

CASE REPORTS

Vaping-associated lung injury case report: A community hospital's perspective

Rachel E. Herr*¹, Christopher R. Wing¹, Walter C. Rustmann²

¹Edward Via College of Osteopathic Medicine, Auburn, AL, United States

²White Wilson Medical Center Pulmonology, Critical Care, and Sleep Medicine, Fort Walton Beach, FL, United States

Received: March 25, 2020

Accepted: June 1, 2020

Online Published: June 16, 2020

DOI: 10.5430/crim.v7n2p9

URL: <https://doi.org/10.5430/crim.v7n2p9>

ABSTRACT

Electronic Nicotine Delivery Systems (ENDS) aerosolize cannabis oils, nicotine, and other chemicals by heating alcohols and flavorants in order to produce a vapor for inhalation. With the rise in popularity of these devices, there is a rapidly growing number of life-threatening electronic-cigarette or vaping-associated lung injury (EVALI) cases throughout the country. Among the EVALI cases, similarities of presentation, symptoms, respiratory complications, and effective treatments have been reported, but the pathologic mechanisms of injury seem to vary by case. We report a series of two patients presenting with clinical symptoms and imaging findings consistent with vaping-associated lung injury in the setting of heavy nicotine and tetrahydrocannabinol (THC) vaping. The first case is a 19-year-old Caucasian male admitted to the hospital with dyspnea, nausea, emesis, weight loss, and early signs of acute respiratory distress syndrome. The second case is a 24-year-old Caucasian male who presented to the emergency room with a productive cough, fever, myalgias, and tachycardia. Both patients were initially treated as typical cases of community-acquired pneumonia without clinical improvement. After being discharged, the patient from case 2 was readmitted with new onset emesis and worsening dyspnea. Utilizing extensive laboratory testing, chest imaging, bronchoscopy, and lung biopsy, we established a diagnosis of EVALI in both cases. Both patients did well after appropriate treatment with intravenous steroids and empiric antibiotics. Despite the similarities among clinical presentations, discrepancies in the literature exist regarding the clinical outcomes and pathophysiology of EVALI. These case-by-case variations may result from differences in time to diagnosis, temporal factors in amount and timing of vape use, and the chemical composition of the products vaped. Our case reports highlight the increasing need for clinical awareness of EVALI, improved diagnostic tools for a timely diagnosis, and effective treatments of this potentially fatal respiratory illness.

Key Words: Vaping, Vaping-associated lung injury, Vape lung, EVALI, Acute lung injury, Lipid-laden macrophages

1. INTRODUCTION

A significant surge in reported cases of vaping-associated lung injury has led to speculation over the various injury mechanisms and presentations associated. The Center of Disease Control and Prevention (CDC) has reported 2,807 hospitalized cases of lung injury associated with e-cigarettes and vaping across all 50 U.S. states and 2 U.S. territories. As

of February, 2020, 68 deaths have been confirmed across 29 states and the District of Columbia. All 68 patients confirmed using e-cigarettes or vaping products and the majority admitted to using THC containing products in combination or alone. The majority of these cases occurred in men under the age of 35. Over half of the EVALI cases reported to the CDC provided data pertaining to the sources of their products. Of

*Correspondence: Rachel E. Herr; Email: rherr@auburn.vcom.edu; Address: Edward Via College of Osteopathic Medicine, Auburn, AL, United States.

the patients who vaped THC-containing products, 78% admitted to obtaining the products from informal sources, such as street dealers, friends, or family members. Of the patients who admitted to vaping nicotine-containing products, 69% reported obtaining their products from commercial sources, such as stores. Studies conducted recently on the outbreak of vaping-associated lung injury have detected vitamin E acetate, an additive used in many THC vape products, on bronchoalveolar lavage (BAL) samples from EVALI patients. This finding has led the CDC to mark it as a chemical of concern.^[1] While cases of EVALI have been linked by vaping products and ingredients, radiographic and pathologic similarities have also been recognized. In a case series published by the *American Journal of Clinical Pathology*, 8 patients at 5 separate institutions had chest radiographs exhibiting bilateral ground-glass opacities, and subsequent lung biopsy specimens showing acute lung injury with features of organizing pneumonia, diffuse alveolar damage, or unclassifiable organizing acute lung injury.^[2] These findings parallel our reported case presentations within this manuscript. However, there are still many unknowns to EVALI making it critical that each patient be evaluated for alternative etiologies before a definitive diagnosis is made. The following cases depict two young adult males presenting with dyspnea, tachycardia, abdominal complaints, and a social history of vaping who after substantial testing were diagnosed with vaping-associated lung injury. We aim to highlight the need for increased awareness of this entity within the medical community, a better understanding of variations in pathology, and improved diagnostic tests in order to arrive at a timely diagnosis of vaping-associated lung injury.

2. CASE PRESENTATION

2.1 Patient 1

A 19-year-old Caucasian male presented to an outside hospital reporting one week of nausea, emesis, abdominal pain, and severe dyspnea without improvement after antibiotic therapy and rest. Upon presentation, the patient appeared cachectic, malnourished, and weak. He reported fever, cough, and a weight loss of approximately 20 pounds over the past several months. He denied chills or night sweats. Past medical history was significant for chronic pain syndrome, infectious mononucleosis, medical marijuana use, insomnia, and intravenous drug abuse. Past social history showed a heavy vaping history over the past 4 years with the use of both nicotine and THC vape products. The majority of the patient's THC-containing products were purchased through state-approved businesses and the patient used these products frequently, he stated approximately every ten minutes of the

waking day. The following chest radiograph was obtained upon admission to the outside hospital (see Figure 1).

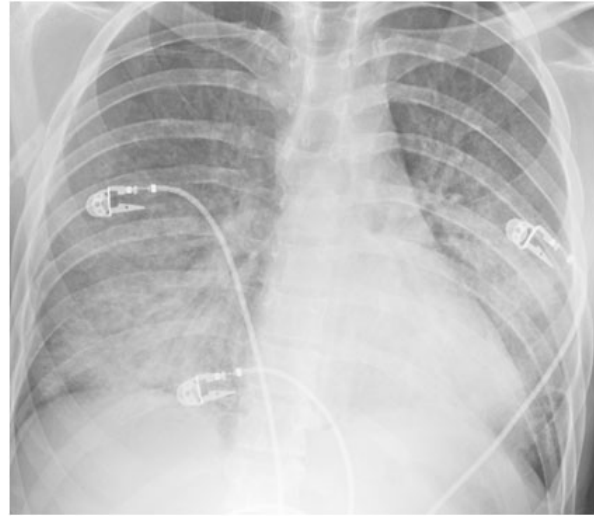
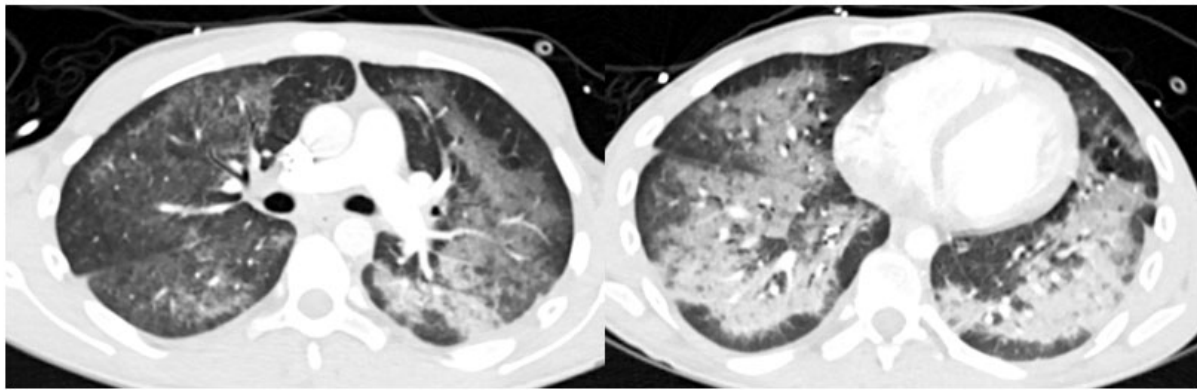


Figure 1. Chest Radiograph Upon Admission. There are bilateral, mid to lower lung zone predominate ground-glass consolidative airspace opacifications.

Table 1. Complete Blood Count & Complete Metabolic Panel values of significance for Patient 1 & Patient 2

Table 1:	Patient 1:	Patient 2:
WBC (10 ³ /μl)	15.0	16.0
Hgb (g/dl)	10.7	13.6
Platelets (10 ³ /μl)	434	350
Sodium (mmol/L)	139	135
Potassium (mmol/L)	3.5	3.5
Neutrophil (10 ³ /μl)	13.7	14.8
Neutrophil (%)	90.8 %	92.7 %
Lymphocyte (%)	14.4%	3.9 %
Eosinophil (%)	0.3%	0.1 %
Basophil (%)	0.1 %	0.1%
AST (IU/L)	55	24
ALT (IU/L)	16	11

Upon transfer to our facility, the patient was tachycardic with anemia, leukocytosis, mild thrombocytosis, and worsening dyspnea, despite being on 3L of oxygen via nasal cannula (see Table 1). Given the patient's history of recent weight loss and abdominal pain, an esophagogastroduodenoscopy (EGD) with biopsy was performed. The EGD was normal and the biopsy results were insignificant. For further evaluation, computed tomographic (CT) images of the chest were obtained, and presented findings consistent with an infectious or inflammatory process (see Figure 2).



2a.

2b.

Figure 2. Chest Computed Tomography Scan Day 2. (a.) There is bilateral mid to lower lobe predominant ground-glass consolidative airspace opacification with subpleural sparing. (b.) Shows the lung bases.

Table 2. Serology & Immunology results of significance for Patient 1 & Patient 2

Table 2:	Patient 1:	Patient 2:
Human Immunodeficiency Virus 1 Ag	Reactive (non-reactive on follow-up)	Non-reactive
Human Immunodeficiency Virus 1 Ab and P24 Ag	Reactive (non-reactive on follow-up)	Non-reactive
Human Immunodeficiency Virus 2 Ag	Reactive (non-reactive on follow-up)	Non-reactive
Human Immunodeficiency Virus 2 Ab and P24 Ag	Reactive (non-reactive on follow-up)	Non-reactive
Adenovirus	-	-
Bordetella holmesii	-	-
Bordetella pertussis	-	-
Bordetella parapertussis/bronchiseptica	-	-
Human metapneumovirus	-	-
Influenza Type A (H1)	-	-
Influenza Type B (H3)	-	-
Influenza Type A (PCR)	-	-
Influenza Type B (PCR)	-	-
Mycoplasma pneumoniae	-	-
Parainfluenza 1,2,3,4 (PCR)	-	-
Respiratory Syncytial Virus Type A (PCR)	-	-
Respiratory Syncytial Virus Type B (PCR)	-	-
Rhinovirus (PCR)	-	-
Tetanus Toxoid IgG Ab	Protective	NA
IgG	WNL	Low
IgG1	WNL	WNL
IgG2	WNL	Low
IgG3	WNL	WNL
IgA	WNL	WNL
IgM	WNL	Low
Rheumatoid Factor	WNL	N/A
ANA	+	N/A
c-ANCA	WNL	N/A
p-ANCA	WNL	N/A
Total Complement (CH50)	WNL	N/A
% CD4 Cells	N/A	Low
Absolute CD4 Count	N/A	Low

Our initial differential included multifocal pneumonia, acute respiratory distress syndrome, and chemical pneumonitis with acute hypoxemic respiratory failure. Infectious disease was consulted, and the patient was placed on airborne precautions, started on cefepime, vancomycin, levofloxacin, and admitted to the intensive care unit for further workup. On hospital day 3, a subsequent chest radiograph was obtained showing persistent bilateral perihilar ground glass opacities with relative sparing of upper lobes and increased bibasilar consolidation. No pleural effusion or lymphadenopathy was seen. To evaluate for cardiac anomalies such as infective endocarditis, an echocardiogram was also obtained and the findings were nonsignificant. Full serologic and immunologic panels were run to evaluate for other etiologies as well (see Table 2). The patient was aggressively treated with intravenous methylprednisolone at a dose of 2mg/kg/day for suspected vaping-induced lung injury and continued on empiric antibiotic therapy. Bronchoscopy with BAL was preformed to assess for cytology, lipid-laden macrophages, acid-fast bacilli, and cultures (see Table 3). No lung biopsy was performed at that time due to the presence of severe airway inflammation and hemorrhage as the risks to the patient outweighed the benefits. On day 6, the patient no longer required supplemental oxygen and was oxygenating adequately on room air. Subsequent chest imaging demonstrated radiographic improvement, supporting his improving clinical picture (see Figure 3).

Table 3. Bronchoalveolar Lavage results of significance for Patient 1 & Patient 2

Table 3:	Patient 1:	Patient 2:
Neutrophils (%)	3%	64%
Eosinophils (%)	2%	20%
Lymphocytes (%)	85%	10%
Macrophages (%)	5%	5%
Blood (%)	5%	1%
Lipid-Laden Macrophages	-	-
Acid-Fast Bacilli Culture	-	-
Acid Fast Bacilli Smear	-	-
Legionella pneumophila DFA	NA	-
Fungal Culture	-	-
Fungal Smear	-	-
Gram Stain	NA	No Organisms Seen
Routine Culture	No Organisms Seen	No Organisms Seen

The patient was discharged on hospital day 7 with a steroid taper and was advised to follow-up with his outpatient pulmonologist. Two weeks post-hospital follow-up, communi-

cation with his outpatient physician revealed that the patient had returned to his pre-illness baseline. Since discharge, the patient has resumed vaping and is, again, experiencing associated symptoms such as decreased appetite, malnutrition, and weight loss. The patient has not required any further medical assistance known to date.

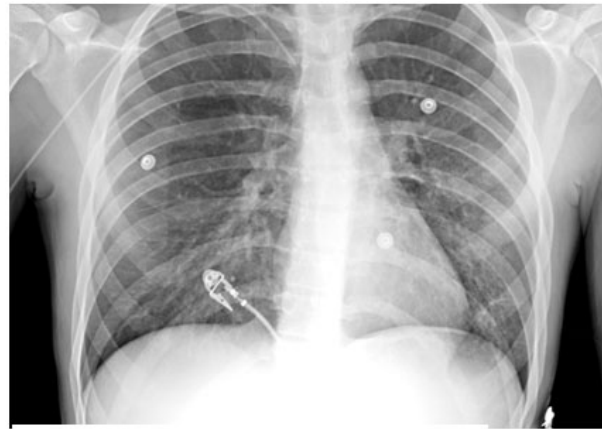


Figure 3. Resolving Chest Abnormalities Day 6. There is marked improvement with interval resolution of consolidative opacification and mild ground-glass opacities in the lower lung zones.

2.2 Patient 2

A 24-year-old Caucasian male with a history significant for cigarette smoking and THC vaping presented to the emergency department endorsing a history of productive cough, subjective fevers, and myalgias for the past week. He denied cigarette use within the past week but admitted to current THC vaping. Questioning revealed that the majority of the patient’s cannabis-containing products were purchased off of the street from unregulated local dealers.

Vital signs upon arrival were notable for tachycardia and a pulse oximetry of 93% on room air. Initial labs demonstrated a leukocytosis (see Table 1) and a chest radiograph obtained in the emergency room showed possible multifocal airspace disease suspicious for atypical pneumonia. The patient was treated with nebulized bronchodilators, and methylprednisolone intravenously. The patient was given an initial diagnosis of community-acquired pneumonia and was subsequently discharged with an albuterol inhaler and a three-day course of azithromycin. He was instructed to follow up with his primary care provider or return if symptoms worsened.

On readmission, the patient developed new onset emesis and worsening dyspnea. He was tachycardic with worsening respiratory status, a pulse oximetry of 89% on room air. Serum analysis showed a continued leukocytosis and a mild hyponatremia. A subsequent radiograph showed worsening multifocal airspace disease suspicious for a multilobar

pneumonia (see Figure 4). To evaluate for pulmonary embolism, chest CT angiographic images were obtained with findings consistent with non-cardiogenic pulmonary edema and some features of organizing pneumonia. No acute pulmonary embolus was seen (see Figure 5). The radiologist's impression read that the CT findings were most consistent with vape-induced lung injury, raising our clinical suspicion for possible EVALI. The patient was admitted to the floor for further workup and infectious disease was consulted.



Figure 4. Chest Radiograph Upon Hospital Admission. There are bilateral perihilar ground-glass opacities with sparing of the upper lobes.

The patient's preliminary differential diagnosis consisted of community-acquired pneumonia, human immunodeficiency virus, acute respiratory distress syndrome, and hypersensitivity pneumonitis. Similar to patient 1, patient 2 was placed on an aggressive medication regimen, consisting of linezolid, trimethoprim/sulfamethoxazole, ceftriaxone, azithromycin, oseltamivir, methylprednisolone, ipratropium bromide/albuterol and budesonide. On hospital day 5, full serologic and immunologic panels were drawn (see Table 2). The patient was taken for bronchoscopy to obtain BAL samples and assess for cytologic findings of lipid-laden macrophages, acid fast bacilli, and cultures (see Table 3). Brush biopsies and transbronchial biopsies were obtained from the right middle and lower lobes and the left lower lobe. The right lower lobe biopsy showed evidence of severe acute lung injury, specifically acute diffuse alveolar damage, characterized by extensive hyaline membrane formation, reactive type II pneumocytes, and a mildly thickened interstitium. The biopsy also revealed mildly elevated CD68 positive interalveolar macrophages (see Figure 6). Taken together, in the context of his vaping history, we gave a clinical diagnosis of vaping-associated lung injury by diagnosis of exclusion.

Throughout the patient's hospital stay, his oxygen requirements varied, but by day 10, his respiratory distress resolved, and he was aerating well on room air. Serial chest radiographs demonstrated that the infiltrates were slowly resolving. He was discharged with a steroid taper and nebulizer therapy and was instructed to follow up with his primary care physician, infectious disease specialist, and pulmonologist. Since discharge, the patient has admitted to resuming both smoking and vaping nicotine but has denied any type of inhaled THC usage. The patient has not required further medical treatment known to date.

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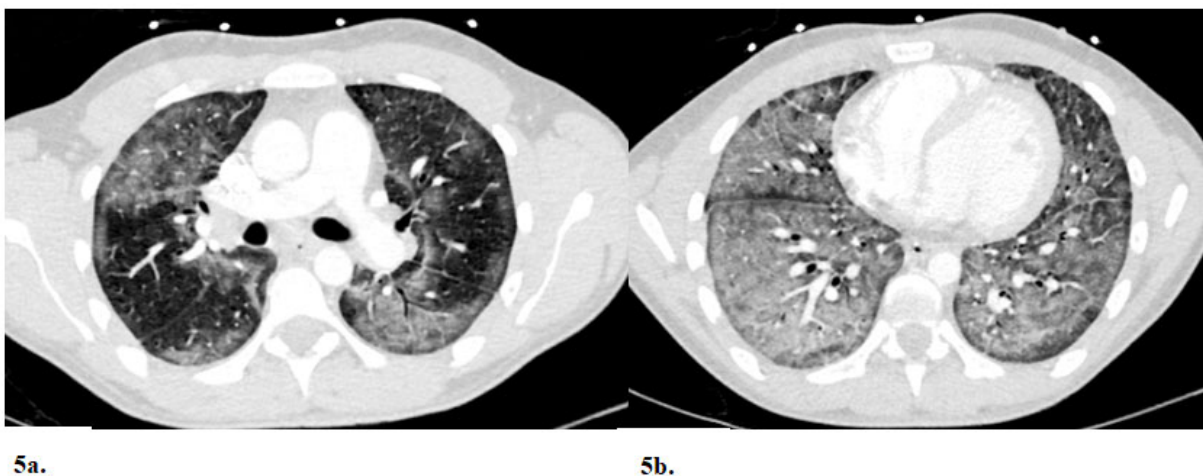


Figure 5. Chest Computed Tomography Upon Admission. (a.) There is mid to lower lobe bilateral, ground-glass airspace opacification with subpleural and secondary lobular sparing. (b.) Shows the lung bases.

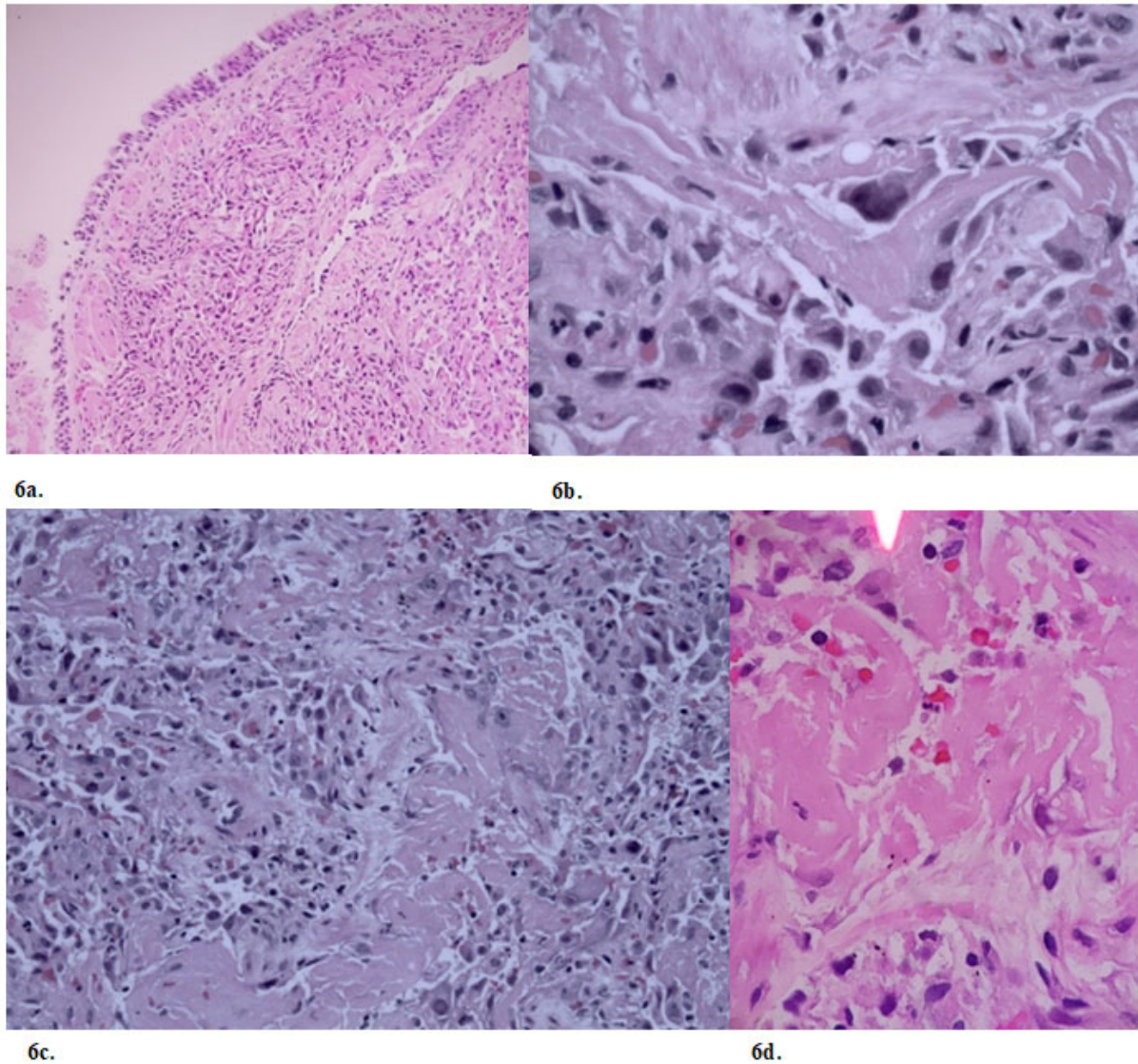


Figure 6. Right Lower Lobe Lung Biopsy. (a.) This is a bronchial wall image showing diffuse alveolar damage in the acute phase with extensive hyaline formation and bronchial wall sparing. (b.) There is intra-alveolar hyaline membrane formation with reactive type II pneumocytes. (c.) There are scattered intra-alveolar macrophages without a lipid pneumonia background showing acute phase inflammation. (d.) There is dense intra-alveolar hyaline membrane formation.

3. DISCUSSION

Our two case reports of vaping-associated lung injury provide clinical scenarios paralleling previously reported EVALI cases and provide added pathologic evidence of acute lung injury. The complete diagnostic workup performed on both patients demonstrated severe aseptic pulmonary inflammation leading to acute lung injury with diffuse alveolar damage. Our cases coincided clinically and radiographically to other reported cases, but various laboratory and histologic test results varied from those in literature. For example, lipid-laden macrophages are a well-known BAL finding obtained in EVALI patients, but were not found in either of our patients' BAL washings. We speculate that the absence of

lipid-laden macrophages, as well as other lab disparities, in our two cases may be secondary to variations in the timing of tests, products vaped, and host inflammatory responses. The relative rarity of EVALI, the risk factors, the etiologies, the pathophysiology, and the fact that there is no known pathognomonic histology to date has resulted in EVALI remaining primarily a diagnosis of exclusion. With the increasing incidence and reporting of this disease process earlier this year, it is important to expose the specific causes and presentations as a means to prevent, treat, and inform consumers about the risks associated with vaping.

To date, current literature is beginning to better understand trends of patient demographics, presentations, laboratory val-

ues, imaging, and clinical courses associated with EVALI. A study by Leyden et al. (2020) consisted of 98 patients with confirmed or probable confirmed EVALI cases and showed that many patients presented with respiratory, gastrointestinal, and constitutional symptoms. Eighty-nine percent of these 98 patients reported THC use in e-cigarette devices, although there was a range of products used. The majority of patients showed signs of tachycardia with bilateral chest infiltrates seen unanimously on imaging. Serum analysis typically showed a leukocytosis with neutrophilic predominance, elevated inflammatory markers, and elevated liver function tests. Of the 23 BAL samples obtained, 13 exhibited lipid-laden macrophages, but 8 of those 13 reported scant to minimal lipid-laden macrophages present.^[3] Our two patients followed a clinical and histological course similar to these findings, raising our clinical suspicion to a diagnosis of EVALI. Previously reported cases helped conclude our diagnosis after exclusion of other etiologies, but early recognition of significant radiographic findings was also imperative to the diagnosis.

The patients' social histories of vaping, clinical hypoxemia, systemic inflammation, and chest imaging upon admission, begged for vaping-associated lung injury to remain in the differential diagnosis while other etiologies were being evaluated for. While it was on the differential, our radiologist adding the possibility of vaping-induced lung injury into his evaluation brought added support to EVALI. Early clinical recognition is essential and increased awareness of the radiographic features associated with EVALI could assist in early diagnosis and treatment of this disease. Variable diagnostic test results among EVALI patients prove a difficult obstacle for clinicians attempting to make a timely diagnosis. The *American Journal of Roentgenology* published a study suggesting temporal factors in the pathogenesis of EVALI as a plausible explanation to some of the radiographic and laboratory variations among patients.^[4] As described, Patient 2 was admitted to the hospital later after symptom onset compared to patient 1, and concurrently, the CT scan from patient 2 showed an organizing pneumonia pattern with subacute lung injury where patient 1 had more diffuse findings. There is a possibility that as the lung injury progresses and the inflammatory response evolves in EVALI cases, the pathological findings also change, resulting in variability among test results. Interestingly, the patient in case 2 also had elevated eosinophils in BAL washings (see Table 3), as opposed to the washings from case 1. His chest CT, however, did not have the typical imaging features of upper and middle lobe lung pathology seen in acute eosinophilic pneumonia and the overall percentage of eosinophils did not exceed 25% to support a diagnosis. These findings emphasize that the

timeline for and the type of the immunological response to the inciting agent in EVALI cases require further research to better understand this disease and to differentiate temporal variations from discrepancies caused by products vaped or other variables.

Vitamin E acetate, a known lipid soluble additive in THC vape products, is a relatively new agent potentially responsible for the EVALI pathogenesis. Vitamin E acetate has been present in BAL samples among EVALI cases causing it to be a topic of concern. The *New England Journal of Medicine* published a study on BAL fluid samples that were collected from 51 patients, all of whom had probable or diagnosed EVALI. BAL samples were also collected from 99 healthy patients consisting of nonusers, nicotine only e-cigarette smokers, and cigarette smokers. Interestingly, 48 of those 51 BAL samples tested positive for vitamin E acetate, while samples from the healthy participants showed no vitamin E acetate on BAL fluid results.^[5] This data demonstrates quite clearly the association between a lipid-soluble chemical and the EVALI disease course. However, recent literature has shown that EVALI bears little resemblance to a classic lipid pneumonia and suggests that vaping injury parallels more of an airway-centered chemical pneumonitis. In another study, CD68 positive macrophages were present in 8 lung biopsy samples, but only 3 of these cases showed the evidence of lipid-laden macrophages with foamy cytoplasm. Coarsely vacuolated cytoplasm was not present in any of the biopsies as well. Previously reported EVALI cases that were given a diagnosis of lipid pneumonia were often given that diagnosis solely due to positive oil red O stains on bronchoalveolar lavage samples. Lung biopsies on these patients were rarely performed and of the few biopsies that were reported, the literature often notes the absence of typical exogenous lipid pneumonia features.^[2] Whether lipid-laden macrophages are also a temporal finding of the EVALI progression, or they are from certain additives such as vitamin E acetate, lipid-laden macrophages are known to have a poor sensitivity for diagnostic criteria. Lipid-laden macrophages can accumulate endogenously from epithelial injury and engulfment of cellular debris, surfactant, or resident pulmonary cellular membranes. Inherent limitations within the assay performed to assess for lipid-laden macrophages cannot differentiate exogenous from endogenous lipids and should not be the sole factor in the diagnosis of EVALI.^[6] Therefore, our patients' lack of lipid laden macrophages in their BAL samples holds little to no support for the exclusion of EVALI from our differential. Rather, our diagnostic results, radiologic findings, tissue biopsy results, and clinical picture led to the diagnosis of EVALI. A study by the *American Journal of Clinical Pathology* discusses the similarities in lung biopsies among

EVALI patients which includes hyaline membranes, fibrous exudates in airspaces, chronic inflammation, and acute inflammatory cells.^[2] Similarly, the lung biopsy obtained in the patient from case 2 shows numerous acute phase inflammatory cells, amorphous hyaline membranes, and atypical type II pneumocytes (see Figure 6). A CD68 stain confirmed the presence of numerous CD68 positive macrophages, but the macrophages were determined to be the result of an inhalation lung injury, not the result of a lipoid pneumonia. Our biopsy samples were initially viewed by a pathologist in-hospital, but were also subsequently sent out to Cleveland Clinic in order to verify the diagnosis of acute lung injury. Acute lung injury was confirmed, and the pattern of lung injury seen in our samples was noted to parallel the results seen in the previous 8 biopsies reported by Mukhopadhyay et al. (2020).^[2] EVALI is still a relatively novel diagnosis and it is imperative to rule out other possible etiologies of disease before concluding vaping as the primary offender.

During the course of both admissions, labs (see Table 2), bronchoscopy with bronchoalveolar lavage (see Table 3), and transbronchial biopsies (see Figure 6) were taken to assess for bacterial, fungal, viral, rheumatologic, and malignant etiologies. A diagnosis of vaping-associated lung injury was made based on the histologic findings of diffuse alveolar damage, the rule out of infectious agents, and the strong history of vape use. In an effort to try to prevent cases such as these in young adults, the Food and Drug Administration issued more than 1,300 warning letters and civil money penalty fines in late 2018 to retailers selling e-cigarette products to minors.^[7] Lung injury in young adults is a finding that we do not see often and with new viruses and infections constantly arising, young adults with lung injury from EVALI may add a new demographic of people now at risk for other pathologies. Lung injury can be difficult, if not impossible, to reverse and we advise both the youth and the elderly to stay away from vaping due to the known risk of injury as well as the many unknowns that we are still facing.

In this paper, we present two additional patients to the existing EVALI literature that correspond both clinically, as

well as histologically, to previously reported cases of vaping-associated lung injury. These cases provide further evidence to support the acute lung injury that vaping products can cause and aim to shed light on the pathologic mechanisms behind this disease process.

4. CONCLUSION

Much remains to be learned about vaping-associated lung injury. More so, the pathophysiology, offending chemicals, proprietary agents, and demographics beg scientific inquiry. Although vaping-associated lung injury is a rapidly growing diagnosis, there is still a lack of positivity and confirmed pathologic cases. With lab and imaging variations being seen among reported EVALI cases, we beg the question of whether time to diagnosis, vape product composition, and temporal factors of the disease could explain these discrepancies. While information regarding the potentially harmful side effects of ENDS has increased over the past months, EVALI remains a diagnosis of exclusion for healthcare providers and future development of universal diagnostic markers for vaping-associated lung injury is still required to better serve our patients. Our two case presentations emphasize the need for increased clinical awareness, improved diagnostic tools, and better treatments for EVALI patients. Until more is known about vaping associated lung injury and its sequelae, users should remain prudent about the attenuated risks of electronic nicotine delivery systems and further use should be cautioned in the interim.

ACKNOWLEDGEMENTS

The authors would like to thank interventional radiologist, Dr. Bryan Belikoff, for his contribution to the case and assistance interpreting radiographic images and scans. We would also like to thank pathologist, Dr. Neil Asthana, for assistance with histological findings on biopsies, as well as infectious disease physician, Dr. Hemant Kade, for consult and assistance in treatment.

CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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