TRAINEE ARTICLE

Severe Necrotizing Pneumonia and Persistent Bacteremia in a Teenager with a History of Vaping

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INTRODUCTION

After being introduced into the market in 2004, electronic cigarette (e-cigarette) use has gained immense popularity worldwide as a safe alternative to cigarettes.[1] This trend has become especially prominent among the youth, with an estimated 4.9% of middle school and 20.8% of high school students reported having used e-cigarettes in 2018.[2] Vaping devices contain 4 basic components: a cartridge or a pod to hold e-liquid or e-juice, a heating element known as an atomizer, a battery and a mouthpiece used to inhale the vapor.[3] The most popular form of vaping among teenagers is JUUL®, a vaping device shaped like a small USB flash drive. A JUULpod is made from loose tobacco leaves and contains 2 ml of liquid nicotine (59 mg/0.7 ml of liquid) which is equal to one pack of cigarettes.[4]

Although long term health effects of vaping have largely remained unknown, vaping and e-cigarette use has been associated with a recent national outbreak of acute or subacute life-threatening respiratory illness, later termed e-cigarette or vaping-associated lung injury (EVALI). Initially recognized in the summer of 2019, there have been a total of 2,409 hospitalized EVALI cases with 52 deaths reported to the Centers for Disease Control and Prevention (CDC) as of December 10, 2019.[5] Vitamin E acetate is strongly linked to the EVALI outbreak. It has been found in product samples tested by FDA and state laboratories and in patient bronchoalveolar-lavage samples tested by CDC from geographically diverse states. Vitamin E acetate has not been found in bronchoalveolar-lavage fluid of people that do not have EVALI.[6]

EVALI is a diagnosis of exclusion and patients usually present with non-specific symptoms including shortness of breath (85%), cough (85%), nausea (66%) and vomiting (61%).[7,8] While the working case definition of EVALI specifically excluded individuals with microbiologically confirmed infections, there is mounting data suggesting a relationship between viral and bacterial infectious etiologies and EVALI that remains to be elucidated. Here, we present the case of an adolescent boy with a history of frequent vaping who developed severe necrotizing staphylococcal pneumonia and persistent bacteremia in the setting of influenza B infection. We go on to propose that his vaping increased his susceptibility to infection while also increasing the virulence of the infection itself.

CASE DESCRIPTION

A previously healthy 15-year-old Caucasian boy presented to his primary care provider with cough and a one-day history of fever (maximum of 106.3°F). He was diagnosed with a viral illness and discharged home. Over the next 3 days, he developed nausea, vomiting, diarrhea, and fatigue. He was taken to an emergency center where a throat swab was positive for influenza B, chest X-ray was consistent with a viral infection, and he was discharged home. Oseltamivir was not prescribed, as it had been greater than 72 hours since the onset of his symptoms.

Over the next 3 days, he worsened and returned to the emergency center where he was found to have dehydration, electrolyte disturbances, lactic acidosis and pre-renal azotemia. He received intravenous fluids and ceftriaxone and was transferred to the children's hospital for further management. Soon after his admission to the general floor he developed respiratory distress and was subsequently transferred to the pediatric intensive care unit (PICU) where he was placed on bilevel positive airway pressure (BiPAP) for acute hypoxic respiratory failure. He reported vaping JUUL® flavored nicotine pods: 1-2 per day for the last 2 years. He denied vaping THC or any other substance use. A repeat chest X-ray was concerning for development of bacterial pneumonia. A chest computed tomography (CT) scan showed significant bronchiectasis and bilateral areas of dense opacities consistent with necrotizing pneumonia (Figure 1). Sputum and blood cultures were positive for oxacillin-resistant *Staphylococcus aureus* (ORSA) susceptible to vancomycin, clindamycin, linezolid, gentamicin, and trimethoprim-sulfamethoxazole. He received vancomycin through a peripherally inserted central catheter (PICC). However, his blood cultures remained positive for the following 10 days while his antibiotic regimen was escalated to also include gentamicin, linezolid, and ceftaroline. Once the blood cultures were negative, antibiotics were deescalated and his PICC was removed. He was weaned off BiPAP to high flow nasal cannula and then to room air. He was switched to oral antibiotics upon transfer to the floor. Prior to discharge, he was counseled on the dangers of vaping and nicotine use and he agreed to quit. He was discharged home after a 22-day hospital stay. After discharge, the patient continued to receive oral antibiotic therapy (mainly as oral clindamycin) for 3 more weeks thus completing a total of 46 days of antibiotics (37 days of treatment after his first negative blood cultures).

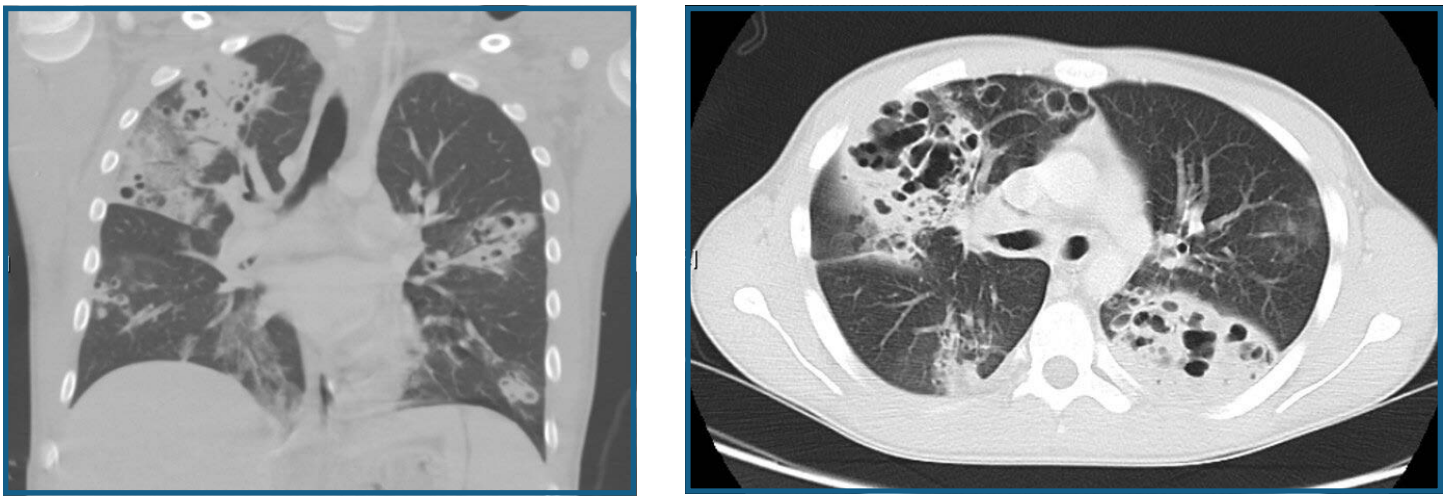

Figure 1: Computerized tomography (CT) scans of the chest demonstrating multifocal areas of dense opacification surrounding large cystic spaces throughout the lung lobes. Some of these may be filled with debris or mucous.

Two weeks after discharge, on follow up in the pediatric infectious diseases clinic, he reported some shortness of breath and was still found to have wheezing and crackles in both lung fields posteriorly. A repeat chest X-ray showed improvement with some residual necrotizing pneumonia. Four weeks later, he continued to experience shortness of breath on moderate exertion but had a normal lung exam.

DISCUSSION

Severe respiratory illness and lung injury related to vaping has been well documented, however its relationship to viral and bacterial infections is not well described. The case of this adolescent who vaped nicotine through a vape pen several times daily for about 2 years and developed influenza B and severe ORSA necrotizing pneumonia with bacteremia contributes to our understanding. Secondary bacterial co-infection is relatively common in adolescents infected with influenza.[9] A population based analysis on influenza and bacterial coinfection demonstrated bacterial coinfection in 2% of children hospitalized with

influenza between 2003 and 2010.[10] *Staphylococcus aureus* accounted for 28% of these infections, and was the second most common bacteria after *Streptococcus pneumoniae*, which accounted for 35%.[10] Although *S. aureus* colonizes the nares in about 50% of the population, it infrequently acts as a primary infectious agent in the development of community acquired pneumonia.[11] The suggested mechanism for secondary staphylococcal infection involves disruption of the lung epithelial barrier with impairment of mucociliary clearance. Additionally, there is modulation of the host immune response leading to increased host susceptibility to subsequent bacterial infection.[11]

Patients who develop bacterial pneumonia secondary to influenza can either present with abrupt worsening of clinical status, clinical deterioration after initial improvement or recurrent fever one to two weeks after recovering from the viral illness. In murine models, infection was seen to most commonly develop 7 days post-viral infection.[12] However, bacterial infection was observed as early as 3 days post-viral infection in those with enhanced susceptibility prior to initial viral infection.[12] The patient described here experienced an abrupt worsening of his clinical status about 4 days after first experiencing symptoms and 1-2 days after testing positive for influenza B. This suggests that he was at increased susceptibility for developing secondary bacterial infection prior to contracting influenza B. We propose that his frequent vaping increased his susceptibility to secondary bacterial pneumonia. Vaping and e-cigarette use alter the structure and function of lung epithelial cells and decreases both the number of cilia and ciliary beat frequency.[13] This causes impairment of mucociliary clearance in the lung leading to increased risk for bacterial infection. Furthermore, an in vivo study showed that mice exposed to e-cigarette aerosols for two weeks had impaired bacterial clearance when compared to mice exposed to air. An effect partially attributed to reduced phagocytosis by alveolar macrophages.[14] Therefore, this patient's vaping may have led to both direct epithelial damage impairing bacterial clearance as well as alveolar macrophage dysfunction reducing his host defenses.

Since the patient had not received a seasonal influenza vaccine, it is difficult to speculate whether his frequent e-cigarette use increased his risk for contracting influenza. However, in a recent study, mice exposed to e-cigarette aerosol had higher viral titers in the lung and higher rates of viral induced illnesses and death than unexposed mice.[15] Vaping use may have increased the virulence of our patient's influenza infection contributing to the severity of his initial presentation, including a markedly high fever of 106.3°F.

Necrotizing pneumonia usually follows infection by particularly virulent bacteria.[16] We propose that this patient's vaping led to the development of a more virulent infection capable of producing a necrotizing pneumonia through the direct effect of nicotine aerosols on both bacterial virulence and host defenses. A study in mice involving ex vivo exposure to e-cigarette vapor showed that *S. aureus* became more virulent when exposed to e-cigarette vapor, potentially by inducing biofilm formation, invasiveness, and resistance to antimicrobial peptides.[15] Vaporized nicotine has also been shown to decrease glutathione levels, which plays a key role in maintaining oxidant induced epithelial cell lung function.[17] Decreased glutathione levels in the lung leads to increased oxidative stress which in turn increases the severity of bacterial lung infections through direct cellular damage and impairment of signaling pathways.[18] Multiple studies have also shown statistically significant increases in lung inflammation after exposure to e-cigarette aerosols, even with short-term exposure, through various mechanisms including increased endothelial permeability and increased production of pro-inflammatory cytokines.[15,19,20]

Vaping has been associated with necrotizing pneumonia in a case report of a previously healthy girl who developed *Fusobacterium necrophorum* infection of her lung without having any traditional predisposing conditions. The girl described had a history of vaping "several times each hour" for about 9 months' time. The authors propose that her vaping was the predisposing factor for her developing the infection.[21]

Further research on the association between vaping-induced injury to the lung and predisposing the host to severe infection is warranted. Our case can help increase awareness among providers of the dangers of vaping in teens, both directly on the lungs but also contributing to development of more severe infections.

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