed ground-glass opacities will be present. CT is not required for diagnosis. Confirmation of diagnosis is made with lung biopsy; however, a lung biopsy is not necessary if history and bronchoalveolar lavage (BAL) are consistent with diagnosis.[10] It can be distinguished from chronic eosinophilic pneumonia by its lack of peripheral eosinophilia and more acute presentation with high fever.

Chronic Eosinophilic Pneumonia

Chronic eosinophilic pneumonia (CEP) is an idiopathic disorder characterized by polymorphonuclear eosinophils within the lung interstitium and the alveolar spaces.[10] CEP is rare and women are twice as likely as men to develop the disease.[11] It predominately affects patients in the third and fourth decades of life and has a strong association with asthma, which is present in approximately 50% of cases.[12] Most patients present with vague symptoms such as cough, fever, shortness of breath, wheezing, and weight loss. They will typically present less acutely without overt respiratory failure. Patients with CEP often experience approximately 4–5 months of symptoms before the correct diagnosis is made. Physical exam typically reveals diffuse wheezing, and crackles are present in approximately 38% of cases.[13]

There is no specific laboratory marker for chronic eosinophilic pneumonia, but in the setting of the symptoms described above usual laboratory studies include complete blood count with differential, blood urea nitrogen, creatinine, hepatic function tests, and urinalysis. Peripheral blood eosinophilia is common, with elevated eosinophil counts >6%.[12] The classic finding on both chest x-ray and CT consists of bilateral peripheral or pleural nonsegmental, consolidative opacities termed "photographic negative."[14]

Medications and Toxins

The clinical presentation for pulmonary eosinophilia associated with medication and toxin exposure varies and ranges from chronic cough to drug reaction with eosinophilia and systemic symptoms (DRESS). Common medications to consider include NSAIDs, antibiotics, (like sulfonamides), ACE inhibitors, and amiodarone, but many others have been implicated.[15] Environmental factors, including heavy metals and other particulates associated with building materials also appear to play a role.[16,17] The history plays an important role in diagnosing and ruling out these potential causes.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

This is a vasculitis that typically presents in the setting of asthma, sinusitis, and peripheral blood eosinophilia (≥1500/mcL). It presents more commonly with extrapulmonary manifestations on the skin and affects other organs such as heart and kidneys. Antineutrophil cytoplasmic antibodies (ANCA) are found in less than 50% of cases, and a tissue biopsy will usually confirm the disease. There is some overlap between chronic pulmonary eosinophilia and Churg-Strauss syndrome.[18] The work-up for this diagnosis is beyond the urgent care setting, but it is important to keep it on the differential in order to place appropriate referral.

Parasitic Infection

Infections caused by organisms such as *Ascaris* and *Toxocara* will present with peripheral blood and BAL eosinophilia. Helminth infection is a broad topic and is beyond the purview of this article but must always be considered in this setting. Again, good history-taking will include or exclude this differential diagnosis based on recent travel or residence in a high-risk area.

Bacterial vs Viral Pneumonia

Bacterial and viral pneumonia will have similar symptoms; however, a chest x-ray will typically show no reticular or ground-glass opacities. Take a good history to exclude environmental causes. A complete blood count will usually be without eosinophilia, but eosinophilic pneumonia can occur with exposure to certain drugs and toxins as discussed previously.[19]

Work-Up and Diagnosis

Bacterial/viral pneumonia and elimination of possible drug and toxin exposures lie withing the capabilities of the urgent care setting. The need for further bloodwork, imaging, and possible BAL require referral to other specialists (eg, pulmonology, hematology, infectious disease). However, the important takeaway is to perform a thorough history and physical exam, recognizing which patients need immediate referral to an emergency department and those who can safely be treated and referred on an outpatient basis. This patient's 0_2 saturation was

stable and he was resting comfortably without signs of respiratory distress. He was speaking in full sentences without difficulty or accessory muscle use. Therefore, it was deemed safe to treat him outpatient.

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Case Discussion and Treatment

Despite the nonspecific diagnosis of pulmonary eosinophilia listed in his chart, on further review of his record this patient had had a previous CT with consolidative opacities and peripheral eosinophilia. A subsequent BAL confirmed pulmonary eosinophilia. These findings, along with a previous history of asthma and treatment with mepolizumab, pointed towards CEP. However, the patient's smoking history and occupation in construction with exposure to heavy particulates had contributed to this multifaceted presentation.

Ultimately, both AEP and CEP are treated similarly. Initial therapy for CEP is prednisone dosed at 0.5 mg/kg a day continued for 2 weeks after symptoms resolve. Due to frequency of relapses in these patients, therapy is typically continued for 3 months and can be continued for up to 9 months.[20] For AEP, an oral dose of prednisone is started between 40 and 60 mg per day and again continued for 2 weeks after resolution of symptoms. After this, the dose is reduced by 5 mg each week until cessation.[21] The monoclonal antibody mepolizumab has started to be used to treat CEP with successful reduction in use of glucocorticoids.[22]

Due to his initial improvement on a 12-day taper of corticosteroids with a starting dose of 60 mg and subsequent relapse when tapering down to 20 mg from 40 mg, a 3-week course of 0.5 mg/kg a day of prednisone was initiated. The risks and benefits of an extended course of steroids was discussed, and the patient opted for treatment. His insurance had recently been reinstated and he had follow-up with his hematologist in 2 weeks for reassessment.

It is rare to initiate such a long course of glucocorticoid maintenance therapy in an urgent care center, especially without a definitive diagnosis. The findings on CT, results of the BAL, and previous medication regimen made it likely that he suffered from CEP. His history of asthma, previous tobacco abuse, and occupation all likely contributed to his condition and acute episodes. This condition had been undertreated and required a much longer course of steroids than previously prescribed in the ED. Since he had initial improvement on the higher dose of corticosteroids and close follow-up with hematology, initiation of an extended course was deemed to be appropriate in this setting. This would help prevent relapse or and unnecessary bounceback. ■

References

1. McKay R, Mah A, Law MR, et al. Systemic review of factors associated with antibiotic prescribing for respiratory tract infections. *Antimicrob Agents Chemother*. 2016;60:4106.
2. Infectious Diseases Society of America. COVID-19 Prioritization of Diagnostic Testing. Available at: https://idsociety.org/globalassets/idsa/public-health/covid-19-prioritization-of-dx-testing.pdf. Accessed on February 13, 2021.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2020 Report. Available at: http://goldcopd.org. Accessed on February 11, 2021.
4. Cordier JF, Cottin V. Eosinophilic pneumonias. In: Schwarz MI, King TE, eds. *Interstitial Lung Disease*. 5th ed. Shelton, CT: People's Medical Publishing House-USA; 2011:833-893.
5. Allen JN, Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med*. 1994;150:1423.
6. Badesch DB, King TE, Schwartz MI. Acute eosinophilic pneumonia: a hypersensitivity phenomenon? *Am Rev Respir Dis*. 1989;139:249-252.
7. Rhee CK, Min KH, Yim NY, et al. Clinical characteristics and corticosteroid treatment of acute eosinophilic pneumonia. *Eur Respir J*. 2013;41:402.
8. Uchiyama H, Suda T, Nakamura Y, et al. Alterations in smoking habits are associated with acute eosinophilic pneumonia. *Chest*. 2008;133:1174-1180.
9. Retzky SS. FDA encourages reporting of tobacco product adverse experiences. *Chest*. 2016;150:1169.
10. Cordier JF, Cottin V. Eosinophilic pneumonias. In: Schwarz MI, King TE, eds. *Interstitial Lung Disease*. 5th ed. Shelton, CT: People's Medical Publishing House-USA; 2011:833-893.
11. Marchand E, Reynaud-Gaubert M, Lauque D, et al. Idiopathic chronic eosinophilic pneumonia. A Clinical and follow-up study of 62 cases. The Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine (Baltimore)*. 1998;77:299-312.
12. Marchand E, Etienne-Mastroianni B, Chanez P, et al. Idiopathic chronic eosinophilic pneumonia and asthma: how do they influence each together? *Eur Respir J*. 2003;22:8-13.
13. Marchand E. Idiopathic chronic eosinophilic pneumonia. A clinical and follow-up study of 62 cases. Medicine (Baltimore) 1998;77:299-312.
14. Jeong YJ, Kim Kl, Seo IJ, et al. Eosinophilic lung diseases: a clinical radiologic, and pathologic overview. *Radiographics*. 2007;27:617-637.
15. Camus P. The drug-induced respiratory disease website. Eosinophilic pneumonia (pulmonary infiltrates and eosinophilia). Available at: https://www.wasog.org/action/core/search/?pattern=camus&hideForm=1 . Accessed September 22, 2020.
16. Schwarz YA, Kivity S, Fischbein A, et al. Eosinophilic lung reaction to aluminium and hard metal. *Chest*. 1994;105:1261-1263.
17. Rom WN, Weiden M, Garcia R, et al. Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. *Am J Respir Crit Care Med*. 2002;166:797-800.
18. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*. 2013; 65:1-11.
19. Chung MK, Lee SJ, Kim MY, et al. Acute eosinophlic pneumonia following secondhand cigarette smoke exposure. *Tuberc Respir Dis (Seoul)*. 2014;76:188-191.
20. Naughton M, Fahy J, Fitzgerald MX. Chronic eosinophilic pneumonia. A long-term follow-up of 12 patients. *Chest*. 1993;103(1):162-165.
21. Rhee CK, Min KH, Yim NY, et al. Clinical characteristics and corticosteroid treatment of acute eosinophilic pneumonia. *Eur Respir J*. 2013;41:402-409.
22. Brenard E, Pilette C, Dahlqvist C, et al. Real-life study of mepolizumab in idiopathic chronic eosinophilic pneumonia. *Lung*. 2020:198:355-360.