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Acute Eosinophilic Pneumonia Presenting with an Elevated Procalcitonin Level: A Rare Laboratory Finding

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Female, 33
Final Diagnosis: Acute eosinophilic pneumonia
Symptoms: Respiratory failure
Medication: —
Clinical Procedure: —
Specialty: Pulmonology

Objective: Challenging differential diagnosis
Background: We present the case of a 33-year-old female who was transferred to a tertiary care hospital because of acute respiratory failure.
Case Report: History, imaging, and laboratory testing (including an elevated procalcitonin level) were consistent with a diagnosis of bacterial pneumonia. However, despite broad spectrum intravenous antibiotics, her condition worsened. Shortly after transfer to our hospital, she required intubation and mechanical ventilation. Bronchoscopy with bronchoalveolar lavage (BAL) was performed and a diagnosis of acute eosinophilic pneumonia was made. After discontinuation of antibiotics and initiation of steroids she improved quickly.
Conclusions: Our case highlights the importance of considering alternative diagnoses in patients who appear to have bacterial lower respiratory tract infection, even in those with elevated procalcitonin levels.

MeSH Keywords: Pneumonia • Pulmonary Eosinophilia • Respiration, Artificial

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Background

Eosinophilic pneumonia is a rare respiratory illness. It is divided into acute and chronic subtypes. Acute eosinophilic pneumonia (AEP) usually presents with cough, fever, and dyspnea. It has a rapid onset, progressing over the course of days to weeks [1]. It is more common in tobacco smokers, though many cases are idiopathic [2]. Its severity varies, but serious cases can lead to respiratory failure and even death. Radiography usually reveals diffuse ground glass and reticular opacities, and pleural effusions.

Procalcitonin is a protein precursor produced by human epithelial cells. In bacterial lower respiratory tract infections, it is elevated; conversely, in viral infections it is suppressed. This characteristic makes it a useful test in distinguishing bacterial lower respiratory tract infections (LRTIs) from viral LRTIs.

Case Report

A 33-year-old Caucasian female presented to an outside hospital following 24 hours of worsening dyspnea, cough, and fever. Apart from a mild upper respiratory infection several years before, which had resolved with oral antibiotics, she had experienced no previous respiratory illness. Her medical history was notable for a methylene-tetra-hydrofolate reductase gene mutation, which had led to 3 previous transient ischemic attacks. She had resumed smoking tobacco 8 months prior to this presentation, after several years of abstinence, and was smoking half a packet of cigarettes each day. She stated that she had not recently changed the amount she was smoking. She was not taking any medications regularly. She had not been exposed to any sick contacts or hazardous environmental toxins. She worked as a customer service agent in a store.

At the outside hospital, a computed tomography (CT) scan of the chest showed diffuse groundglass opacities in all lobes as well as small bilateral pleural effusions. A diagnosis of bacterial community-acquired pneumonia was made, and she was started on oxygen by high-flow nasal cannula (HFNC) as well as vancomycin, ceftriaxone, and azithromycin. She was treated with this regimen for 48 hours. During this time, she remained febrile, tachypneic, tachycardic, and was becoming increasingly hypoxemic on minimal exertion, even while using high-flow oxygen. Because her condition was worsening, she was transferred to our hospital, a tertiary care center, for evaluation by the pulmonary service.

On arrival to our hospital, her respiratory rate was approximately 35 breaths per minute, and her heart rate was 130 beats per minute, in sinus rhythm. Physical examination revealed increased work of breathing and inspiratory crackles in all lung fields. White blood

Figure 1. Bilateral diffuse interstitial and alveolar infiltrates.

cell count was 14.2 k/mm^3 with 90% neutrophils, 3.5% lymphocytes, 2.3% monocytes, and 3.2% eosinophils. An arterial blood gas, obtained while on 5 L of oxygen via nasal cannula, revealed a pH of 7.43, a PCO_2 of 39 mmHg, pO_2 of 68 mmHg, and a bicarbonate of 26 mEq/L. Her procalcitonin level was 2.46 ng/mL (reference range $<0.05 \text{ ng/mL}$). Chest radiograph showed diffuse infiltrates (Figure 1). A respiratory viral polymerase chain reaction pathogen panel, urinary streptococcal and legionella antigens, sputum culture, and blood cultures from the outside hospital were all negative. Antibiotics were continued and it was planned to perform a bronchoscopy the following morning.

Ten hours after arrival to our hospital (that is, approximately 60 hours after initial presentation at the outside hospital and before the scheduled bronchoscopy), her respiratory condition had steadily worsened, despite now being on HFNC at an FiO_2 of 80% and a flow rate of 50 L/min; because of concern for pending respiratory arrest, she was intubated and started on mechanical ventilation. Bronchoscopy with bronchoalveolar lavage (BAL) was performed almost immediately after intubation. BAL fluid revealed a white blood cell count of $738/\text{mm}^3$, of which 45% were eosinophils. Culture of bronchoalveolar lavage fluid did not grow any organisms.

After the bronchoalveolar lavage results were known, antibiotics were discontinued, and 125 mg of intravenous methylprednisolone every 12 hours was started. She improved rapidly and was extubated to supplemental oxygen by nasal cannula 24 hours after initiation of steroids. During the subsequent 24 hours, supplemental oxygen was weaned off completely. A repeat procalcitonin obtained 72 hours after the initial level was 0.45 ng/mL. She was transitioned to 60 mg of oral prednisone once daily and the dose was reduced by 10 mg each week during the following several weeks. She was discharged 4 days after admission to our hospital.

Figure 2. Resolution of infiltrates at 8 weeks.

She was seen in clinic 8 weeks after discharge. She did not endorse any persistent respiratory symptoms and felt back to normal. A chest radiograph showed resolution of infiltrates (Figure 2). She was counseled on the importance of abstaining from tobacco

Discussion

The most notable feature of our case is the finding of an elevated procalcitonin level in a patient with AEP, who did not have community-acquired pneumonia. Procalcitonin is a protein expressed by the C-cells in the thyroid gland and by neuroendocrine cells in the lungs and intestines. In normal circumstances, its level is undetectable. Multiple stimuli can lead to its secretion, and the stimuli for its expression by the thyroid and by other organs differ. Stimuli for its expression by the C-cells of the thyroid include hypercalcemia, glucagon, and gastrin. Stimuli for its expression by non-thyroid sources include bacterial endotoxins and inflammatory cytokines: these cytokines include tumor necrosis factor (TNF), interleukin (IL)-1, IL-2, and IL-6 [3]. In our case, we could not be certain by what mechanism procalcitonin became elevated, though the literature on the topic suggests 5 possible explanations. First, it has been demonstrated that patients with AEP have higher levels of IL-2 than healthy volunteers and patients with CEP [4]. Second, while the pathogenesis of AEP involves multiple cells of the immune system, it appears that T-helper 2 (Th2) cells play a prominent part, and one of the cytokine triggers of Th2 cells is IL-2 [4]. Third, there is indirect evidence that IL-1 may also be elevated during episodes of AEP [5]. Fourth, we already know that there are multiple inflammatory conditions

besides bacterial LRTIs which can cause elevated procalcitonin levels (fungal infections, burns, trauma, pancreatitis, all types of shock) [6], so it is not an unreasonable hypothesis that AEP too might cause an elevation. Fifth, it is established that other eosinophilic conditions can cause elevations in procalcitonin levels [7].

There are case reports of patients with AEP, with normal procalcitonin levels [8–11], while there are also cases in which procalcitonin has been elevated [12–14]. This raises the possibility that the underlying pathophysiology may differ between cases of AEP.

As already mentioned, one of the features of procalcitonin is that in bacterial LRTIs it is elevated, whereas in viral LRTIs it remains low. This characteristic makes it useful clinically in distinguishing bacterial LRTIs from viral LRTIs, and in guiding antibiotic use. A recent meta-analysis showed that the use of procalcitonin measurement in acute respiratory infections reduces antibiotic exposure, side effects, and improves survival [15]. However, given the myriad conditions which can cause it to be elevated, physicians need to be cautious in interpreting its results.

Our patient's illness fulfilled all 4 criteria needed to make a diagnosis of AEP: an acute respiratory illness of less than 1 month's duration, pulmonary infiltrates on imaging, more than 25% eosinophils in BAL fluid, and the absence of any other specific pulmonary eosinophilic disease [1,16]. There were a few features that raised the possibility of CEP, such as her gender and age (CEP is more likely to occur in women aged between 30 and 50 years old). An influential paper on CEP states that the features which distinguish AEP from CEP are its rapid onset, greater severity, and increased likelihood of respiratory failure, all of which were observed in our patient [16]. Her use of tobacco, lack of atopic disease, the diffuse infiltrates on imaging (not the predominantly peripheral infiltrates often seen in CEP, the so-called "photographic negative" of pulmonary edema) and the presence of bilateral pleural effusions are also more consistent with AEP (an estimated 90% of patients with AEP have bilateral effusions) [17].

In our case, it might be argued that an infectious process could account for the procalcitonin elevation and our patient's clinical improvement was due to the antibiotics she received for 2 and a half days; arguing strongly against this is the fact that while on antibiotics she deteriorated to the point where she required mechanical ventilation, and improved rapidly after initiation of corticosteroids (and discontinuation of all antibiotics). A rapid response to steroids is a hallmark of AEP. Furthermore, the findings of eosinophilia on BAL and her meeting all the other diagnostic criteria for AEP make AEP by far the more likely diagnosis.

AEP is a rare condition and most physicians have limited experience of it. One of the barriers to making a diagnosis is that the conditions which AEP closely resembles are seen much more frequently, particularly bacterial pneumonia [18]. It is vital to make the diagnosis quickly, because treatment of AEP differs from bacterial pneumonia, and patients may experience a precipitous decline without appropriate treatment, even to the point of death.

Conclusions

To our knowledge, this is one of the few cases reporting an association between acute eosinophilic pneumonia and an

elevated procalcitonin level. Physicians need to be aware that elevated procalcitonin levels do not rule out AEP. We think that measurement of procalcitonin in future cases of AEP will be useful in confirming whether the relationship is causal.

Department and Institution where work was done

Internal Medicine and Pulmonology Departments in Baystate Medical Center, Springfield, MA, U.S.A.

Conflict of interest

None.

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