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Acute Eosinophilic Pneumonia Secondary to Menthol Cigarette Use: A Rare Phenomenon With a Review of Literature

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Abstract

Idiopathic acute eosinophilic pneumonia (AEP) is a very rare disease with fewer than 200 cases reported. It has been hypothesized to be a hypersensitivity reaction to an unidentified antigen. The clinical presentation typically involves fever, nonproductive cough, shortness of breath, and bibasilar inspiratory crackles within the first week of antigen exposure. Chest imaging usually reveals bilateral reticular and/or ground-glass opacities. Bronchoalveolar lavage demonstrates >25% eosinophils. Corticosteroids are the mainstay of treatment with good results; however, optimum dose and length of treatment are unclear. We present a case of a 31-year-old male who presented with 2 days of shortness of breath, cough, pleuritic chest pain, fevers, chills, nausea, and poor appetite in the setting of initiation of menthol-flavored cigarettes 2 weeks before presentation. He rapidly progressed to respiratory failure requiring intubation despite broad antibiotic coverage. His course was complicated by severe acute respiratory distress syndrome, circulatory shock, and renal failure. He underwent bronchoalveolar lavage testing that revealed 60% eosinophils. He was treated with steroids and was subsequently extubated and discharged. Eosinophilic counts in the blood peaked on the 10th day of admission to 34%. One week later, the patient was completely free of symptoms. The initiation of menthol cigarette use in this patient is the likely reason for ensuing acute eosinophilic pneumonia, hence adding to the sporadic reports on the role of menthol-flavored cigarettes. This case emphasizes a greater reliance on risk factors, as opposed to eosinophilic markers, for the diagnosis and treatment of acute eosinophilic pneumonia to prevent subsequent respiratory failure and intubation in such patients.

Keywords

acute eosinophilic pneumonia, menthol-flavored cigarettes, respiratory failure

Introduction

Idiopathic acute eosinophilic pneumonia (AEP) was first proposed as a cause of acute respiratory failure in 1989.[1] Fewer than 200 cases of AEP have been reported in the current literature. While the exact incidence is unknown, a study on military personnel deployed near Iraq reported 9.1 cases per 100 000 population per year.[2] The exact cause of AEP is unknown. A popular hypothesis suggests it to be a hypersensitivity reaction to an unidentified inhaled antigen in immunocompetent individuals.[3] There have been multiple cases and one review that has linked antigen exposure with AEP, commonly implicating tobacco smoking,[2,4-10] antibiotics, nonsteroidal anti-inflammatory drugs, antipsychotic drugs,[11] dust, or other environmental factors.[12] Current literature points toward the possible role of eosinophil-related chemoattractants like eotaxin, T-cell-expressed chemokines, IL (interleukin)-5, and IL-8 in the causation of AEP as evidenced by diffuse alveolar damage due to edema and fibroblast proliferation with alveolar eosinophils and interstitial lymphocytes on lung biopsies.[10,13,14]

Clinical features typically involve fever, nonproductive cough, and shortness of breath within the first week of antigen exposure in the majority of cases with myalgias, night sweats, and pleuritic chest pain.[15] Physical examination usually reveals tachypnea and bibasilar inspiratory crackles. The most severe complications include hypoxemic respiratory failure and the need for mechanical ventilation.[16]

Imaging findings typically include bilateral reticular and/or ground-glass opacities (airspace, interstitial, or both) that expand as the disease progresses. Laboratory investigations reveal bronchoalveolar lavage (BAL) fluid significant for

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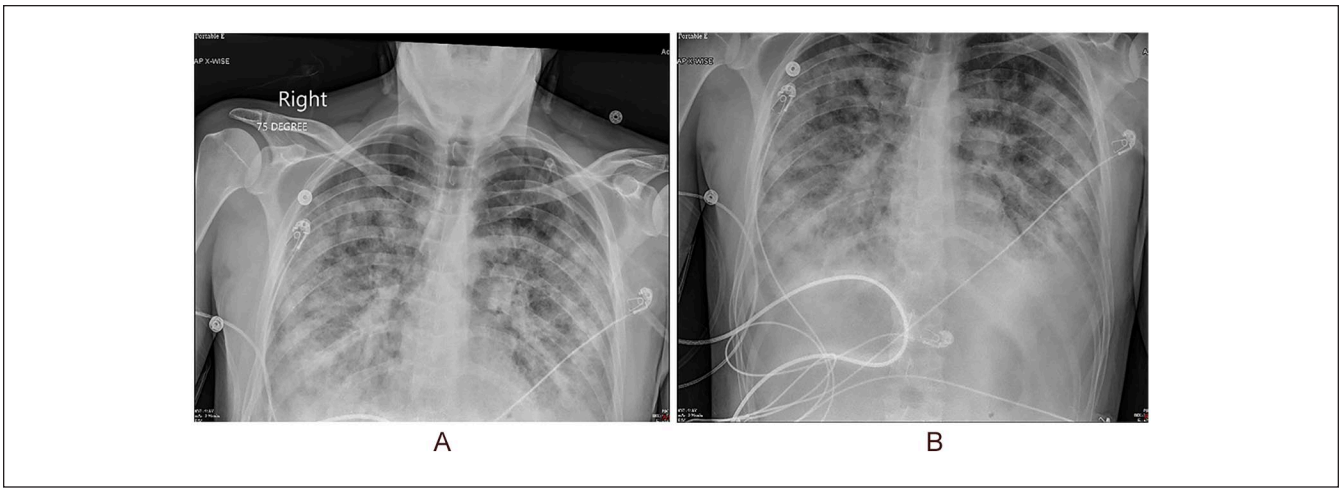

Figure 1. (A and B) Chest X-ray on presentation (day 1) revealing bilateral patchy and confluent opacities with bilateral pleural effusions.

>25% eosinophils of all white blood cells in almost all cases.[16] Peripheral eosinophilia is commonly present with absolute eosinophil count >1000 cells/μL. Elevated immunoglobulin E levels are also witnessed in roughly half the patients diagnosed with AEP.[17]

Corticosteroids (intravenous followed by oral maintenance therapy) are the mainstay of treatment with good results; however, the optimum dose and length of treatment are unclear.

In this article, we present a young male who suffered from life-threatening complications due to rapid progression and delay in diagnosis of AEP. Menthol-flavored cigarettes were the likely culprit.

Case Presentation

We present the case of a 31-year-old male with a past medical history of asthma, accepted as a transfer from an outside hospital due to shortness of breath, wheezing, cough productive of white sputum, and pleuritic chest pain that started 2 days prior. He complained of fever, chills, sweating, headaches, nausea, loss of appetite, fatigue, and malaise. The patient had a 10 pack per day smoking history and 2 weeks before the presentation started smoking menthol cigarettes. His symptoms started with a mild cough and subjective fevers. Surgical, family, and allergy history were unremarkable.

On physical examination he appeared to be in respiratory distress, desaturating to <88% on room air and required 3 L NC (nasal cannula) to saturate to 96%. He had coarse rales at the lung bases and reduced bilateral breath sounds. He was tachycardic to 104 beats per minute. The rest of his physical examination was unremarkable.

On presentation, laboratory work showed creatinine of 0.77 mg/dL, white blood cell count of 17.8×10^3 cells/mm^3, and an absolute eosinophil count of 0.29×10^3 cells/μL (within normal limits). The chest radiograph showed diffuse bilateral patchy opacities and bilateral pleural effusions (Figure 1).

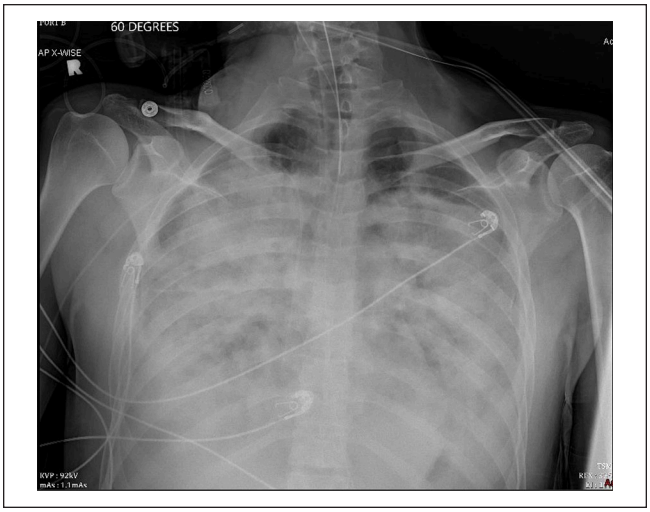

Figure 2. Chest X-ray on day 1, 12 hours into admission, depicting significant worsening of airspace opacities and pleural effusions.

Initially, the patient was thought to have acute hypoxemic respiratory failure due to pneumonia and was thus started on broad-spectrum antibiotics including vancomycin, piperacillin/tazobactam, azithromycin, and voriconazole along with respiratory treatments with albuterol and ipratropium.

As per Infectious Diseases recommendations and high suspicion for fungal infection, he was switched from voriconazole to liposomal amphotericin B.

The patient's oxygen requirements progressively increased from 3 L NC to 15 L facial mask over the next 12 hours that progressed to hypoxemic respiratory failure warranting intubation. A chest radiograph showing worsening diffuse opacities bilaterally (Figure 2). He was placed on airway pressure release ventilation setting due to severe acute respiratory distress syndrome (PaO_2/FiO_2 ratio <150).[18] He also was found

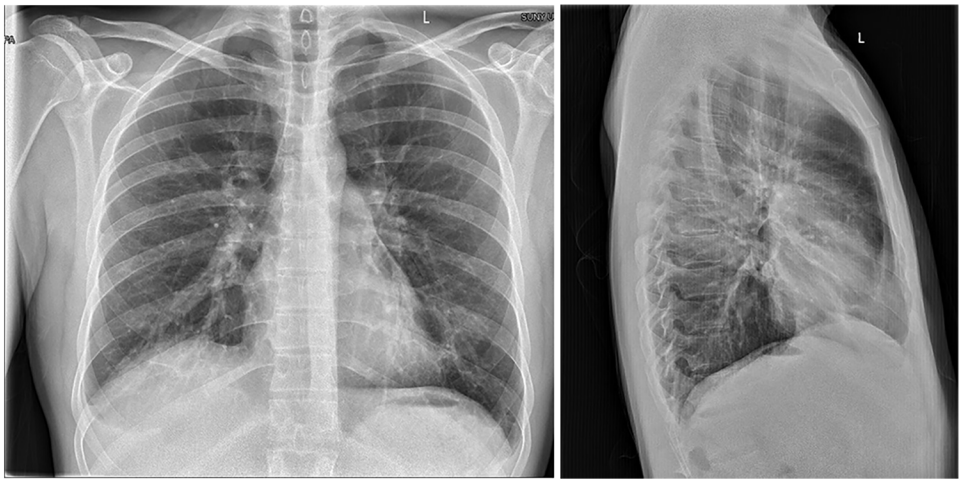

Figure 3. (A and B) Chest X-ray on day 7, after completion of 5 days of intravenous methylprednisolone 500 mg daily, depicting interval improvement in previously noted opacifications. Persistence of interstitial reticular prominence with mild pleural effusion was noted.

to be in circulatory shock requiring pressor support with norepinephrine. His urine output progressively dropped requiring continuous veno-venous hemofiltration.

Autoimmune panel for ANA, β-glycoprotein, anticardiolipin, RF ANCA, and anti-GBM were negative. BAL was performed. AFB culture and fungal blood culture were negative. Testing for histoplasmosis, blastomycosis, coccidioidomycosis, aspergillosis, and strongyloidiasis was negative. The results of the BAL showed 60% eosinophils. Patient's absolute eosinophil count was 1.34×10^3 cells/μL (10%) in the serum on the fifth day of presentation.

The patient was diagnosed with AEP with hypocomplementemia. He was treated with methylprednisolone 500 mg intravenously daily for 5 days, at which point there was a clinical improvement (Figure 3). Repeat chest radiograph showed improvement in pulmonary edema bilaterally. All antibiotics were discontinued. Bactrim was started for pneumocystis pneumonia prophylaxis in the setting of high-dose steroid use. The patient was extubated to 3 L NC and a maintenance dose of prednisone 60 mg was initiated.

Peripheral eosinophilia peaked on the 10th day of admission to 10.95×10^3 cells/μL (34%) and decreased to 5.69×10^3 cells/μL at the time of discharge. He was discharged on room air and maintenance dose of prednisone 60 mg daily for 2 weeks. On outpatient follow-up 1 week later, the patient's eosinophilic count was zero and he was free of symptoms. He was adherent to quitting menthol-flavored cigarettes (Figure 4).

Discussion

Eosinophilic pneumonia is a rare disorder with incidence largely unknown. Shorr et al[2] studied AEP in military personnel in Iraq to estimate a prevalence of 9.1 cases per 100 000, which lacks generalizability. The etiology of eosinophilic pneumonia remains largely unknown. Studies have hypothesized it to be an acute hypersensitivity reaction secondary to inhaling certain antigens in the environment like rubble from demolition, debris from a firework, fumes after a fire, fine sand, dust particles, or certain drugs.[3,12] There have been cases to suggest an association with initiation or resumption of cigarette smoking and the development of AEP.[2,4-10] Miki et al[10] observed the effect of menthol-flavored cigarettes on 3 cases of AEP and so did Ogura et al,[5] which we also believe was the central etiological agent triggering AEP in our patient given the temporal relation of menthol cigarette smoking in the setting of a long-standing history of smoking nonflavored cigarettes.

The existing literature proposes that menthol has a direct downstream effect on the TRP melastin 8 receptor, which leads to increased expression of IL-6 and IL-8 production, which are central to airway inflammation.[19] Additionally, menthol is noted to increase the threshold for cough reflex leading to retention of smoke.[20] However, this needs further investigation for the exact pathway delineation.

Interestingly, he continued to smoke nonflavored cigarettes after discharge and remained symptom-free from AEP, which can be explained by a study conducted by Lin et al,[21] which showed that menthol cigarette extract potentiates a greater IL-8 response through TRPM-8 as compared with non-menthol cigarette extract.

The mainstay of treatment for severe AEP is glucocorticoid therapy with excellent response rate; however, there are no guidelines for dose and length of therapy as data from established clinical trials is lacking. This has to be supplemented

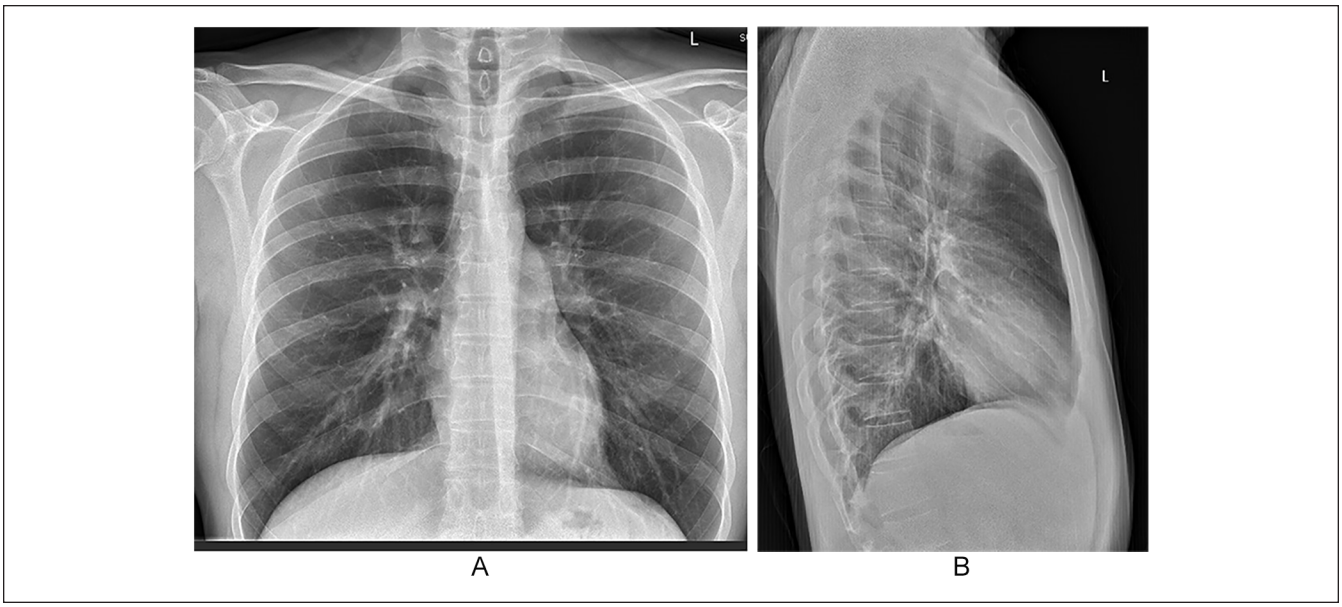

Figure 4. (A and B) Chest X-ray performed as an outpatient revealing complete resolution of disease with no remnant evidence of disease.

with discontinuation of the exogenous offending agent, when applicable and at times that is sufficient. Spontaneous resolution without the use of corticosteroids has been reported,[22,23] where patients had a less severe course.

Pope-Harman et al[24] treated 15 patients with AEP with methylprednisolone at a dose of 60 mg to 125 mg every 6 hours, while Badesch et al[3] used 125 mg every 6 hours to achieve clinical response as compared with our patient where we used 125 mg every 6 hours for 5 days to visibly see clinical improvement. After the resolution of hypoxemia and extubation, our patient was treated with 60 mg prednisone daily in line with studies conducted previously.[3,24]

Conclusion

Perhaps the most predisposing factor leading to a delayed diagnosis of eosinophilic pneumonia is the fact that it is a rare disease. The overlapping features with bacterial/fungal pneumonia add to the diagnostic dilemma; hence, treating broadly at presentation is not unreasonable. This patient's presentation and course of hospitalization is a testament to how important it is for physicians and intensivists to have a lower threshold for suspecting AEP, especially in young, immunocompetent individuals without any explicit precipitant of acute respiratory distress syndrome to avoid life-threatening complications of AEP. Second, peripheral eosinophilic counts are in the normal range during the initial patient presentation and tend to peak as the course of the disease progresses, as seen in our patient. This trend warrants greater reliance on AEP risk factors stated in the history (ie, debris inhalation, cigarette smoking, menthol inhalation), as opposed to eosinophilic markers, for the diagnosis of AEP. The initiation of menthol cigarette use in this patient is the likely reason for ensuing AEP, hence adding to the sporadic reports on the role of menthol-flavored cigarettes. Early risk factor assessment, diagnosis, and initiation of treatment can prevent subsequent respiratory failure and intubation in such patients.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient(s) for their anonymized patient information to be published in this article.

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