Anaerobic Necrotizing Pneumonia: Another Potential Life-threatening Complication of Vaping?

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An adolescent girl with a history of frequent electronic cigarette use of nicotine was hospitalized with severe necrotizing pneumonia. Blood cultures obtained before the administration of empirical broad-spectrum intravenous antibiotics had positive results for the growth of *Fusobacterium necrophorum*. The pathogen is an uncommon but well-known cause of anaerobic pneumonia with unique features that are collectively referred to as Lemierre syndrome or postanginal sepsis. The syndrome begins as a pharyngeal infection. Untreated, the infection progresses to involve the ipsilateral internal jugular vein, resulting in septic thrombophlebitis with direct spread from the neck to the lungs causing multifocal necrotizing pneumonia. The teenager we present in this report had neither a preceding pharyngeal infection nor Doppler ultrasonographic evidence for the presence of deep neck vein thrombi, leading us to explore alternative mechanisms for her pneumonia. We propose the possibility that her behavior of frequent vaping led to sufficient pharyngeal irritation such that *F necrophorum* colonizing her oropharynx was inhaled directly into her lungs during electronic cigarette use. Preexisting, but not yet recognized, vaping-related lung injury may have also contributed to her risk of developing the infection. The patient was hospitalized for 10 days. At follow-up one month later, she still became short of breath with minimal exertion.

The current epidemic of electronic cigarette or vape product use–associated lung injury (EVALI) has led to heightened vigilance by local, state, and federal agencies in association with legislative proposals for more aggressive regulation of the sales of vaping devices and their cartridges.[1] As of December 17, 2019, 2506 cases of hospitalized EVALI, including 54 EVALI-associated deaths, have been reported to the US Centers for Disease Control and Prevention.[2] Several states have already banned the use or sales of flavored vaping products. The current working definition used during the epidemiological investigation of suspected cases specifically excludes those in which an infectious etiology for the new-onset severe lung disease has been identified. Here, we present the case of an adolescent girl with a history of frequent electronic cigarette (e-cigarette) use who developed severe necrotizing anaerobic pneumonia. We go on to propose a novel mechanism for the pathogenesis of her infection, including possible contributions of her vaping behavior that may also apply to other cases under investigation.

PATIENT PRESENTATION

A previously healthy 15-year-old girl presented to the emergency

abstract

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Dr El Chebib (a pediatric resident) performed the literature search, wrote the first draft of the discussion, and reviewed and revised the manuscript; Ms McAurthur and Ms Gorbonosov (both fourth-year medical students) reviewed the national and New York state–specific epidemiology of electronic cigarette use, the current guidance, and legislative efforts related to vaping and severe lung disease, wrote the first draft of the introduction and case presentation, and reviewed and revised the manuscript; Dr Domachowske recognized the novel aspects of the case, obtained informed consent from the parents, gained informed assent from the patient to prepare a report for publication in the medical literature, mentored the coauthors on the process of developing the case report, identified and prepared the image used for Figure 1, prepared the responses to the reviewers, revised the manuscript accordingly, formatted revision 1 for submission to *Pediatrics*, uploaded the work for consideration by the editors, and merged, reviewed, and revised several drafts of the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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department in early September 2019 with a chief complaint of difficulty breathing. She reported that her illness began one week before with cough, shortness of breath, and fever as high as 41°C. Over the next 6 days, as her respiratory symptoms progressed, she also experienced 2 to 3 episodes of nonbilious vomiting and watery diarrhea each day. Symptomatic care was advised during 2 separate visits to her primary care provider. One day before hospitalization, she complained of severe shortness of breath and right-sided chest pain. Her parents brought her to the hospital when they noted she was "panting" to breathe. The patient denied recent symptoms of nasal congestion, nasal discharge, sore throat, or difficulty swallowing. Her substance use history was significant for daily vaping of nicotine "several times each hour" for the past 9 months, going through a prefilled nicotine cartridge every 1 to 2 days. She reported purchasing both disposable and refillable penlike vape devices, 16 mg/mL nicotine cartridges, and "various" flavors, including apple, mango, cotton candy, and birthday cake, from a local vendor. Two e-cigarette devices, described as "pens," that were used by the patient immediately before and at the onset of her illness and an unopened, unused tobacco flavored cartridge containing 16 mg of nicotine were sent to the New York State Department of Health for analysis before the medical team had an opportunity to inspect them. The patient specifically denied using devices that had been modified by an end user, purchasing vaping cartridges on the street or via the Internet, or practicing behaviors known as "hacking" (refilling single-use cartridges with homemade substances), "dripping" (applying liquid directly onto a device's heating coil to achieve higher concentrations of the substance in the aerosol), or "dabbing" (superheating substances already containing high concentrations of tetrahydrocannabinol or related chemicals). She stated that she smokes marijuana once or twice each month but has never smoked cigarettes or vaped tetrahydrocannabinol- or cannabidiol-containing substances. She is fully immunized.

On presentation, the patient was visibly distressed, taking rapid shallow breaths. Her vital signs showed a temperature of 39°C, a pulse of 150 beats per minute, respirations of 50 to 60 per minute, and a blood pressure of 100/70 mm Hg. Room air pulse oximetry was 78%, correcting to 92% with high-flow supplemental oxygen delivered via nasal canula. Her mucous membranes were dry and posterior pharynx erythematous without exudate. She was tachycardic with a hyperdynamic precordium and bounding peripheral pulses. Crackles were heard in all lung fields with decreased breath sounds at both bases. The remainder of her physical examination was unremarkable. The patient was stabilized with intravenous fluid resuscitation and supplemental oxygen and treated empirically with broad-spectrum antibiotics. Adjunctive therapy with intravenous methylprednisolone was considered but not used.

Laboratory results showed a total leukocyte count of 23 200 cells per μL with 71% neutrophils, 15% bands, 8% lymphocytes, 5% monocytes, 1% eosinophils, a hemoglobin of 10 g/dL, and a platelet count of 44 000 per μL. A metabolic panel was significant for a blood urea nitrogen of 54 mg/dL and creatinine of 1.81 mg/dL. A fourth-generation diagnostic test for HIV had negative results. Total serum concentrations of immunoglobulin G, A, and M were elevated. A chest radiograph identified infiltrates in the lower lobes of both lungs and a right-sided parapneumonic effusion. Computer tomography of the chest identified extensive multilobar necrotizing pneumonia with early cavity formation and right-sided parapneumonic effusion (Fig 1). No previous chest imaging had been performed, so preillness images were not available for comparison. Computer tomographic angiography of the chest showed no evidence for pulmonary embolism. A thoracentesis was performed for both diagnostic and therapeutic purposes. Pleural fluid showed 210 000 leukocytes per μL with 90% neutrophils, a lactate dehydrogenase of 1773 U/L, and a glucose of 44 mg/dL. Gram-stain showed 4+ white blood cells and no bacteria or yeast forms. Cultures remained sterile. Bronchoscopy and spirometric measures of pulmonary function were deferred because of the patient's tenuous respiratory status. Results of a 22-plex polymerase chain reaction–based respiratory panel were negative. The blood cultures collected before administering broad-spectrum empirical antibiotics showed growth of Gram-negative rods in the anaerobic broth 36 hours later. The organism was subsequently identified as *F necrophorum.* Doppler ultrasonography of the neck showed no evidence of internal jugular or subclavian vein thromboses.

The patient was monitored under intensive care for 6 days but never required mechanical ventilation or inotropic support. Supplemental oxygen was necessary to maintain oxygen saturations >90% until hospital day 8. The patient was discharged after a 10-day hospitalization to complete 21 days of intravenously administered piperacillin plus tazobactam. One month after completing the course of antibiotics, the patient was still unable to climb more than one flight of stairs or walk quickly from one class to another during the school day without becoming winded. Spirometric measures of pulmonary function and additional radiographic imaging of the chest during convalescence have not yet been performed. Her parents confirmed the patient's attestation that she no

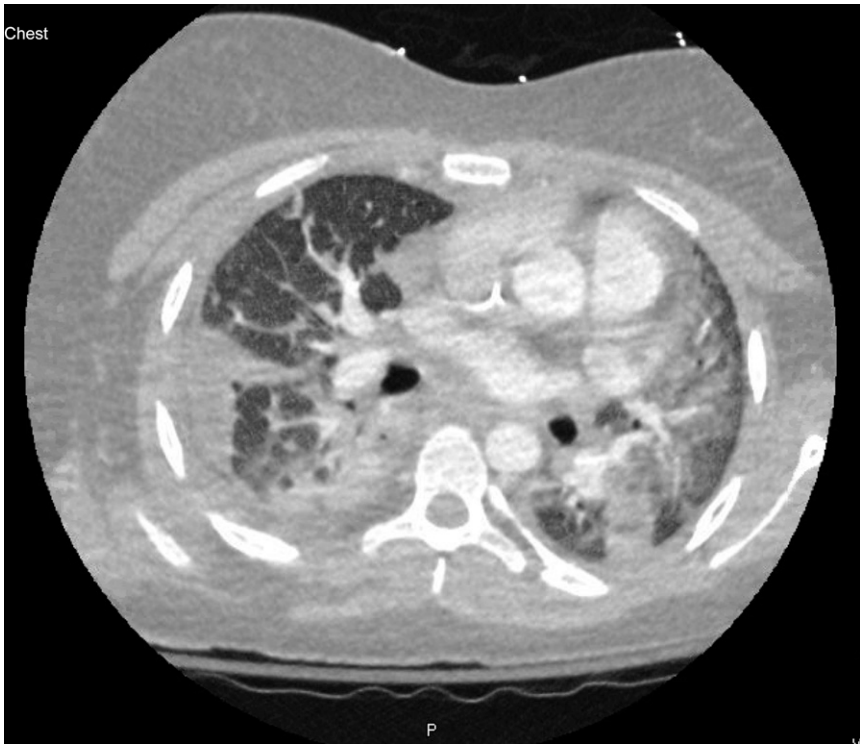

FIGURE 1
Computer tomography image of the lower thorax demonstrating extensive multilobar necrotizing pneumonia.

longer vapes and has not started smoking cigarettes. An analysis of residual fluid taken from the cartridge the patient last used confirmed the presence of nicotine but absence of tetrahydrocannabinol, cannabidiol, and tocopherols.

DISCUSSION

The adolescent described in this report developed severe necrotizing pneumonia and sepsis caused by the strict anaerobe *F necrophorum* without evidence of suppurative jugular vein thrombophlebitis or a recent pharyngeal infection. This observation is important because the vast majority of such cases begin as a parapharyngeal infection that progresses to involve neighboring deep neck veins. The ensuing septic thrombophlebitis allows direct extension of *F necrophorum* to the lungs, resulting in anaerobic pneumonia, a condition referred to as Lemierre syndrome, or postanginal septicemia.[3,4] Complications of Lemierre syndrome include parapneumonic fluid collections, lung abscess formation, sepsis, and death, with a case fatality rate exceeding 6%.[5,6] Rare cases of *F necrophorum*–associated necrotizing pneumonia have been described in patients without internal jugular vein thrombosis[7,8]; however, in each of the reported cases, the development of pneumonia was preceded by symptomatic pharyngitis. In the case published by Shiber et al,[9] the authors purported that "even without internal jugular thrombosis, the same mechanism of disease exists, and therefore, the same morbidity, prognosis, and treatments are applicable." On the basis of their observation, the authors suggested that such cases be referred to as "incomplete" Lemierre syndrome.

The absence of a preexisting pharyngeal infection and failure to identify deep neck vein thromboses by Doppler ultrasonography in our patient led us to consider alternative mechanisms to explain how the pathogen gained entry to the lungs. We suspect that the patient's vaping led to chronic irritation of her pharyngeal mucous membranes, thereby facilitating direct inhalation of *F necrophorum* from her colonized oropharynx. Once inhaled, vaping-associated chronic irritation of the patient's airways likely contributed to the permissive conditions needed for the bacteria to escape clearance via the mucociliary escalator and other innate defenses and establish a highly destructive infection.

Widespread cytotoxic and genotoxic effects are seen in cultures of human oropharyngeal mucosa that are exposed to e-cigarette liquids in vitro,[10] but clinical evidence for an association between vaping and oropharyngeal irritation is sparse. A 2019 report from a large clinical trial, however, suggests that it occurs in the majority of e-cigarette users. The trial, designed to compare 1-year smoking-abstinence rates in subjects who were randomly assigned to use either e-cigarettes or nicotine replacement, found that 65.3% of the participants assigned to the e-cigarette group reported mouth or throat irritation.[11] Reports describing the detrimental effects of e-cigarette components on the respiratory tract using tissue culture[12–14] and animal models[14,15] specifically linking cytotoxic effects to oxidative stress, DNA damage, and chronic inflammation have also been published.[12–15]

Studies performed in vitro[16–19] and in animal models[20–22] also suggest that e-cigarette components impair host defense mechanisms. Chronic exposure to nicotine and propylene glycol from e-cigarettes impairs mucociliary clearance,[16,21] the flavor-enhancing substances cinnamaldehyde and ethyl vanillin reduce neutrophil oxidative burst activity, and benzaldehyde propylene

glycol acetal and benzaldehyde impair neutrophil phagocytic function.[19] E-cigarette vapor extract has also been shown to blunt innate antiviral responses to polyinosinic: polycytidylic acid in vitro,[17] and mice exposed to e-cigarette vapor show impaired pulmonary defenses against both viruses and bacteria.[22] In a similar animal model, Hwang et al[20] showed that the innate immune dysfunction seen with e-cigarette exposure was associated with increased virulence of colonizing bacteria.

As of December 3, 2019, children 13 to 17 years of age accounted for 16% of reported hospitalized EVALI cases in which age was known.[2] Ongoing efforts to identify the cause(s) of vaping-associated lung disease strongly implicate vitamin E acetate; however, the working case definition at the time of this report specifically excludes individuals with microbiologically confirmed infections.[2] Although current data support that the primary cause(s) of vaping-associated severe lung disease are not infections, the possibility of concurrent processes should still be considered. Moreover, because the signs, symptoms, and radiographic findings of vaping-related lung disease overlap with those seen with moderate to severe community-acquired pneumonia, diagnostic testing and empirical antibiotic treatment of infectious etiologies is considered appropriate unless or until an alternative diagnosis has been confirmed. Treatment with systemic glucocorticoids has met with anecdotal success but is not recommended routinely. Consideration for their use should be made on a case-by-case basis.

This case of severe *F necrophorum* necrotizing pneumonia without evidence for a preceding pharyngeal infection or associated internal jugular vein septic thrombophlebitis led us to consider the possibility that unlike the pathogenesis seen with Lemierre syndrome, vaping may be associated with secondary effects that are permissive for the pathogen to gain entry to the lungs by inhalation during e-cigarette use. Anaerobic necrotizing pneumonia could likely represent yet another life-threatening complication of vaping. Future research in this area may benefit from both heightened awareness and active surveillance for bacterial pneumonia as a complication of e-cigarette use, with particular attention being paid to the importance of collecting anaerobic cultures during the diagnostic evaluation.

ABBREVIATIONS

EVALI: electronic cigarette or vape product use–associated lung injury
e-cigarette: electronic cigarette

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