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Vaping-associated lung injury causing organizing pneumonia: A case report

The case of a 64-year-old male diagnosed with organizing pneumonia after switching from smoking combustible cigarettes to using e-cigarettes. This report highlights the manifestations of e-cigarette–related lung damage as well as a need to increase public awareness about the harmful effects of vaping.

ABSTRACT: A 64-year-old male with no previous history of lung disease presented with intermittent pleuritic chest pain and shortness of breath. The patient had a 20 pack-year smoking history but had recently quit and had started using electronic cigarettes (e-cigarettes). An initial CT scan of his chest revealed right lower lobe opacification with associated ground glass, and over the next 6 months he developed bilateral opacifications in a centrilobular fashion. Infection, connective tissue disease, and cardiac disease were ruled out through preliminary investigations and bronchoscopy. Given the concerns over malignancy, an open lung biopsy was performed and the pathology results indicated an organizing pneumonia. A multidisciplinary team discussion favored a diagnosis of lung injury secondary to inhaled agents or a drug reaction. The patient was found to meet the diagnostic criteria for e-cigarette, or vaping, product use–associated lung injury (EVALI) based on his history of vaping, the presence of bilateral pulmonary infiltrates, and the absence of infection. His symptoms abated with cessation of e-cigarette use, and further intervention was not required. This case of inhalational lung disease secondary to nicotine use through electronic delivery systems raises concerns about the rapid uptake and growth of vaping, especially among adolescents, and the need for product regulation.

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Electronic cigarettes (e-cigarettes) are a type of nicotine delivery system that consists of a cartridge that contains a liquid, an atomizer (heating element), and a battery. Commonly used liquids contain various substances, including nicotine, cannabinoids such as tetrahydrocannabinol (THC), flavoring, and additives such as glycerol and propylene glycol.[1] Use of these aerosolized devices (colloquially termed vaping) has risen substantially among the Canadian population, in particular among younger individuals. In 2017, 15.4% of Canadians aged 15 years and older (4.6 million) reported having tried an e-cigarette, and 2.9% (~863 000) had used an e-cigarette in the previous 30 days.[2] Among adolescents in grades 8, 10, and 12 in the United States, vaping prevalence more than doubled in each of the three grades from 2017 to 2019.[3] In 2019, it was estimated that more than 25% of students in the 12th grade in the United States had vaped during the previous 30 days, while 12% of students stated that they vaped daily.[4] Multiple case series were published in autumn 2019 when hospitalizations linked to lung disease and electronic nicotine delivery systems increased throughout the United States. These cases are now known collectively as e-cigarette, or vaping, product use–associated lung injury (EVALI).[4,5] As of November 2019, there have been more than 2800 cases of EVALI in North America, which have displayed a heterogeneous pattern of lung pathology that includes organizing pneumonia, acute respiratory distress syndrome, acute eosinophilic pneumonia, lipoid pneumonia, diffuse alveolar damage, diffuse alveolar hemorrhage, and hypersensitivity pneumonitis.[6] Given the increased incidence and potential severity of EVALI, renewed focus has been placed on the pathophysiology and corresponding health effects of vaping, and on the need for product regulation.

Case data

In July 2017, a 64-year-old male with a 20 pack-year smoking history presented to his family physician with complaints of intermittent pleuritic chest pain and shortness of breath for several months. He had quit smoking combustible cigarettes 4 years previously and had transitioned to an e-cigarette, with increasing daily use. He had used a single variety of nicotine fluid with no THC. He was a retired office

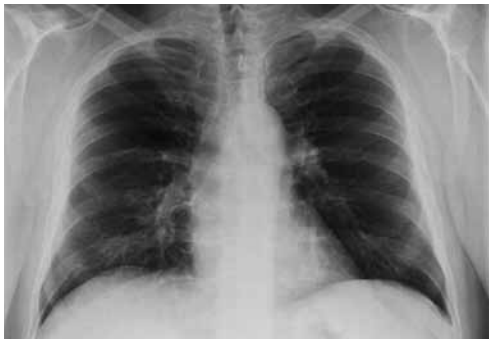

FIGURE 1. Initial chest X-ray from July 2017 showing lung parenchyma, heart, mediastinal structures, and pleura with no abnormalities.

manager and had not traveled recently or had environmental exposures, such as home renovations or living with pets. His medical history included hypertension, diabetes, and dyslipidemia, and his medications included metformin, pantoprazole, candesartan, indapamide, and atorvastatin.

An X-ray of the patient's chest in July 2017 revealed no abnormalities **[Figure 1]**, but a CT scan with contrast in November 2017 revealed right middle and lower lobe opacifications with associated ground glass opacity **[Figure 2]**. Given the clinical and radiographic findings, a broad differential diagnosis that included atypical infections, inflammatory conditions, hemorrhage, and malignancy was considered, and a respirology referral was made.

The patient's cardiovascular and respiratory exam showed no abnormalities, and there was no peripheral stigmata of chronic lung disease. Pulmonary function tests done shortly after the patient's initial CT scan demonstrated an FEV_1 of 2.6 litres (90% predicted) and FVC of 3.7 litres (95% predicted). The ratio of FEV_1 to FVC was low normal at 0.70, and no reversibility was seen with bronchodilators. The patient's bloodwork revealed a CBC with no eosinophilia, and his tests for C-reactive protein, antinuclear antibodies, rheumatoid factor, and antineutrophil cytoplasmic antibodies were all negative, as were tests for hepatitis B and C, and HIV.

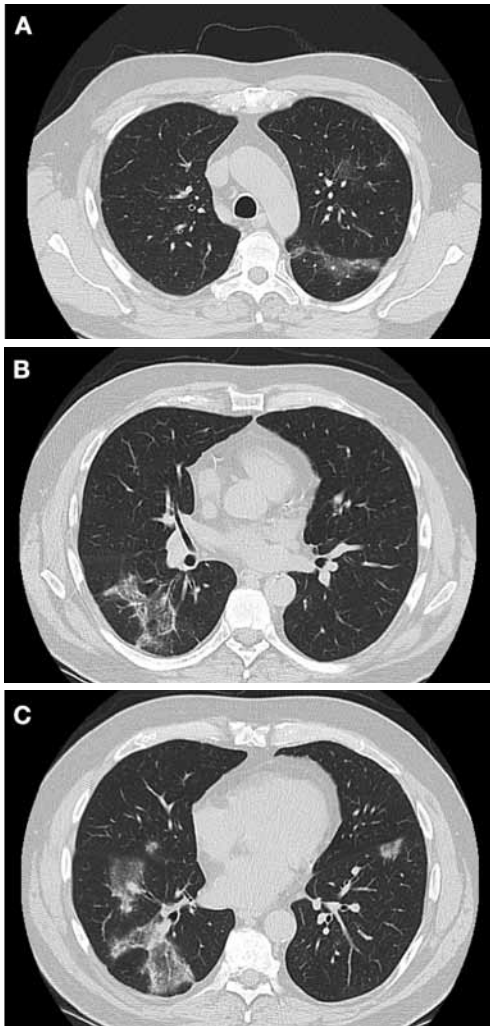

FIGURE 2. Transverse axial CT images of the patient's chest from November 2017 showing nonspecific patchy areas of mixed airspace (A) and ground glass opacity in the right lung (B), and ground glass opacity in the left upper lobe (C).

Because of concerns about malignancy given the patient's smoking history and the initial images obtained, a CT scan of his chest was repeated in January 2018 **[Figure 3]**. Airspace opacities within the right middle lobe and right lower lobe were seen to have persisted and to have increased in size relative to the November 2017 scan. Many of the lesions had peripheral consolidation with central ground glass opacity, known radiographically as the reversed halo sign (atoll sign), a finding specific to organizing pneumonia.[7] Similar patchy airspace opacities had also developed in the left upper and lower lobes. The changing appearance of the patient's lungs on the CT scans over a short interval

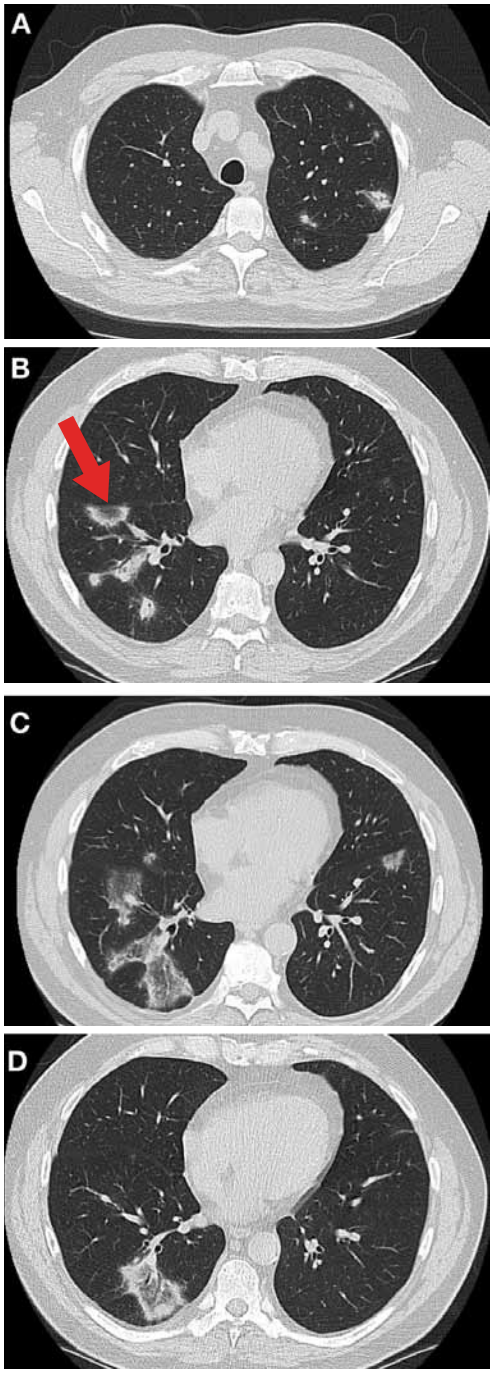

FIGURE 3. Transverse axial CT images from one study of the patient's chest from January 2018. Patchy airspace opacities can be seen in the left upper lobe (A) and airspace opacities within the right middle lobe and right lower lobe (B, C, and D). Many of these lesions have peripheral consolidation with central ground glass opacity (reversed halo/atoll sign; see arrow).

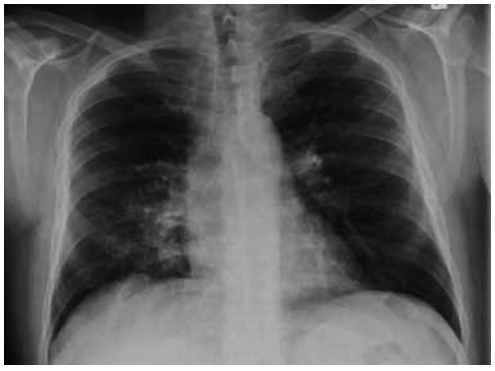

FIGURE 4. Repeat chest X-ray from May 2018 showing right lower lobe opacities with no heart, mediastinal structure, or pleural abnormalities.

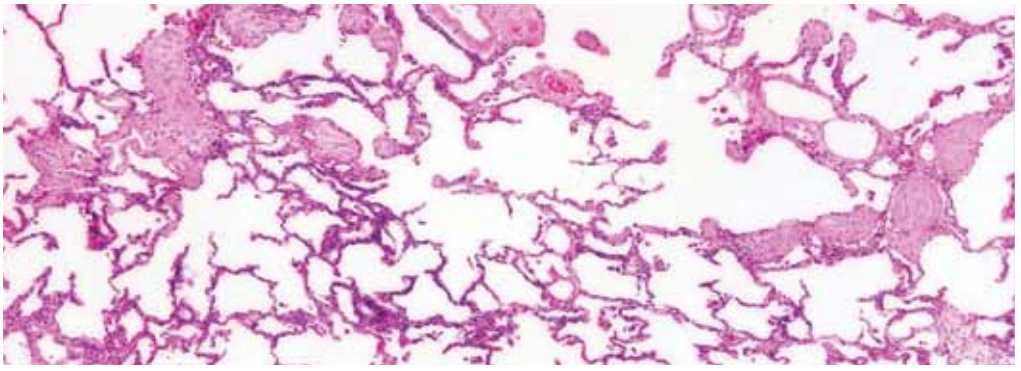

FIGURE 6. A wedge resection sample of the patient's left lower lobe showing cicatricial organizing pneumonia. A few centrilobular patches of mild interstitial fibrosis associated with organizing pneumonia can be seen. In places, the organizing pneumonia has turned into bands of dense collagen.

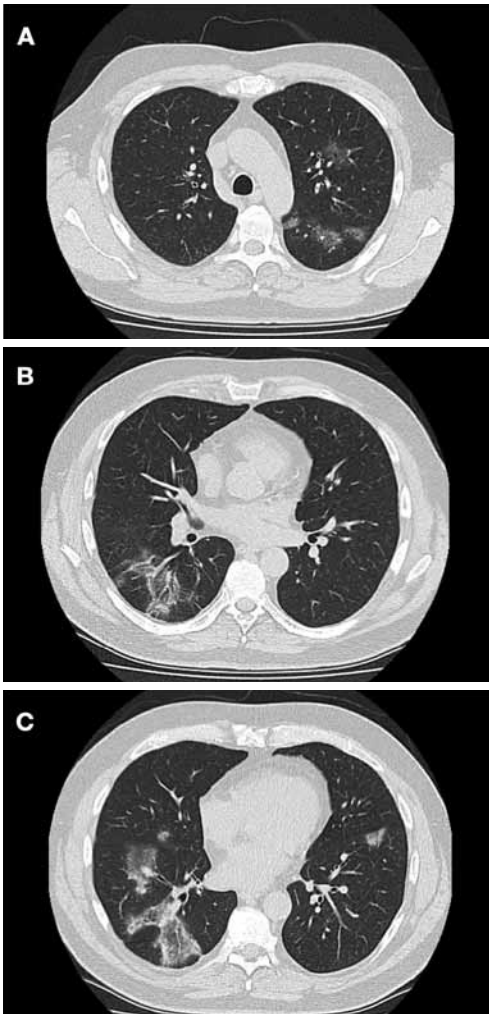

FIGURE 5: Transverse axial CT images of the patient's chest from May 2018. Ongoing evolution of consolidation and central ground glass opacity can be seen in the left upper lobe (A). A wider area of parenchymal involvement can also be seen in the right lower lobe (B). The regions of consolidation in the right lower lobe (C) appear to have more ground glass opacification.

narrowed the differential diagnoses to include organizing pneumonia, eosinophilic pneumonia, vasculitis, pulmonary lymphoma, and alveolar hemorrhage.

After the patient's second CT scan, a bronchoscopy was undertaken to obtain tissue samples by wash, brush, and biopsy. Endobronchial anatomy, including the right lower lobe, showed no abnormalities upon inspection. Bronchoalveolar lavage of the RB6 bronchus (superior segment of the right lower lobe) demonstrated numerous pulmonary macrophages and a moderate number of mixed inflammatory cells. Cultures for bacteria and fungi were negative as were results from a respiratory viral panel, and no antigen was found for *Pneumocystis jiroveci*. Tissue biopsies of the RB9 and RB10 segments showed intra-alveolar macrophages, mild interstitial inflammation, and mild fibrosis.

Given the diagnostic uncertainty and persistent changes in the right lower and left upper lobes on imaging from November 2017 and January 2018, another chest X-ray **[Figure 4]** and additional CT images **[Figure 5]** were obtained in May 2018 to facilitate a wedge resection by thoracic surgery. The new CT scan showed wider areas of consolidation, coalescing lesions in the right lower and left upper lobes, and increasing amounts of associated ground glass opacification. The patient underwent a thoracoscopy and wedge resection of the superior segment of the left lower lobe; pathology from that biopsy showed evidence of cicatricial organizing pneumonia **[Figure 6]**. Interestingly, after the patient ceased e-cigarette use, his symptoms completely resolved over a matter of weeks and were gone prior to his May 2018 CT scan and wedge resection despite radiographic progression. In consultation with the chest radiologists and pathology department at Vancouver General Hospital, lung injury secondary to inhaled agents, a drug reaction, or connective tissue disorders were thought to be the most likely diagnoses given the distinctly centrilobular localization and the odd radiologic waxing and waning over 6 months. He did not require the use of corticosteroids, although he continues to require follow-up with serial CT scans.

Discussion

The patient presented with respiratory complaints consisting of pleuritic pain and intermittent shortness of breath and underwent serological testing, spirometry, and bronchoscopy. Persistent radiographic changes, including bilateral consolidations and associated ground glass opacities, were seen over a 6-month period, and pathology results from a wedge resection of the left lower lobe indicated an organizing pneumonia. Classically, organizing pneumonia has been categorized as cryptogenic or secondary, with secondary causes being related to another lung pathology (vasculitis, hypersensitivity pneumonitis, eosinophilic pneumonia, interstitial lung diseases) or lung injury (infection, drug toxicity, inhalation of toxic gas, aspiration of gastric contents, organ transplant, radiotherapy).[8] The patient underwent extensive testing to rule out secondary causes of his clinical and radiographic features. The consensus diagnosis by a multidisciplinary team favored a drug

reaction or inhalation exposure that caused an organizing pneumonia. A search of the online database Pneumotox for information on the patient's medications indicated that atorvastatin can cause a drug-related interstitial lung disease; however, a large cohort analysis of more than 6000 individuals published in 2013 showed no link between statins and interstitial lung disease.[9] Therefore, other inhalation exposures were considered, with particular focus on the patient's use of e-cigarettes.

A Wisconsin and Illinois cohort series proposed diagnostic criteria for EVALI, which include use of an e-cigarette or related product in the previous 90 days, lung opacities on chest X-rays or CT scan, exclusion of infection, and absence of other likely alternatives such as heart failure or connective tissue disease.[5] In a recent Centers for Disease Control and Prevention report, more than 2800 cases of EVALI and more than 60 related deaths were described.[5] The most common symptoms were cough, shortness of breath, and fatigue; other symptoms included fever, chest pain, weight loss, nausea, and diarrhea.[6] Most of what we know about toxic inhalation syndromes comes from studies of patients with high levels of exposure in occupational settings or from house fires.

At present, there are many questions about the pathophysiology of EVALI. The aerosols produced by e-cigarettes are highly heterogeneous, which makes in vitro models difficult to study. The composition of the aerosol depends on the ingredients in the liquid, the electrical characteristics of the heating element, the temperature reached, and the characteristics of the wick.[10] E-cigarette liquids generally consist of glycerol (vegetable glycerin), propylene glycol, and nicotine.[10] In Layden and colleagues' case series of persons who vaped and developed EVALI, 60% used a combination of THC and nicotine, 27% used THC alone, and 11% used nicotine alone.[5] Vaping fluids containing THC have been formulated with oils, such as vitamin E acetate, whereas most nicotine-only products are mixed with propylene glycol and glycerin.[11,12] Vitamin E has been implicated in the bronchoalveolar-lavage fluid in EVALI patients.[11] Flavoring agents such as diacetyl, which is commonly found in e-fluids containing nicotine, have been shown to cause bronchiolitis obliterans and other severe respiratory diseases in exposed plant workers.[13] However, even though several large cohort studies were published in 2019, no single constituent was common to all cases. Butt and colleagues reviewed lung biopsies from 17 patients, all of whom had a history of vaping and were clinically suspected of having vaping-associated lung injury.[14] In all cases, histopathological findings showed patterns of acute lung injury, including acute fibrinous pneumonitis, diffuse alveolar damage, or organizing pneumonia, as seen in the case discussed in this article.

Currently, there is no standardized treatment for EVALI. Initial treatment usually focuses empirically on more common causes of lung injury, such as infection or underlying lung disease. If EVALI is suspected, most patients are treated with supportive management, including hospital admission and supplemental oxygen if indicated and critical care if progression to acute respiratory distress syndrome occurs. Findings from case series have suggested that patients with worsening hypoxia despite other treatment efforts may benefit from a trial of corticosteroids, but evidence is limited.[5] It is suggested that patients be followed in the community until their symptoms resolve and imaging indicates improvement.[5]

Given our patient's vaping history, investigation results, and radiographic findings, a presumptive diagnosis of EVALI was made. His significant clinical improvement with cessation of e-cigarette use also makes EVALI the most likely explanation for his clinical syndrome.

Summary

A 64-year-old male with no previous history of lung disease underwent investigations after presenting with intermittent pleuritic chest pain and shortness of breath. A multidisciplinary team discussed the laboratory, imaging, and pathology results and concluded that a drug reaction or inhalation exposure had caused organizing pneumonia. The patient's symptoms abated with cessation of his e-cigarette use and further intervention was not required. Based on a history of vaping, the presence of bilateral pulmonary infiltrates, and the absence of both infection and a likely alternative diagnosis, the patient was found to meet the diagnostic criteria for EVALI.

This case and others reported recently demonstrate a link between electronic nicotine delivery systems and chemically induced acute lung injury. This case also highlights questions about the mechanism of toxicity and the unpredictable clinical course of EVALI. Given the dramatic rise in e-cigarette use, especially among adolescents, continued efforts should be made to increase public awareness of the harmful effects of e-cigarettes. ■

Competing interests

None declared.

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