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CASE REPORT

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A 22-year-old man with fevers, chills, and a non-productive cough

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KEYWORDS E-cigarette or Vaping Product Use Associated Lung Injury; Bronchoalveolar Lavage; Critical Care; Oil Red O Stain; Pneumonia

1. Case presentation

A 22-year-old man with bipolar disorder and anxiety presented with fevers, chills, nausea, vomiting, and a non-productive cough for four days. He reported a fever up to 40°C at home and an inability to tolerate oral intake for approximately two days. His cough was dry and not associated with sputum production or hemoptysis. He endorsed headaches and diarrhea as associated symptoms. He reported a significant tetrahydrocannabinol (THC) and nicotine vaping history, which included the use of two nicotine cartridges and one THC cartridge daily. His last use was approximately 1 week prior to presentation. He denied neck pain and stiffness, leg swelling, dysuria, and abdominal pain. There was no personal or family history of thromboembolism. His home medications, taken daily, included lamotrigine and escitalopram. He had no recent travel history or sick contacts. The patient lived in a college dormitory in a major U.S. city. He had no pets or recent contact with birds. He denied any known exposure to heavy metals, agricultural chemicals, or any dyes, foams, and resins. The patient had also never been exposed to toxic gases such as chlorine. It should be noted that this patient presented to the hospital for care approximately four months before the first U.S. case of COVID-19, and as such, this is not investigated as part of the work-up.

2. Physical examination findings

His temperature was 37.8°C, blood pressure 140/65 mmHg, heart rate 102 beats/min, respirations 22 breaths/min, and oxygen saturation 90% on room air. He was well-developed and in no acute distress with decreased bilateral breath sounds in the lower lung fields on auscultation but no audible wheezes, rales, or rhonchi. His cardiovascular exam was unremarkable except for tachycardia. His abdomen was soft, nontender, and nondistended with normoactive bowel sounds. There was no peripheral edema.

3. Diagnostic studies

The initial WBC count was 13,110 cells/μL with 93% neutrophils. A lactic acid level was unremarkable. Procalcitonin was elevated to 1.06 ng/mL, CRP to 24.12 mg/dL, and ESR to 91 mm/hr. In the ER, a chest x-ray showed bilateral focal and infiltrative opacities, left greater than right. Subsequent CT angiography of the chest was negative for pulmonary embolus and showed extensive bilateral infiltrates (Figure 1). His clinical condition deteriorated and on day 3 of admission, he was intubated and subsequently underwent bronchoscopy. Bronchoalveolar lavage was bloody in appearance with 9000 RBCs and 1546 WBCs. Bronchial cytology showed numerous acute inflammatory cells and Oil Red O stain positive macrophages (Figure 2A-C).

The infectious work up for this patient was notable only for a positive monospot test, EBV IgG, and *M. pneumoniae* IgG. EBV and *M. pneumoniae* IgM were negative, indicative of a past infection. Cultures were unremarkable, including negative blood, sputum, and fungal cultures. Results of testing for HIV, respiratory viruses, influenza, HSV, VZV, CMV, *p. jirovecii*, and aspergillus antigen were all negative.

The patient also displayed an elevated C3 complement level of 118.3 mg/dL and an elevated IgE level of 148 kU/L. However, results of testing were negative for C4 complement, antineutrophil cytoplasmic antibody (ANCA), Jo-1 antibody, centromere B antibody, rheumatoid factor, double-stranded DNA, anti-nuclear antibody, Sjogren's antibody, and cyclic citrullinated peptide antibody.

Question: What is the diagnosis?

Diagnosis: E-cigarette or Vaping Product Use Associated Lung Injury (EVALI)

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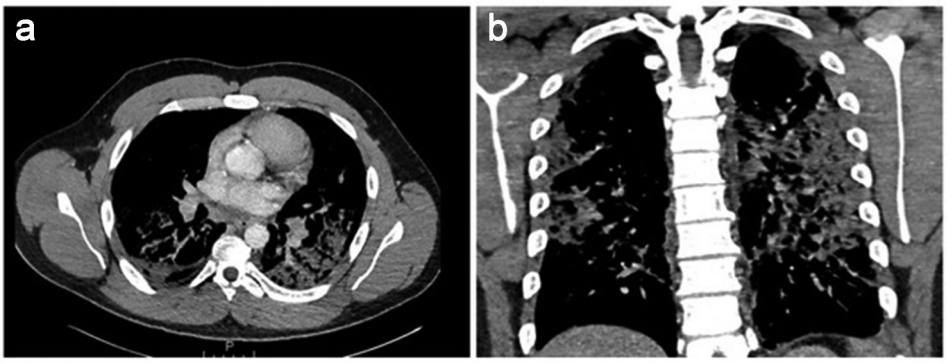

Figure 1. (A) Transverse slice of the initial CT angiogram of the chest with contrast showing extensive bilateral infiltrates. (B) Coronal slide of the same CT angiogram shown in (A).

4. Discussion

E-cigarettes and vaping products are battery powered devices that allow users to inhale various aerosolized substances such as nicotine, THC, and cannabidiol (CBD). These products are often heavily marketed as a 'healthy' alternative to cigarette use. However, the aerosol is not harmless and has been previously shown to contain various pollutants such as volatile organic compounds and heavy metals, as well as endotoxin and glucan concentrations above the limit of detection (LOD). According to the U.S. Surgeon General, e-cigarettes are the most commonly used tobacco product among youths with increasing prevalence over the last several years.

There has been an outbreak of lung injuries associated with the use of e-cigarettes and vaping products in the USA. As of February, 2020, a total of 2,807 hospitalized cases or deaths have been reported to the CDC from all 50 states, the District of Columbia, and two U.S. territories. Individual case reports have detailed a range of pulmonary illnesses including, but not limited to, hypersensitivity pneumonitis, acute eosinophilic pneumonia, organizing pneumonia, acute respiratory distress syndrome (ARDS), and diffuse alveolar hemorrhage. At present, the molecular mechanism governing the lung injury is not well understood. Transcriptomic analysis has shown that two e-cigarette flavoring chemicals, diacetyl and 2,3-pentanedione, impair cilia function in airway epithelia, likely contributing to lung injury. Additionally, analysis of bronchoalveolar lavage (BAL) fluid has identified vitamin E acetate as a chemical of concern.

The first large series of pulmonary illnesses associated with the use of e-cigarettes (vaping) was described by Layden *et al.* from 2019 to 2020, noting 98 patient cases in Wisconsin and Illinois, 26% of which required intubation and mechanical ventilation during hospitalization. Among these patients, common symptoms included cough, shortness of breath, nausea, vomiting, and abdominal pain. A high percentage of their patients displayed diffuse pulmonary opacities on imaging, leukocytosis with a neutrophil predominance, and elevated ESR. Additionally, lipid laden macrophages were seen with Oil Red O staining in BAL samples. Overall, this large series analysis prompted others to report very similar findings including a group from the University of Utah Health who posited that lipid laden macrophages may become a useful marker of this disease.

Since the presenting symptoms and imaging are often mistaken for pneumonia, patients are commonly placed on an initial course of antibiotics. Testing of blood and BAL fluid will generally not reveal any evidence of infection. Patients have been treated successfully with high-dose IV glucocorticoids leading to improvement in clinical condition and eventual resolution of symptoms. With regards to long term complications from vaping, data remains extremely limited. The first and only longitudinal analysis by Bhatta et al. (2019) assessed associations between e-cigarette use and respiratory disease. It concluded that the use of e-cigarettes is an independent risk factor for respiratory disease.

5. Clinical course

Given the extensive consolidations, fevers, and mild leukocytosis, the initial differential diagnosis focused on treating community acquired pneumonia. The patient was empirically treated with azithromycin, ceftriaxone, and bactrim. Despite continued treatment, the patient's WBC count remained elevated with no clear source of infection and his respiratory status worsened, requiring elective intubation on day 3 of admission. A suspicion for an e-cigarette or vaping product use associated lung injury (EVALI) prompted the patient to be started on stress dose

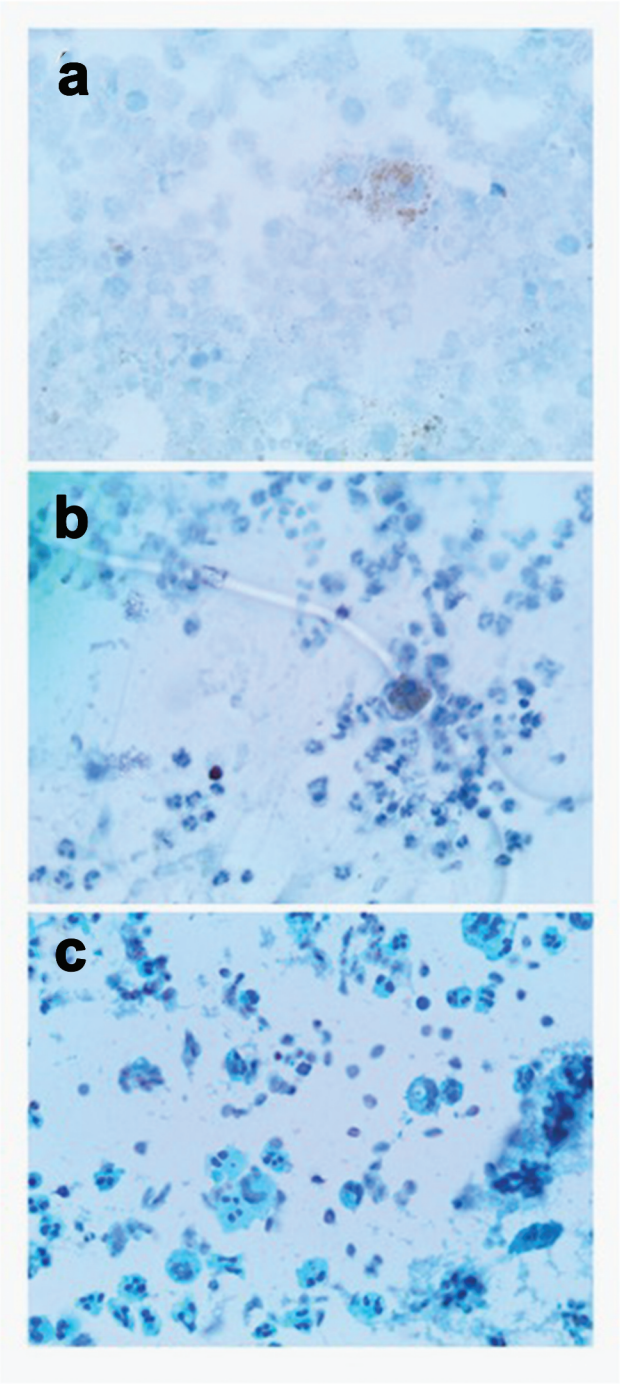

Figure 2. (A-C) Samples from bronchoalveolar lavage (BAL) demonstrating Oil Red O stain positive macrophages.

methylprednisolone. The patient's respiratory status greatly improved with steroids, and he was able to be extubated without complication on hospital day 5. In a clinic visit one week after discharge, his cough and fevers had resolved, and his pulmonary exam was unremarkable. A follow-up CT Chest showed resolution of the bilateral infiltrates (Figure 3).

6. Clinical pearls

(1) EVALI are a clinically significant issue in the U.S. with increasing prevalence. Patients commonly present with cough and shortness of breath but also frequently complain of fevers, nausea, vomiting, and abdominal pain. Imaging of the chest often reveals bilateral pulmonary opacities. Labs may show leukocytosis with a neutrophil predominance, elevated ESR or CRP, and a negative infectious work up.

(2) In cases of respiratory distress or deteriorating clinical condition, intubation and mechanical ventilation may be necessary.

(3) The diagnosis of an EVALI is essentially a diagnosis of exclusion in patients with a history of vaping. Atypical and opportunistic infections must be ruled out initially. The

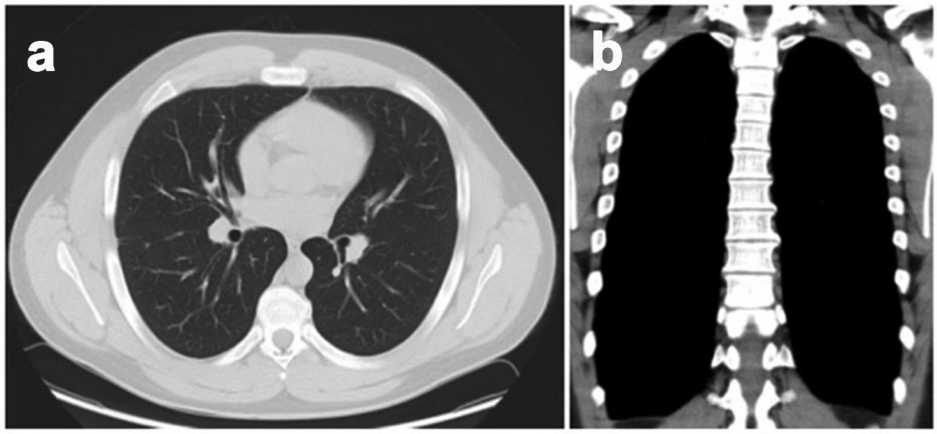

Figure 3. (A) Transverse slice of a CT chest without contrast preformed two weeks after the initial CT angiogram shown in Figure 1. (B) Coronal slice of the CT chest in (A).

diagnosis can be supported by the presence of lipid laden pulmonary macrophages (stained positive with Oil Red O) in bronchial cytology. However, there is no sensitivity or specificity associated with this marker yet and the presence or absence of this finding cannot dictate the diagnosis.

(4) Improvement in clinical condition and resolution of symptoms has been observed after treatment with high-dose IV glucocorticoids.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Suggested Reading

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