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E-Cigarette or Vaping Product Use-Associated Lung Injury

A Review for Pathologists

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- **Context.**—Vaping is the inhalation of heated aerosol from a small battery-powered device as a method to deliver nicotine or other substances. A recent outbreak of severe respiratory illness primarily in the United States has put a spotlight on vaping and its potential risks.

- **Objective.**—To familiarize pathologists with vaping, the cytopathic and histopathologic features of vaping-associated acute lung injury, and the role of pathology in this diagnosis.

- **Data Sources.**—A targeted literature review was performed.

- **Conclusions.**—Most cases of vaping-associated lung injury have been linked to vaping products containing tetrahydrocannabinol or other cannabinoids. Lung biopsies show a spectrum of nonspecific acute lung injury patterns (organizing pneumonia, diffuse alveolar damage, acute fibrinous, and organizing pneumonia, or combinations of the above), accompanied by prominent, foamy macrophage accumulation. Injury is usually accentuated around small airways. Lipid-laden macrophages can be identified in bronchioloalveolar lavage fluid in most patients and these can be highlighted using lipid stains, such as oil red O, but the clinical utility of this finding remains unclear, as lipid-laden macrophages can be seen in a wide variety of processes and should not be relied upon to make the diagnosis. Classic histologic features of exogenous lipoid pneumonia have not been identified in tissue samples. Lightly pigmented macrophages, similar to those seen with traditional cigarette smoking, are present in some cases but are usually a minor feature. To date, no specific pathologic features for vaping-related injury have been identified, and it remains a diagnosis of exclusion that requires clinicopathologic correlation.

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**WHAT IS VAPING? A PRIMER ON DEVICES, CONTENTS, AND TERMINOLOGY**

"Vaping" is the inhalation of an aerosol (vapor) generated by heating a liquid in a small battery-powered device.1-3 This activity has increased dramatically worldwide in recent years, particularly among adolescents.4-8 In contrast to smoking tobacco cigarettes, vaping is not associated with formation of tobacco combustion products and consequently, marketing campaigns have been touting vaping as a safer alternative to smoking.9 In addition, this activity has been marketed as a method for smoking cessation.10 The 2 main substances vaped are nicotine and tetrahydrocannabinol (THC), the active ingredient in marijuana. Cannabidiol (CBD) and other cannabinoids can also be used. “Dabbing” is a related activity where a user will perform an extraction of marijuana typically with butane or another organic solvent to produce a highly concentrated extract that can be inhaled, smoked, or used in an e-cigarette device.11 Features common to all vaping devices include a reservoir, a heating element (atomizer), and a battery.1 Figure 1 illustrates the main components of a vaping device. Devices intended to produce a nicotine-containing vapor are known as electronic nicotine delivery systems, “electronic cigarettes” or “e-cigarettes.” The liquid used in these devices—commonly referred to as e-juice, e-liquid, vape juice, or vape liquid—contains nicotine and is water-soluble. It also typically contains propylene glycol and vegetable glycerin (glycerol), and may contain flavoring agents.12 Larger customizable devices—where users can vary the flavoring or nicotine concentration—are known as “tanks” or “mods.”

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Another class of vaping devices ("THC vape pens," "weed pens," "e-joints") is intended to generate a THC-containing aerosol. These devices are usually sold in marijuana dispensaries and often use pen-style batteries that can be charged with a Universal Serial Bus cable. The reservoir tank in these devices is a disposable cartridge ("cart") that holds variable amounts of THC- and/or cannabinoid-containing oil. The heating element is often made of ceramic, glass, or quartz.

VAPING TRENDS IN THE UNITED STATES

Vaping devices were first patented in 2003 and were introduced into the United States market in 2007. By 2018, vaping had grown into a 1.7 billion dollar industry. The majority of liquids contain nicotine at variable concentrations and there has been a shift toward devices that contain higher concentrations (>5%) of nicotine salts that can be more easily absorbed and also used by lower powered devices that now encompass 66% of the market. Some devices are sold without nicotine, but these encompass less than 0.3% of the reported market. While many of the devices are constructed by legitimate suppliers, there is also an industry of poorly regulated gray and black market products and a community that supports user modification of the devices. This results in a large spectrum of devices that use a highly variable composition of liquids. There is a relative paucity of data regarding the sales and use of cannabis vape products, in part because of the variable legal status of these products and production in the gray or black markets. However, in a survey of North Carolina high school students in 2017, 1 in 10 respondents reported vaping marijuana. A recent meta-analysis demonstrated young adults and adolescents that used e-cigarette devices were more likely to use cannabis.

Vaping is common in the United States, with 4.6% of the population reporting use of e-cigarette devices in 2017. The practice is even more common in adolescents, with 13.2% of youths nationally reporting active use of e-cigarettes in 2017. More recent data from 2019 demonstrates 40.5% of Grade 12 and 20.7% of Grade 8 students have reported using a vaping device. Data from the United States Centers for Disease Control and Prevention (CDC) support the contention that vaping is very common in youths (Figure 2, A) across the country but is less common in adults (Figure 2, B), although vaping occurs in all age groups, including the elderly. Devices used for vaping are small and often resemble Universal Serial Bus portable “thumb” drives, making it easy for children to use them surreptitiously in schools. E-cigarettes are also commonly sold in flavors (mint/fruit/candy/sweet) that may appeal to younger individuals. Given that many vaping fluids contain relatively high amounts of nicotine, this may be especially damaging to young individuals, as nicotine exposure during this critical developmental stage can cause deleterious effects on development in the prefrontal cortex and can lead to decreased cognitive function and severe addiction. Furthermore, given the increasing use of these products by women of child-bearing age, this raises an important question of potential developmental toxicity and teratogenic effects that are currently poorly understood.

There has been a recent outbreak of acute lung injury in patients using vaping devices. The first cases were identified in the summer of 2019 with the number of cases peaking in September 2019 (Figure 2, C). These cases have been defined by the CDC as “E-cigarette, or Vaping, product use-associated Lung Injury” (EVALI) and have occurred across the United States and Canada (Figure 2, D). With repeated reports from the CDC highlighting the key role of illicit, counterfeit, or bootlegged vape cartridges in the current outbreak, the supply chain for illicit vape pen hardware is receiving attention in the media. It has been claimed that more than 90% of illicit vape pen hardware in the United States is manufactured in the Bo’An district of Shenzhen, China and then arrives in Los Angeles wholesale markets.
Here, illicit empty vape carts can be purchased with cash, including cartridges used for nicotine vaping and THC vaping. Vitamin E acetate (tocopheryl acetate)—typically used as a skin cosmetic or dietary supplement—is used in THC vaping as a diluent or “cutting agent.” It is used to make THC oil more viscous, creating a false impression of higher purity that misleads consumers who use oil viscosity as a proxy for purity. It has been reported the use of illicit vitamin E acetate oil as a cutting agent peaked in the summer of 2019, coinciding with the onset of the current outbreak of vaping-associated lung disease in the United States. In a recent study in which vaping samples used by individuals with lung illness were tested by gas chromatography-mass spectrometry by the Minnesota Department of Health, products obtained from 12 patients in 2019 contained vitamin E acetate. Importantly, none of the vaping products seized by the Minnesota Department of Health in 2018 contained vitamin E acetate, although all THC-containing products seized and tested in September 2019 contained vitamin E acetate. These results were expanded in a subsequent study to include 51 EVALI patients from 16 different states and compared with 99 healthy controls. Vitamin E acetate was detected in 94% of bronchioloalveolar lavage (BAL) samples from patients with EVALI and in 0% of the healthy controls. In 1 patient both coconut oil and vitamin E acetate were detected, and in another patient limonene but not vitamin E acetate was detected. No other tested oil was identified in the BAL fluid. While it is not possible to definitively conclude that vitamin E acetate is the causative agent of EVALI based on these findings, these results and the timing of the introduction of vitamin E acetate into the market as a cutting agent are highly suggestive that it is the underlying cause of EVALI. Importantly, at this time it is unknown if other potential cutting agents or contaminants could produce a similar lung injury and a potential for additional EVALI cases.

**VAPING FOR SMOKING CESSATION**

While there are significant concerns regarding vaping, proponents of this practice argue e-cigarettes are an effective aid for smoking cessation. A recent randomized clinical trial identified that use of e-cigarettes was more effective for cigarette cessation compared with traditional

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**Figure 2.** A and B, Representation of data from the United States Centers for Disease Control and Prevention (CDC) State Tobacco Activities Tracking and Evaluation System showing the percentage of current e-cigarette users among high school youth (A) and adults (B) in each state across the United States. C, Data from the CDC (as of January 14, 2020) outlining the surge and subsequent decline in reported cases of e-cigarette, or vaping, product use-associated lung injury (EVALI) in late summer and fall 2019, based on dates of symptom onset and admission to the hospital. D, Data from the CDC and Heath Canada (as of January 14, 2020) demonstrating the distribution of cases of EVALI across the United States and Canada.
nicotine replacement models. In this study the 1-year abstinence rate was 18% in the e-cigarette group, compared with 9.9% in the nicotine-replacement group, although 80% of users continued to use e-cigarettes after the 52nd week. Therefore, while vaping may be an effective way for some users to stop smoking (and avoid exposure to toxic combustibles derived from tobacco), it does not allow complete cessation of nicotine use and introduces new risks derived from use of vaping devices. It is notable that e-cigarettes have been shown to be an independent risk factor for respiratory disease in adults. Furthermore, data suggest most smokers adopt a dual use pattern in which they both smoke and vape, a use pattern that is even riskier than using either combustible cigarettes or e-cigarettes alone. Opponents of vaping argue it exchanges one vice (smoking) with another (vaping) that has unclear health consequences, and proponents of vaping argue it transitions users from use of combustible cigarettes to nicotine-free products.

E-CIGARETTE OR VAPING PRODUCT USE-ASSOCIATED LUNG INJURY

The intense national focus on vaping has largely been a consequence of a recent (2019) outbreak of acute pulmonary illness associated with vaping. Reports of significant pulmonary illness in vapers first began to appear in August 2019 from around the United States. One seminal study reported 53 cases from Illinois and Wisconsin. Shortly thereafter, the CDC introduced the term EVALI for this emerging public health problem. Additional reports of EVALI soon followed from across the United States and have now been reported in all 50 states. The latest epidemiologic data on EVALI from the CDC are shown in Figure 2, C.

The CDC has also developed definitions for confirmed and probable cases of EVALI, as outlined in Table 1. CDC criteria for a “confirmed case” of EVALI include a history of use of e-cigarette (vaping) or dabbing during the 90 days before symptom onset AND opacities on chest X-ray or ground glass opacities on computed tomography AND negative testing for infections (eg, microbiologic cultures, respiratory viral panel, influenza PCR or rapid test, and/or other tests as applicable) AND no evidence of alternative plausible diagnoses (eg, cardiac, rheumatologic, or neoplastic processes). These injury patterns have a long list of potential causes, including infection, connective tissue disease, drug-related lung injury, lung damage caused by toxic inhalants, and aspiration. Less commonly reported imaging patterns include those suggesting diffuse alveolar hemorrhage and hypersensitivity pneumonitis. The latter pattern is highly reminiscent of hypersensitivity pneumonitis to the radiologist because of the concomitant presence of ground-glass opacities, poorly defined centrilobular nodules, and air trapping, but it should be noted that, to date, no histologic

<table>
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<th>Table 1. CDC Definitions of EVALI</th>
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<tr>
<td><strong>Confirmed Case</strong></td>
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<tr>
<td>Use of e-cigarette (vaping) or dabbing during the 90 days before symptom onset AND</td>
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<tr>
<td>Opacities on chest X-ray or ground glass opacities on computed tomography AND</td>
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<tr>
<td>Negative testing for infections (eg, microbiologic cultures, respiratory viral panel, influenza PCR or rapid test, and/or other tests as applicable) AND</td>
</tr>
<tr>
<td>No evidence of alternative plausible diagnoses (eg, cardiac, rheumatologic, or neoplastic processes)</td>
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Abbreviations: CDC, United States Centers for Disease Control and Prevention; EVALI, e-cigarette, or vaping, product use-associated lung injury; PCR, polymerase chain reaction.

* Data derived from Reference 29.

are similar to a confirmed case with the exception of the work-up for infection. Probable cases are allowed to have incomplete infectious testing or some positive test results for infection the clinical team believes do not explain the underlying illness.

CLINICAL AND LABORATORY FINDINGS

EVALI has been reported in a broad age range but is most common in young males between the ages of 18 and 24 years. Patients typically present with an acute or subacute illness with nonspecific respiratory symptoms, including shortness of breath, chest pain, cough, and/or hemoptysis. The majority of patients also report gastrointestinal symptoms (nausea, vomiting, and/or diarrhea) and/or constitutional symptoms (subjective fever, chills, weight loss, and/or fatigue). Most patients have nonspecific laboratory findings, including elevated white blood cell counts and an elevated erythrocyte sedimentation rate. As outlined in Table 1, infectious conditions need to be excluded in order to meet the CDC definition of a “confirmed case” of EVALI.

IMAGING FINDINGS

The imaging findings in EVALI are also relatively nonspecific. The most commonly reported finding is bilateral ground-glass opacities with areas of consolidation, often with a peculiar pattern of subpleural sparing. Representative chest computed tomography images from patients with EVALI are shown in Figure 3, A through D. It is important to note that fat attenuation—a hallmark of exogenous lipoid pneumonia—has not been observed in reported cases thus far; therefore, exogenous lipoid pneumonia is not a strong consideration in the differential diagnosis from an imaging standpoint. The imaging findings typically bring up a differential diagnosis that includes infection and a variety of acute lung injury patterns, including organizing pneumonia and diffuse alveolar damage. These injury patterns have a long list of potential causes, including infection, connective tissue disease, drug-related lung injury, lung damage caused by toxic inhalants, and aspiration. Less commonly reported imaging patterns include those suggesting diffuse alveolar hemorrhage and hypersensitivity pneumonitis. The latter pattern is highly reminiscent of hypersensitivity pneumonitis to the radiologist because of the concomitant presence of ground-glass opacities, poorly defined centrilobular nodules, and air trapping, but it should be noted that, to date, no histologic
confirmation of hypersensitivity pneumonitis has been reported in EVALI.

TREATMENT AND CLINICAL COURSE

Patients with EVALI have a variable clinical course, with the majority of patients hospitalized for acute respiratory failure. Many patients require admission to the intensive care unit and intubation is required in a subset of cases. As with virtually any cause of acute respiratory failure, current treatment recommendations include supportive care and consideration for early use of corticosteroids as well as coverage with antimicrobials. Corticosteroids are the mainstay of therapy in EVALI, with a fairly rapid response to treatment in most cases, but fatalities can occur. As of the time of this writing (January 14, 2020), data from the CDC indicate that 57 deaths have been reported because of EVALI. Most deaths have occurred in middle-aged and older adults, but they have been reported across all ages. As mentioned previously, most patients do not require lung biopsies or other sampling for diagnosis, and are diagnosed on clinical and radiologic grounds alone. Lung biopsies and/or BAL may be performed in some cases to exclude infection or other alternative diagnoses, when patients fail to respond to therapy, or when the diagnosis is unclear.

PATHOLOGIC FINDINGS IN EVALI

To date, 2 published series have focused on defining the histopathology of EVALI, which is summarized in Table 2. Both reported similar histologic findings, with a spectrum of acute lung injury ranging from organizing pneumonia to diffuse alveolar damage. Cases with mixed acute lung injury patterns have also been reported, and some cases mainly feature fibrinous airspace exudates or acute injury with the so-called acute fibrinous and organizing pneumonia pattern. This variability is not surprising, as it reflects not only the variable severity of injury that can occur from case to case, but also the time-dependent repair response of the lung to acute injury of any cause. Representative images of biopsies from patients with EVALI are shown in Figure 4. In both series, the patients that ultimately succumbed to EVALI had biopsies with features of diffuse alveolar damage, which is not surprising as this pattern reflects injury of a more severe nature. No specific histologic features of vaping were identified in either series. All cases described by Butt et al had some degree of foamy intra-alveolar macrophage accumulation and Mukhopadhyay et al described variable numbers of foamy macrophages in 3 of 8 cases. Although foamy macrophages are common in biopsies from EVALI, it is important to
Figure 4. Spectrum of histopathologic changes in e-cigarette, or vaping, product use-associated lung injury (EVALI). Hematoxylin-eosin (H&E) stained sections in some cases demonstrate (A) a distinctive micronodular acute lung injury process with pronounced bronchiocentric distribution ($\times 40$); (B) at higher power, airway-centered organizing pneumonia and bronchiolitis are present ($\times 200$). In other cases, (C) acute lung injury and inflammatory changes are more extensive but still tend to be accentuated around small airways ($\times 40$); (D) at higher power, organizing pneumonia is accompanied by type II pneumocyte hyperplasia ($\times 200$). (E) Other cases show abundant intra-alveolar fibrin, marked alveolar septal edema, and variable degrees of organization, corresponding to an acute fibrinous and organizing pneumonia (AFOP) pattern ($\times 400$). Many cases have (F) prominent neutrophils that

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Table 2. Pathologic Features of EVALI in Different Specimen Types

<table>
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<tr>
<th>Specimen Types</th>
<th>Features</th>
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<tr>
<td>Transbronchial lung biopsies or surgical lung biopsies</td>
<td>Spectrum of acute lung injury ranging from organizing pneumonia to acute fibroinflammatory and organizing pneumonia and diffuse alveolar damage</td>
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<tr>
<td></td>
<td>Injury usually accentuated around small Airways with bronchiolitis, sometimes also with mucosal ulceration</td>
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<tr>
<td></td>
<td>Nonspecific accumulation of foamy and/or pigmented macrophages in most cases, usually also with vacuolated pneumocytes</td>
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<tr>
<td></td>
<td>Chronic interstitial inflammation and interstitial edema in most cases</td>
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<td></td>
<td>Neutrophils prominent in up to half of cases</td>
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<tr>
<td></td>
<td>If present, eosinophils are usually few but can rarely be prominent</td>
</tr>
<tr>
<td></td>
<td>No histologic features of exogenous lipoid pneumonia</td>
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<tr>
<td></td>
<td>No granulomas or definite features of hypersensitivity pneumonitis</td>
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<tr>
<td></td>
<td>Negative histochemical stains for fungal and acid-fast organisms</td>
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<tr>
<td>Cytology</td>
<td>No specific or diagnostic features</td>
</tr>
<tr>
<td></td>
<td>Variable numbers of nonspecific macrophages (foamy, with or without enlarged cytoplasmic vacuoles) and oil red O positivity, sometimes with cytologic atypia</td>
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<tr>
<td></td>
<td>Negative histochemical stains for infection</td>
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<tr>
<td>Autopsy</td>
<td>Features of acute lung injury with acute fibroinflammatory and organizing pneumonia or diffuse alveolar damage in most cases</td>
</tr>
<tr>
<td></td>
<td>Other changes similar to those seen in lung biopsies</td>
</tr>
<tr>
<td></td>
<td>Negative histochemical stains for fungal and acid-fast organisms</td>
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Abbreviation: EVALI, e-cigarette, or vaping, product use-associated lung injury.

emphasize they are not specific for vaping, because they are commonly seen in other conditions that cause inflammation or lung injury as shown in Figure 5, A and B, including infections, bronchial obstruction, connective tissue diseases, hypersensitivity pneumonitis, adverse reactions to a variety of drugs (including but not limited to amiodarone), and immune checkpoint inhibitor toxicity.\(^\text{40-41}\) Other histologic findings seen in EVALI include interstitial chronic inflammation and eosinophils, which if present are usually rare, but occasionally eosinophils can be more prominent (H.D.T. and B.T.L., unpublished data, December 2019). Notably, neutrophilic infiltrates may be prominent in some cases, in a fashion closely mimicking infection, and acellular granular eosinophilic debris in airspaces can also be present, associated with degenerating inflammatory cells. For the pathologist, evaluation for infection is the most critical component of the assessment, as this will change the diagnosis and impact clinical management. Pathologists should always evaluate biopsies with acute lung injury for evidence of infection and consider performing special stains for microorganisms, even if EVALI is suspected clinically.

**BAL FINDINGS**

Many reports of EVALI have included descriptions of foamy alveolar macrophages in BAL fluid that stained positive with the oil red O histochemical stain (Figure 6, A and B).\(^\text{39-42, 46}\) Based upon these findings the underlying cause of EVALI was initially suggested to represent “lipoid pneumonia.” Only a single series of EVALI describes a subset of cases with macrophages having enlarged cytoplasmic vacuoles, similar to those seen in exogenous lipoid pneumonia, as well as reactive cytologic atypia.\(^\text{37}\) However, no histologic evidence of exogenous lipoid pneumonia has been identified in lung tissue,\(^\text{36, 37}\) suggesting there is more to the story than simply lipid accumulation in the lung. As shown in Figure 6, C and D, exogenous lipoid pneumonia has a characteristic appearance with large globules of lipid highlighted by the oil red O stain. Biopsies from patients with an exogenous lipid pneumonia also have histiocytes with large coarse vacuolization in the air spaces and interstitium as well as multinucleated giant cells in some cases and variable degrees of interstitial fibrosis (Figure 6, E and F), a pattern of changes that is very different than EVALI. If vitamin E acetate is playing a role in EVALI, lipid accumulation does not appear to be the primary driver of injury and some other mechanism of injury may be at play, perhaps a direct toxic effect or from toxic byproducts formed when the vape liquid is heated. Regardless, as with the histologic findings in EVALI, the BAL findings in EVALI are also nonspecific and must not be viewed as “confirmatory.”\(^\text{48}\)

**IMPLICATIONS FOR PATHOLOGISTS**

For the practicing pathologist, it is critical to recognize the histopathology of EVALI is nonspecific, and serves mainly as a means of confirming acute lung injury and excluding infection and other alternative diagnoses. As mentioned previously, CDC criteria for EVALI are based on a history of vaping, opacities on imaging, and the exclusion of alternative diagnoses. They do not include a “confirmatory test” of any type. Despite these limitations, recognition of an airway-centered acute lung injury process in a lung biopsy with prominent foamy and/or pigmented macrophages or finding macrophages with enlarged cytoplasmic vacuoles in BAL fluid should prompt consideration of EVALI, and the pathologist may be the first person to recognize the possibility of vaping-related injury, particularly in patients who are reluctant to admit they are vaping, and especially when marijuana or illicit substances are being used. Merely suggesting the possibility of EVALI to the clinician may be sufficient to prompt appropriate inquiries about vaping, and in our anecdotal experience, can occasionally enable identification of cases that would otherwise be missed.

It should be remembered that oil red O–positive foamy macrophages in BAL fluid are common and nonspecific,\(^\text{48-50}\) and can also be caused by accumulation of endogenous

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may mimic an infectious etiology (×200). C, Cases with severe injury may show the diffuse alveolar damage (DAD) pattern, with interstitial edema, active fibroelastic proliferation, type II pneumocyte hyperplasia, and eosinophilic hyaline membranes (×100), (H) usually accompanied by prominent foamy macrophages and cytoplasmic vacuolization in the pneumocytes (×400).
lipids from a wide variety of other causes of acute lung injury or airway obstruction. At this time, the clinical utility of oil red O staining of BAL fluid as a diagnostic marker of EVALI remains unknown, and if these stains are performed, they should be interpreted with caution. Education of clinicians on the diagnostic limitations of lipid stains on BAL specimens may be helpful, particularly given the fact these stains have not been routinely performed for many years in adult patients, and pulmonologists may not be aware of these limitations. Lipid stains on BAL specimens are often technically unreliable and have low specificity. It should also be remembered if lipid stains are requested, they require unfixed material and cannot be performed on formalin-fixed, paraffin-embedded tissue or alcohol-fixed BAL specimens. There are currently no published data supporting a change in practice with regard to specimen handling and processing of lung tissue biopsies for the purposes of performing lipid stains. At this point, pathologists should consider processing the entire sample of lung tissue routinely with formalin fixation and paraffin embedding for light microscopy and avoid freezing tissue for lipid staining, especially in the transbronchial biopsy setting, as to avoid compromising the histologic evaluation for infection, aspiration, and other potential causes of acute lung injury.

**FUTURE DIRECTIONS**

Although recent studies have begun to illuminate some issues surrounding EVALI, much remains unknown. In EVALI, the histologic pattern of acute lung injury resembles lung injury from caustic chemical exposures in many respects. Given the diverse chemical composition of vaping products it is possible a chemical component in a subset of vaping fluids is inducing a caustic injury. As outlined in data from the CDC, patients with EVALI have reported using a diverse spectrum of products. While EVALI seems to occur more commonly in users of some brands, it is not clear how this relates to the prevalence of substances in the market given the relatively unreliable data from gray and black market devices, and whether EVALI can be explained by only a single contaminant in the vape liquid supply. Much attention has been given to the recent emergence of vitamin E acetate in the vape liquid supply that was not present in 2018, but there have been cases that occurred outside of this recent outbreak in the United States, suggesting a more complex problem. A recent study identified potentially toxic degradation products of cannabis in vaping devices, including isoprene, methacrolein, benzene, and methyl vinyl ketone, albeit at lower levels than those observed in combustion of marijuana products. Others report contamination of some vaping products with microbial toxins. Interestingly, EVALI also shows a striking resemblance to certain adverse drug reactions, such as amiodarone toxicity. The mechanism of amiodarone toxicity in the lung is thought to be related to the production of oxygen radicals and the accumulation of phospholipids in tissues. Whether a similar free radical–mediated injury underlies EVALI remains unknown. Despite these disparate observations, data implicating vitamin E acetate as a potential culprit are becoming difficult to ignore. One study reported production of toxic ketene gas upon heating of vitamin E acetate, providing a tantalizing clue that could explain how vitamin E acetate produces a severe toxic injury in the absence of significant lipid accumulation. This study highlights the importance of characterizing the chemicals derived from pyrolysis during use of vape devices. It has also been postulated that vitamin E acetate may interfere with surfactant metabolism or lipid homeostasis, which could cause respiratory dysfunction, a notion further supported by data reported in a mouse model of vaping.

While there is clear evidence a subset of patients can develop acute lung injury from vaping, the long-term consequences are less clear. Despite claims vaping is a safer alternative to smoking, the long-term health consequences of vaping are poorly understood and some experimental models have suggested e-cigarettes may have adverse health outcomes. This is an important point because the majority of smokers who switch to e-cigarettes as a smoking-cessation method become long-term users of e-cigarettes. Because EVALI is a recent phenomenon, the
Figure 6. A and B, Papanicolaou stain of bronchioalveolar lavage (BAL) fluid cytology from a patient with e-cigarette, or vaping, product use-associated lung injury (EVALI) demonstrating numerous foamy macrophages containing intracytoplasmic vacuoles that are highlighted with an oil red O histochemical stain (×400). This finding confirms the presence of lipid in these macrophages, but does not imply the lipid is from an exogenous source, as endogenous lipid from accumulated surfactant or cellular debris will also produce this pattern. C and D, Papanicolaou stain of BAL fluid cytology from a patient with exogenous lipoid pneumonia from mineral oil aspiration demonstrating larger vacuoles in the foamy macrophages and globules on the oil red O histochemical stain (×400). E and F, Representative hematoxylin-eosin (H&E)-stained sections of exogenous lipoid pneumonia showing coarsely vacuolated macrophages in the interstitium and air spaces, focal multinucleated giant cells, and variable degrees of interstitial fibrosis (×200). This histologic pattern is very different from the acute lung injury patterns seen in EVALI, and to date, no cases of EVALI with histologic evidence of exogenous lipoid pneumonia have been reported. A through D, courtesy of Margaret Compton, MD.
long-term pulmonary sequelae of lung injury in these patients are unknown. It is possible some individuals might eventually develop small airways disease, obliterator bronchiolitis, or other chronic lung diseases. Additional studies are also needed to determine the causative agent(s) underlying the current outbreak of EVALI cases. Although epidemiologic data on vitamin E acetate in vape liquid and BAL fluid are certainly intriguing, the specific role that vitamin E acetate is playing in EVALI remains unclear. A recent report of a patient who developed giant cell interstitial pneumonia from coital exposure related to a 6-month history of vaping suggests more than one mechanism of injury may occur and the spectrum of vaping-related lung disease may be broader than simply EVALI, particularly in the more subacute or chronic setting. With the increasing legalization of marijuana and cannabis products in many states, hopefully patients will be more willing to share the details of their vaping activities, and hopefully regulatory and research efforts into this problem will become easier. Ultimately, multifaceted research efforts involving animal models and future clinical studies will be required to determine the long-term consequences of vaping on the lung and other organ systems.

References


