Vaping Associated Acute Eosinophilic Pneumonia: A Clinical and Radiologic Mimicker of COVID-19

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Abstract: Acute eosinophilic pneumonia (AEP) is a rare cause of respiratory failure. It is primarily a disease of smokers, either a new smoker or an existing one with a recent increase in cigarette consumption. Other risk factors include toxic gas exposure, inhalational illicit drugs, and smoking marijuana. AEP has also been reported in patients with e-cigarette or vaping associated lung injury (EVALI). We present the case of a 20-year-old male who presented to the hospital with acute respiratory failure. The patient has been vaping heavily for the past three months and started smoking three days before presenting to the emergency department. He was hypertensive, tachycardic, tachypneic, and required high-flow nasal cannula to maintain SpO_2 > 92%. His condition deteriorated in the first 24 hours following hospitalization requiring noninvasive positive pressure ventilation. Bronchoalveolar lavage revealed an eosinophil count of 36%. Bronchoalveolar lavage (BAL) cytology revealed lipid-laden macrophages. He was diagnosed with AEP due to EVALI, and the patient was treated with high dose corticosteroid with subsequent improvement. Before the bronchoscopic evaluation, the clinical and radiologic findings were

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consistent with COVID-19, and the patient was tested twice for SARS-CoV-2 PCR. In the appropriate clinical setting, AEP should be considered in the differential diagnoses of community-acquired pneumonia, acute respiratory distress syndrome (ARDS), and COVID-19, especially in this pandemic era.

Introduction

Acute eosinophilic pneumonia (AEP) is a rare and possibly under-diagnosed etiology of acute respiratory failure that can resemble community-acquired pneumonia, acute respiratory distress syndrome (ARDS), and coronavirus disease 2019 (COVID-19). AEP is characterized by an acute onset of febrile illness with hypoxemic respiratory failure, radiologic chest infiltrate, and >25% eosinophil on bronchoalveolar lavage (BAL) in the absence of any known etiologies of pulmonary eosinophilia (Philit et al., 2002). Although often referred to as idiopathic AEP, several major risk factors are frequently present in patients with AEP. AEP is primarily a disease of smokers, either a new smoker (sometimes after quitting for a period and then resuming) or an existing one with a recent increase in cigarette consumption (De Giacomi et al., 2018). However, AEP has also been reported in patients with exposure to toxic gas (Hirai et al., 2000; Philit et al., 2002), inhaled recreational drugs (McCormick and Nelson, 2007), marijuana (Liebling and Siu, 2013), aroma therapy with essential oil (Kodama et al., 2022), and even in patients with COVID-19 (Murao et al., 2020). Immediately before the COVID-19 pandemic, there was an epidemic of electronic cigarette or vaping associated lung injury (EVALI) in young adults across the United States (Werner et al., 2020). AEP in the setting of EVALI has been reported in a small number of these patients (Arter et al., 2019; Wolf and Richards, 2020). We present the case of a young man with AEP in the setting of combined e-cigarette use and smoking that mimicked COVID-19.

Case report

A 20-year-old young male presented to the hospital with low-grade fever, cough, yellow sputum, wheezing, and dyspnea for three days. He reported generalized fatigue, poor appetite, weight loss, malaise, night sweats, and chills. The patient was initially dyspneic with exertion, which progressed rapidly to resting dyspnea, prompting the emergency department (ED) visit. He had a past medical history of hypertension that was diagnosed at the age of 15. A workup for secondary causes of hypertension was negative. His regular home medication included lisinopril, which he has not been taking for two months. The patient recently lost his father and started using nicotine containing vaping products over the past three months. Due to a higher stress level, the patient started vaping heavily in the past week or so. Additionally, he started smoking combustible cigarettes three days before his symptom onset. He had no known respiratory disease or family history of respiratory illness. He denied any drug use, recent travel, sick contacts, personal history of tuberculosis, or exposure to a patient with tuberculosis. He had no

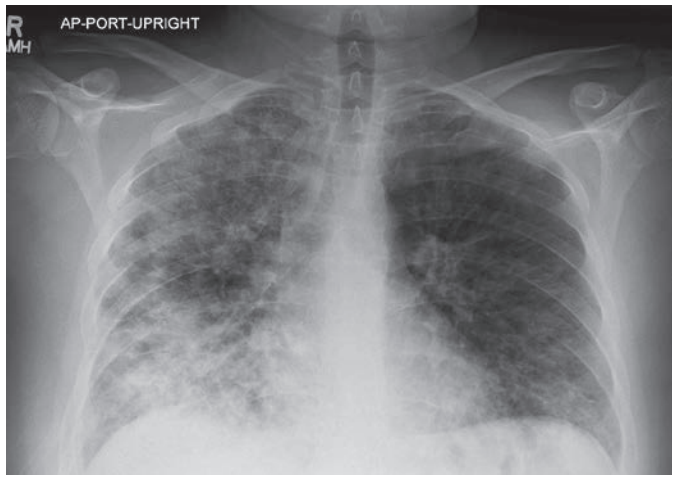

Figure 1 – Chest X-ray showing diffuse bilateral infiltrate. The opacities are both alveolar and interstitial.

pets at home and gave no history of hot tub use or use of feathered pillows. The patient lived in Histoplasma endemic rural United States. He was vaccinated against COVID-19 with two doses of mRNA vaccines.

In the ED, his vital signs were as follows: blood pressure 153/85 mm Hg, pulse 128 beats per minute, temperature 36.8 °C, respiratory rate 28 breaths per minute, and SpO_2 78% on room air, requiring high flow nasal cannula to achieve SpO_2 > 92%. Physical examination revealed a young man in moderate distress. Chest auscultation was significant for crackles at bilateral lung bases without wheezing or rhonchi. There was no rash, clubbing, peripheral edema, or hepatosplenomegaly. The laboratory workup showed leukocytosis of 22,000/μl. The admission peripheral blood absolute eosinophil level was 484 cells/μl (2.2%). There were no electrolyte abnormalities or organ dysfunction. Serum procalcitonin level was normal. The C-reactive protein (CRP) level was elevated at 158.4 mg/l (normal < 10 mg/l).

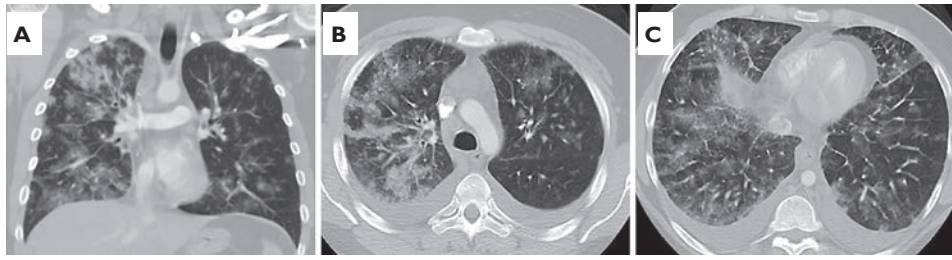

Figure 2 – Coronal section of the computed tomography of the chest showed ill-defined centrilobular nodularity primarily on the left side and areas of ground glass opacity and consolidation on the right (A). Axial section showing small volume bilateral pleural effusion (B). Axial view demonstrated interlobular septal thickening with ground glass opacity of the secondary pulmonary nodule consistent with "crazy paving pattern".

A chest X-ray showed diffuse bilateral alveolar opacity involving all lung zones (Figure 1). A computed tomographic angiogram (CTA) of the chest demonstrated bilateral areas of ground glass opacity, consolidation, and "crazy paving pattern" in the right lower lobe (Figure 2). There was also small bilateral pleural effusion but no pulmonary embolism. A bedside echocardiogram showed normal ejection fraction, no valvular abnormalities, and mitral valve E/septal E' ratio of 6, inconsistent with elevated cardiac filling pressures. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR from the nasopharyngeal (NP) swab was negative. The patient was diagnosed with multilobar pneumonia and started on broad-spectrum antibiotics. Although the SARS-CoV-2 PCR was negative, the chest imaging was concerning for COVID-19, and the patient was started on empiric remdesivir and dexamethasone. As there was also the suspicion of EVALI, the corticosteroid was thought to be the appropriate intervention. The patient was tested a second time for SARS-CoV-2 PCR from another NP specimen, and the study was negative. Due to increasing oxygen requirements, he was admitted to the intensive care unit. His respiratory status worsened over the next 24 hours requiring non-invasive positive pressure ventilation.

A bronchoscopic evaluation showed diffuse airway inflammation and erythema without any active bleeding or mucus impaction. BAL was performed from the medial segment of the right middle lobe. Two 60cc aliquots of saline were instilled and the total fluid return was 45 ml. The fluid was cloudy without any blood tinge. Cell count analysis of the BAL showed 36% eosinophils, 28% lymphocytes, 20% macrophages, 6% neutrophils, and 10% other cells. Cytologic examination of BAL revealed numerous lipid-laden macrophages (LLM) and an increased number of eosinophils (Figure 3). An extensive microbiologic workup, including SARS-CoV-2 PCR was negative. The clinical presentation and BAL findings were consistent with the diagnosis of acute eosinophilic pneumonia. Given the severity of hypoxemia and the necessity of non-invasive positive pressure ventilation, the patient was started on 60 mg of intravenous methylprednisolone every 6 hours with rapid clinical and radiologic improvement within 48 hours (Figure 4). The patient was discharged home

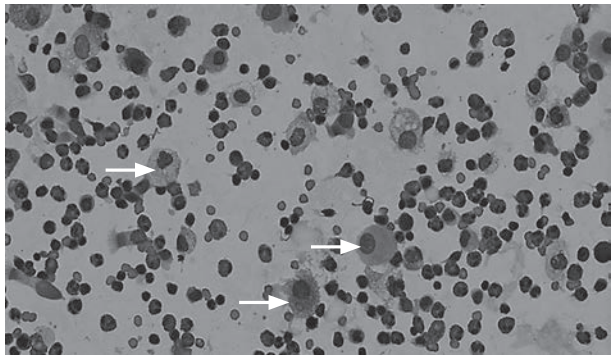

Figure 3 – Cytologic examination of the bronchoalveolar lavage revealed foamy macrophages (arrow) and increased number of eosinophils.

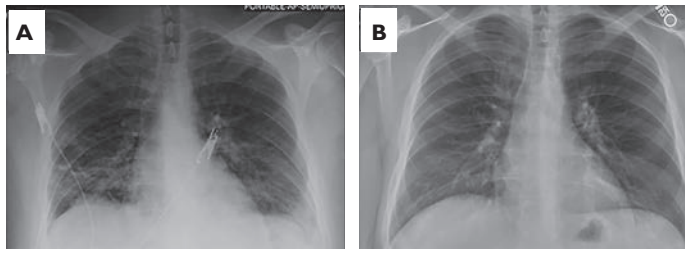

Figure 4 – Chest X-ray 72 hours after initiation of high dose steroid therapy on the day of discharge demonstrated a significant improvement (A). A follow-up X-ray one week after discharge was normal (B).

on 60 mg of prednisone daily (with a tapering plan over the next four weeks) within 72 hours after the initiation of methylprednisolone therapy with minimal oxygen requirement. During outpatient follow-up a week after discharge, he was back to normal without any respiratory complaints. During the course of his illness, the peripheral blood eosinophils reached a peak of 700 cells on day 2.

Discussion

SARS-CoV-2 is the etiologic agent for the COVID-19 pandemic, which has caused more than 6 million deaths worldwide (Saha et al., 2020). Involvement of the lower respiratory tract by SARS-CoV-2 may result in severe COVID-19 requiring hospitalization and intensive care admission. However, the presentation of COVID-19 could be indistinguishable from other respiratory illnesses because of the nonspecificity of the symptoms. Similarly, the radiologic appearance of COVID-19 could also be identical to many other respiratory diseases (Saha et al., 2021). Additionally, false-negative SARS-CoV-2 PCRs are not uncommon, complicating the issue further (Kanji et al., 2021; Saha et al., 2022). Therefore, caution should be practiced to avoid misdiagnosis and provide appropriate patient care.

The use of electronic cigarettes or vaping has become a popular trend among adolescents and teenagers. Unfortunately, the misguided notion that vaping is "safe" has led to nicotine addiction among millions of high school students in the United States (Wang et al., 2020). Starting in August 2019, an epidemic of EVALI has been reported in all states in the US, with a mortality rate of approximately 2.6% (Cherian et al., 2020). Extensive research has suggested the likely culprit is vitamin E acetate in the vaping solution. However, other possible etiologies, including tetrahydrocannabinol (THC), could not be definitively ruled out. The primary histopathologic lesion in EVALI has been acute fibrinous pneumonitis, diffuse alveolar damage (DAD), organizing pneumonia, and bronchiolitis (Butt et al., 2019). Although uncommon, AEP has been reported in a few patients with EVALI during the epidemic in the US and before that (Thota and Latham, 2014; Kamada et al., 2016; Mull et al., 2020; Puebla Neira et al., 2020; Wolf and Richards, 2020; Takigawa et al., 2022; Bonnier et al., 2023).

AEP was first reported in 1989 nearly simultaneously by two independent groups from the United States (Allen et al., 1989; Badesch et al., 1989). The

authors reported a new entity, which, unlike chronic eosinophilic pneumonia, had an acute onset of respiratory symptoms associated with constitutional symptoms, demonstrated diffuse pulmonary involvement on radiologic imaging, and prompt response to systemic corticosteroids (CS). The BAL eosinophil count was elevated (greater than 25%), generally without peripheral eosinophilia. The new entity was considered idiopathic as all known causes of pulmonary eosinophilia were excluded. However, as more cases and small retrospective studies were available, it became clear that most of these patients were smokers (Philit et al., 2002; Shorr et al., 2004; Uchiyama et al., 2008). AEP was reported in patients who were new smokers or resumed smoking after quitting for some time. Also, smokers with a recent increase in cigarette consumption were found to be susceptible. In one of the largest retrospective studies of patients with AEP, 99% of patients were smokers (Rhee et al., 2013). It is important to emphasize that only a minute percent of smokers develop AEP, perhaps highlighting the contribution of one's genetic makeup. Recurrence of AEP following provocation by smoking has been documented in a number of cases (Nakajima et al., 1998). AEP is more prevalent in men than women. There may also be a seasonal variation in the occurrence of AEP, with a higher incidence during the summer months (Yoon et al., 2016).

The exact pathophysiology of AEP is currently unknown. However, it is thought to originate from epithelial and endothelial injury due to inhalational toxins (smoke, vaping products and others). The tissue injury results in the robust expression of interleukin-33 (IL-33), which likely plays the central role in the pathogenesis of AEP (De Giacomi et al., 2018). The IL-33, in turn, causes activation of innate lymphoid cells (ILC)-2 in the airways and dictates a Th2 helper cell-mediated inflammatory response promoting the production of IL-4, IL-5, and IL-13 that is responsible for the recruitment of eosinophils in the lungs. At the same time, neutrophils, alveolar macrophages, and lymphocytes are also recruited by an unknown mechanism and likely contribute to the pathogenesis (Fujimura et al., 1998). High levels of IL-5 in the patients' serum have been reported in patients with AEP (Miki et al., 2002).

There are no specific historical diagnostic clues for AEP, but it is often considered in patients who are new smokers or increased smoking consumption recently. An increasing peripheral blood eosinophil level in hospitalized patients may also prompt the consideration of AEP in differential diagnoses of pneumonia (Jhun et al., 2014). Patients present with fever, cough with or without sputum production, chest pain, and dyspnea. The median duration between onset of smoking (or increased quantity) and AEP has been reported to be 17 days (range 13–26 days) (Rhee et al., 2013). Other studies have shown similar data, with most patients presenting within a month after a change in their smoking behavior (Suzuki and Suda, 2019). In our patient, the duration of smoking onset and symptom onset was only three days, raising the question of whether smoking and vaping could have an additive effect. A previous paper reported the interval between smoking onset and AEP as short as two days (Nakajima et al., 1998).

The diagnostic criteria used for defining AEP have varied among studies. Some authors have included patients with respiratory symptoms for up to one month (Philit et al., 2002; Shorr et al., 2004; Rhee et al., 2013; Jhun et al., 2014; De Giacomi et al., 2017), whereas others have considered one to two weeks (Sine et al., 2018). Some reports have considered fever a crucial component (Philit et al., 2002; Shorr et al., 2004), but others have reported its absence in a significant number of patients (Rhee et al., 2013). The severity of respiratory failure has also varied among studies, with some showing a high rate of respiratory failure requiring mechanical ventilation (Philit et al., 2002; Shorr et al., 2004). In contrast, others have shown many minimally symptomatic patients and a low incidence of intubation (Rhee et al., 2013). AEP likely has a spectrum of presentations that ranges from mild self-limiting illness to respiratory failure resulting in death.

The physical examination findings are nonspecific. Chest auscultation often reveals basilar crackles but could be unrevealing. The radiologic chest imaging typically shows bilateral lung infiltrates, but unilateral involvement may also be seen. Computed tomography (CT) scan of the chest provides a more detailed evaluation. Bronchiolocentric ill-defined centrilobular pulmonary nodule, ground glass opacity, consolidation, bronchovascular bundle thickening, and interlobular septal thickening are seen in patients with AEP (Rhee et al., 2013). Small bilateral pleural effusion is present in nearly two-thirds of patients (Sine et al., 2018). Laboratory evaluation shows leukocytosis with neutrophilia and elevated inflammatory markers, such as CRP and d-dimer. Peripheral eosinophilia may be present in a minority of patients at the time of presentation or develop within the next few days (Jhun et al., 2014).

Bronchoscopy plays a crucial role in the diagnosis of AEP. A BAL eosinophil level greater than 25% is necessary to make the definitive diagnosis. A bronchoscopy could also rule out other causes of pulmonary eosinophilia. We identified lipid-laden macrophages (LLM) on the cytologic evaluation from BAL. LLM or foamy macrophages have been reported in patients with EVALI (Maddock et al., 2019), and some authors have suggested LLM as a marker for EVALI (Guerrini et al., 2020). However, LLM could be seen in a multitude of disease processes including in otherwise healthy smokers (Ghosh et al., 2021). Deposition of lipid particles in the alveolar macrophages (AM) represent improper cycling of the surfactants by the AM. Inhalation of an oil-based compound, as seen in lipoid pneumonia, is another etiology of LLM on BAL (Chieng et al., 2022). The histopathologic examination of the lungs shows eosinophilic infiltration of pulmonary parenchyma and interstitial tissue, eosinophilic abscesses, nonnecrotizing perivascular inflammation, and sometimes diffuse alveolar damage (De Giacomi et al., 2018). Hyperplasia of the interstitial lymphocytes, type-2 alveolar epithelial cells, and intraalveolar organizing exudates are also seen.

Treatment with systemic corticosteroid (CS) is highly effective in AEP. Patients show clinical and radiographic improvement within 48–72 hours. The absence

of improvement within this time frame may point toward a different diagnosis. Patients with respiratory failure requiring intubation typically receive high dose CS (methylprednisolone 60 to 125 mg every 6 hours), whereas less sick individuals could be treated with 40–60 mg of prednisone daily. The CS is typically tapered over 4–8 weeks, but a 2-week course is equally effective (Rhee et al., 2013). No prospective studies have compared different dosing of CS in patients with AEP. Nevertheless, the prognosis is generally good. The presence of peripheral eosinophilia may suggest a more benign disease course (Jhun et al., 2014).

We have reported the case of AEP in a young male likely caused by vaping with a possible contribution from new-onset smoking. The diagnosis was confirmed by bronchoscopic evaluation showing BAL eosinophil > 25% and the absence of any microbiologic cause of pulmonary eosinophilia. The clinical and radiologic manifestations were initially concerning for COVID-19, but an accurate diagnosis was eventually reached after careful evaluation. Therefore, AEP should be considered in the differential diagnoses of community-acquired pneumonia, ARDS, and suspected COVID-19, especially in the presence of risk factors and developing peripheral eosinophilia.

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