AJR FOCUS ON:

Imaging Findings of Vaping-Associated Lung Injury

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OBJECTIVE. E-cigarettes are devices that aerosolize nicotine- or cannabis-based concentrates mixed with other solvents and have been marketed as an alternative to cigarettes. E-cigarette use, or vaping, is increasingly popular but has not been proven to be an innocuous substitute for traditional smoking. Several patterns of vaping-associated inhalational lung injuries have been reported in the past few years. This article reviews many of the imaging patterns that have been encountered in association with e-cigarette use.

CONCLUSION. E-cigarette use is associated with a range of lung injury patterns that have only recently been recognized as use of these products continues to rise. When the radiologist sees one of these patterns of lung injury, it is important to raise the possibility of vaping-induced lung injury because cessation of vaping is an important step in treatment.

Electronic nicotine delivery systems (ENDS), which include electronic cigarettes (e-cigarettes), vapes, vaporizers, vape pens, hookah pens, electronic pipes (e-pipes), "cigalikes" (term for "cigarette-like"), electronic hookahs (e-hookahs), and tank systems were introduced in the United States in 2007 and have been marketed with unsubstantiated claims as being a relatively safe alternative to cigarette smoking. Because of the continuing economic demand, in 2018 there were 288 models of ENDS on the market along with more than 15,500 different flavors or so-called "juices." The effects of vaping nicotine, juices, or marijuana-derived oils on the respiratory system are poorly understood. However, a growing number of case reports in the medical literature and articles in the lay press have begun to reveal deleterious pulmonary manifestations of e-cigarette use. On August 30, 2019, the Centers for Disease Control and Prevention issued a health advisory regarding reports of severe pulmonary disease associated with e-cigarette use [1]; the health advisory states that there were 215 reported possible cases of pulmonary illness and one confirmed death associated with ENDS use as of August 27, 2019 [1].

Physicians from institutions across the United States have encountered numerous different patterns of inhalational lung injury associated with vaping including hypersensitivity pneumonitis (HP), diffuse alveolar hemorrhage (DAH), acute eosinophilic pneumonia (AEP), diffuse alveolar damage, organizing pneumonia (OP), lipoid pneumonia, and giant cell interstitial pneumonia (GIP). The purpose of this article is to familiarize the radiologist with the function of e-cigarettes, summarize imaging findings described in the literature to date, and illustrate some of the diverse imaging manifestations of vaping-associated lung injuries.

What Are Electronic Nicotine Delivery Systems?

ENDS are a diverse group of devices that are designed to aerosolize a liquid for inhalation into the lung, termed "vaping," and include e-cigarettes, vapes, vaporizers, vape pens, hookah pens, e-pipes, cigalikes, e-hookahs, and tank systems. ENDS vary in size, shape, and composition but in general have four main components: a reservoir that holds the liquid to be aerosolized, an atomizer or vaporizer, a battery to power the aerosolizer, and a mouthpiece for inhalation. Although most vape pens typically contain nicotine mixed with other additives including flavoring agents, others contain cannabis-based compounds intended to be a substitute for traditional marijuana [2].

Flavoring agents, although banned from being used in combustible cigarettes, are not restricted with the use of e-cigarettes. Currently, there are more than 15,500 juices on the market that are composed of various al-

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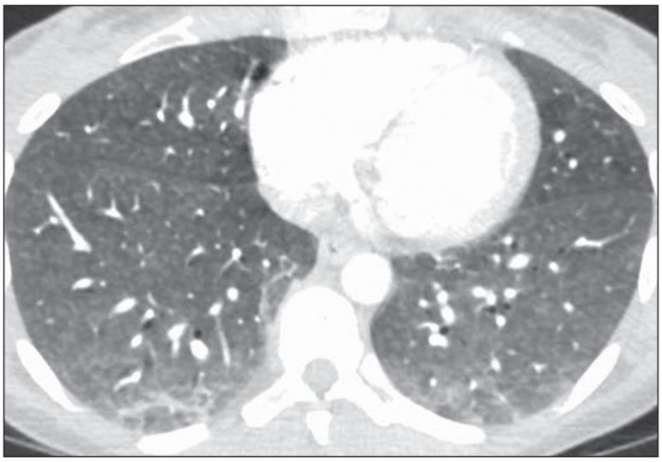

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Fig. 1—31-year-old woman with acute hypersensitivity pneumonitis (HP) pattern of lung injury from vaping.
A and **B,** Axial pulmonary CT angiography images obtained in emergency department (ED) when patient presented with dyspnea show diffuse ill-defined centrilobular ground-glass nodules with slightly more confluent ground-glass opacity (GGO) in lower lobes, which is typical of HP. When asked about exposures, patient confirmed she had been vaping tetrahydrocannabinol mixture as sleep aid for approximately 6 weeks before presenting to ED. Timeline coincided with onset of symptoms.
C, Follow-up CT image obtained after steroid therapy and cessation of vaping shows resolution of GGO.

dehydes and alcohols to create numerous sweet and sour flavors [3, 4]. These flavors, which can be smoked in isolation or combined with nicotine, are thought to be a major driver of vaping among adolescent and teenage ENDS users [5]. Over the past few years, there has been a dramatic increase in the number of adolescents and teenagers vaping. In 2018, 25% and 20.3% of 12th and 10th graders, respectively, reported vaping nicotine or flavoring in the prior month compared with 15.2% and 12% in 2017 [6]. The approximately 1.3 million additional 10th and 12th graders who were vaping between 2017 and 2018 represents the largest 1-year increase of any substance tracked by the Monitoring the Future program over the past 44 years [6].

Vape pens can also be used to inhale tetrahydrocannabinol (THC) or cannabidiol (CBD) as an alternative to smoking marijuana [2]. These devices (also called “oil pens”) use oils, wax, or plant material, and the aerosol created from the high-temperature heating contains compounds derived from the thermal decomposition of marijuana, various chemical compounds, and water vapor [7]. Currently, 11 states and the District of Columbia have legalized recreational use of marijuana and an additional 22 states allow the use of medical marijuana. Although the exact numbers are unknown, one study has shown that 61% of cannabis users have vaped marijuana or its derivatives in their lifetime and 37% had done so in the previous month [8].

The heterogeneity of products and their continued evolution make assessment of biologic effects difficult to discern and predict because there are nearly infinite variables involved. For example, the atomizer may be made of several different heavy metals, the liquid may contain flavoring agents (e.g., diacetyl) known to be toxic to the lung, and the temperature of aerosolization may produce varying amounts of toxic compounds (e.g., formaldehyde). In addition, mixing of flavoring and solvent components can create novel chemical compounds that have unique toxicologic properties [4]. These options are customizable by the user, further complicating assessment of the contents of the vaping product and evaluating their potential effects on the lungs.

Clinical Presentation

The clinical presentations of lung disease related to vaping vary and require a high degree of clinical suspicion to search for exposures. Patients usually present with acute or subacute respiratory symptoms including cough, shortness of breath, or chest pain that may prompt imaging with chest radiography, CT, or both [1]. Moreover, the presentation may be confounded by the concurrent inhalation of other substances including traditional cigarettes, marijuana, or other illicit drugs known to have adverse effects on the lungs.

As of August 30, 2019, there is no standardized case definition for vaping-associated lung injury. In general, the diagnosis of lung injury due to vaping may be made by establishing a temporal relationship between change in vaping habits and onset of lung disease, exclusion of other causes of lung disease (e.g., infection, other drug or exposure, connective tissue disease, and so on), and stabilization or improvement with cessation of vaping and possibly with corticosteroid treatment.

Imaging Manifestations of Vaping

Many patterns of lung injury have been reported with vaping. It is critical for the radiologist to recognize is that any of the following patterns may be seen with vaping, and thus the radiologist may be the first person to prompt the clinical team to ask about relevant exposures.

Hypersensitivity Pneumonitis

An HP pattern has been described in two previous case reports in association with vaping, although neither case report had histologic proof [9, 10]. Historically, HP has been classified into three categories (acute, subacute, and chronic); however, more recent literature has simplified this classification into either acute HP or chronic HP [11]. In both cases, investigators described the onset of symptoms over weeks to months and improvement after cessation of antigen inhalation [9, 10]. Typical findings of acute HP pattern on CT include symmetric upper lung–predominant and midlung-predominant ground-glass opacity (GGO), poorly defined centrilobular nodules, and occasionally mosaic attenuation reflective of air trapping [12] (Fig. 1).

Diffuse Alveolar Hemorrhage

DAH from vaping has been reported in one case report of a 33-year-old man [13]. Patients with DAH typically present with recent onset of cough, fever, and dyspnea, although hemoptysis may be absent in up to one-third of patients. Findings on chest radiography include opacities that may be unilateral or bilateral. Findings on CT include centrilobular nodules, GGO, consolidation, or a combination of these findings that often spare the subpleural lung [14] (Fig. 2). Distinguishing DAH from other causes of acute

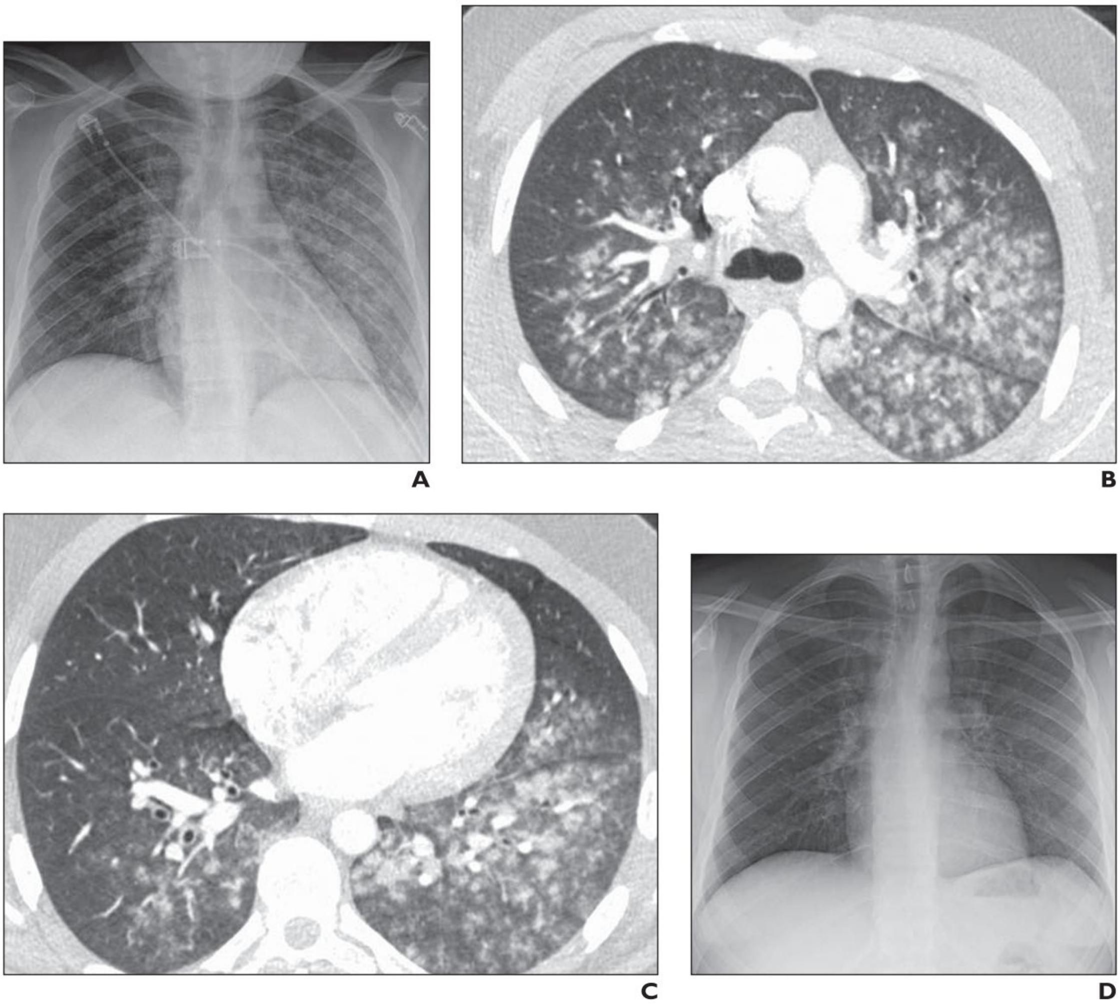
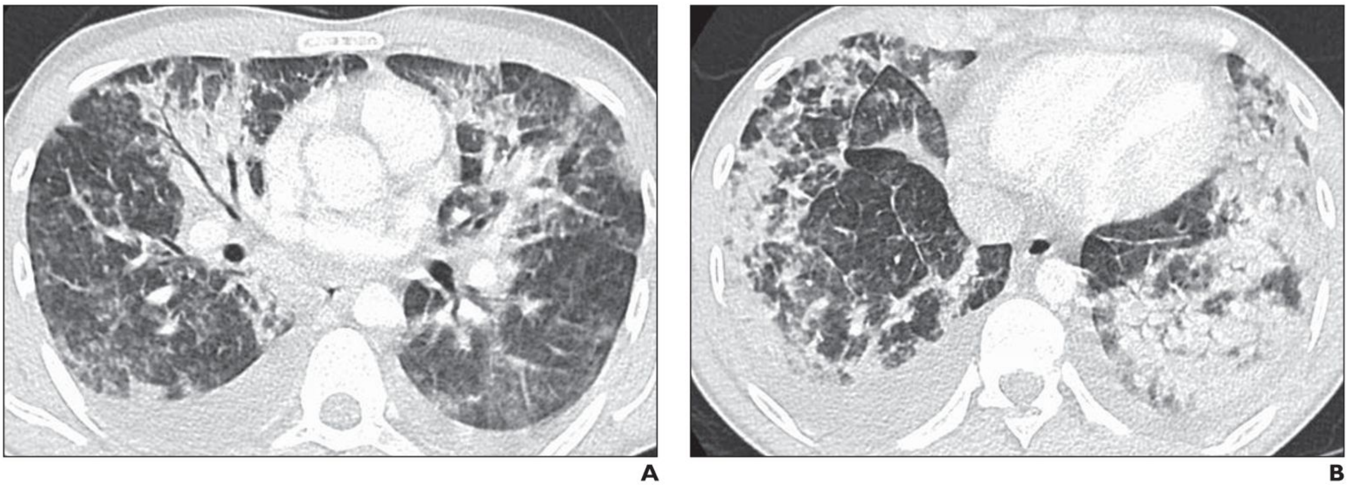


Fig. 2—20-year-old man with diffuse alveolar hemorrhage from vaping who presented with acute onset of dyspnea and hemoptysis.
A, Anteroposterior radiograph obtained at presentation shows bilateral opacities affecting left lung more than right lung.
B and **C,** Axial pulmonary CT angiography images show nodules and consolidation with centrilobular distribution, which are findings consistent with pulmonary hemorrhage. In **B**, mild smooth septal thickening is also present in left upper lobe.
D, Follow-up radiograph obtained 2 days after **A**–**C** and after steroid therapy shows near resolution of findings seen in **A**–**C**.



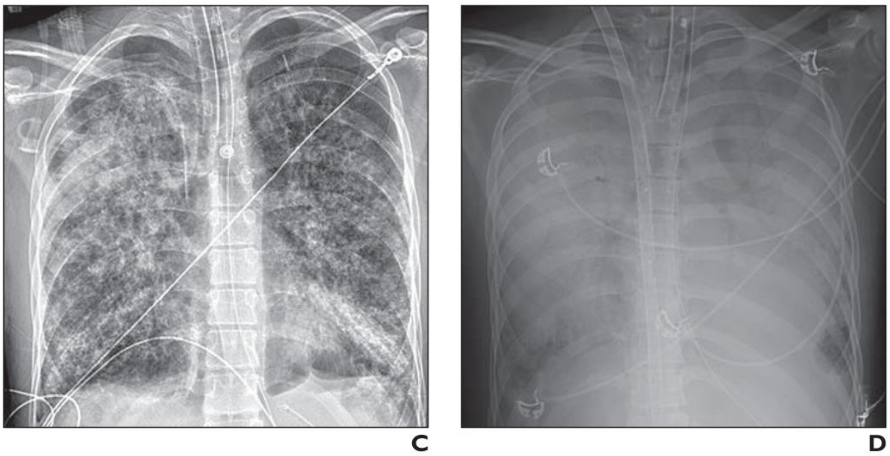


Fig. 3—20-year-old man with acute lung injury necessitating intubation and venovenous extracorporeal membrane oxygenation (ECMO). Patient presented with severe respiratory distress 6 days after trying new vape juice.
A and **B**, Axial CT images obtained at presentation show bilateral consolidation, ground-glass opacities, small effusions, and mild septal thickening.
C and **D**, Radiograph obtained on day 3 (**C**) when patient was intubated and radiograph obtained on day 5 (**D**) when patient was placed on ECMO show worsening diffuse lung opacities. Workup results were negative for infection, and bronchoalveolar lavage revealed acute neutrophilic inflammation with lipid-laden macrophages and 12% eosinophils. Patient recovered after treatment with steroids, and chest radiograph on day 20 (not shown) showed normal findings.

lung opacities including aspiration, edema, and infection can be difficult on the basis of imaging findings alone. Patients may be anemic, and bronchoalveolar lavage (BAL) with persistent or increasingly bloody aliquots confirms the diagnosis.

Acute Lung Injury and Acute Eosinophilic Pneumonia

Acute lung injury (ALI), which histologically manifests as diffuse alveolar damage, has been reported from vaping in one case report of a 46-year-old man presenting with respiratory failure [15]. During the acute exudative phase of ALI, CT initially shows heterogeneous consolidation, GGO, crazy-paving, or some combination of these findings and often has a gravitationally dependent distribution. As findings evolve into the organizing phase, reticulation and traction bronchiectasis may develop. Patients may require mechanical ventilation and extracorporeal oxygenation depending on severity [16] (Figs. 3 and 4).

AEP is another form of acute pulmonary injury often associated with inhalation exposures. Although often secondary to first-time use, an increase in use, a change of brand, or resumption of smoking traditional cigarettes, more recently, cases of AEP have been described in people who vape [17, 18]. AEP can be confirmed when the following clinical criteria are met: acute febrile illness of fewer than 5 days in duration, progression to hypoxemic respiratory failure, abnormal chest imaging findings, BAL eosinophils exceeding 25%, prompt response to steroid therapy, and absence of underlying infection [19]. Pathologically, AEP manifests as diffuse alveolar damage with eosinophilic infiltration in alveolar spaces and tissues [20].

On CT, AEP usually presents with bilateral and often symmetric GGO, consolidation, or both and is difficult to distinguish from other forms of ALIs. Pleural effusions and septal thickening are also often present in the absence of left heart dysfunction and can be a clue to the diagnosis [19] (Fig. 5). However, the diagnosis for radiologists and clinicians can be difficult to make because the imaging manifestations are often nonspecific and peripheral eosinophilia is often absent at the time of presentation.

Organizing Pneumonia

An OP pattern from vaping has been reported in two patients with subacute respiratory symptoms [21]. OP is a common response to lung injury that is characterized by fibroblast proliferation and collagen deposition [22]. Bilateral patchy GGO, consolidation, or both in a peripheral or perilobular distribution are the most typical CT findings of OP. The "reverse halo" sign or "atoll" sign is also associated with OP [22] (Fig. 6).

Lipoid Pneumonia

Lipoid pneumonia is an inflammatory response to inhaled or aspirated lipids and can be endogenous or exogenous, with the latter being more common and due to a wide range of substances including laxatives, petroleum-based lubricants, mineral oils, or hydrocar-

Fig. 4—56-year-old man with respiratory failure and acute lung injury (ALI) from vaping nicotine products. (Courtesy of Franks TJ, The Joint Pathology Center, Silver Spring, MD; and Galvin JR, University of Maryland, Baltimore, MD)
A, Portable anteroposterior radiograph obtained during hospitalization shows coarse bilateral opacities typical of ALI.
B and **C,** Coronal CT reformat images through anterior (**B**) and posterior (**C**) lungs show findings of organizing phase of diffuse alveolar damage including relatively symmetric bilateral reticulation, traction bronchiectasis, ground-glass opacity, and consolidation. Surgical lung biopsy results were consistent with organizing diffuse alveolar damage.

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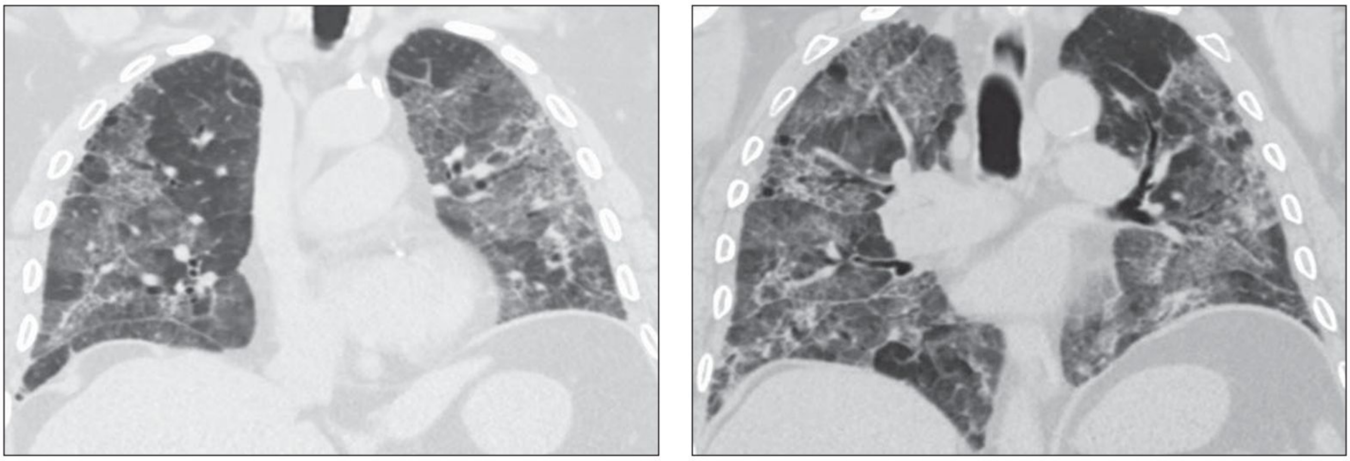

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bons (e.g., "fire-eater's lung") [23]. Three recent cases of lipoid pneumonia from vaping (labeled as such because of the presence of lipid-laden macrophages in lavage fluid) have been reported and attributed to lipid materials in the flavoring agents [24–26]. However, the basic contents of nicotine-containing vaping juices are not oils. Therefore, it is also possible that other juice constituents (e.g., glycerin) may produce a lipoid pneumonia in the form of endogenous phospholipidosis that is analogous to amiodarone-induced lung injury [27]. We use the term "lipoid pneumonia" to refer to both possible mechanisms, when lipid-laden macrophages are found in lavage fluid. As opposed to patients with ALI, patients with lipoid pneumonia may present with subacute to chronic symptoms over the course of months.

On CT, findings of exogenous lipoid pneumonia (ELP) usually affect the dependent lung and include GGO, consolidation, crazy-paving, or a combination thereof. Macroscopic fat attenuation within consolidation (< –30 HU) is virtually diagnostic for ELP but is not present in all cases, particularly acute ELP [23]. The presence of lipid-laden macrophages on BAL or foreign body reaction around lipid at histology can confirm the diagnosis [26] (Fig. 7).

Giant Cell Interstitial Pneumonia

GIP is a rare pneumoconiosis from exposure to hard metal such as tungsten carbide or cobalt [28]. Although there are no previous case reports of GIP associated with e-cigarettes, hard metal contamination of vaping aerosols is well described [29], and these authors have encountered one case of pathologically proven GIP attributable to traces of cobalt in the patient's vape pen (Fig. 8).

On CT, GIP may present as GGO, architectural distortion, and linear opacities in a peribronchiolar distribution [28], corresponding to intraalveolar accumulation of multinucleated giant cells and macrophages and adjacent inflammation and fibrosis. Other patterns of fibrosis such as nonspecific interstitial pneumonia have also been reported in conjunction with hard metal exposure [30].

Other Potential Imaging Patterns

Because of the heterogeneity of both the construction of e-cigarettes and the substances aerosolized, there are likely many other pulmonary manifestations not covered in this article. For example, respiratory bronchiolitis–associated interstitial lung disease (RB-ILD) has been attributed to vaping in one case report of a 33-year-old man (although that patient was reportedly also a cigarette smoker) [31]. In that case, the imaging findings were typical of RB-ILD including upper lobe–predominant, ground-glass–attenuation centrilobular nodules.

Vaping mixtures are also known to contain compounds such as diacetyl [32] that are known to cause other lung injury patterns including constrictive bronchiolitis (e.g., popcorn worker's lung or "flavor worker's lung") [33]. Although there are no confirmed cases of these other lung injury patterns from vaping, this issue is a current topic of discussion in the press [32].

Conclusion

E-cigarette use is associated with a range of lung injury patterns that have only recently been recognized as the use of these products continues to rise. When the radiologist sees one of these patterns of lung injury, it is important to raise the possibility of vap-

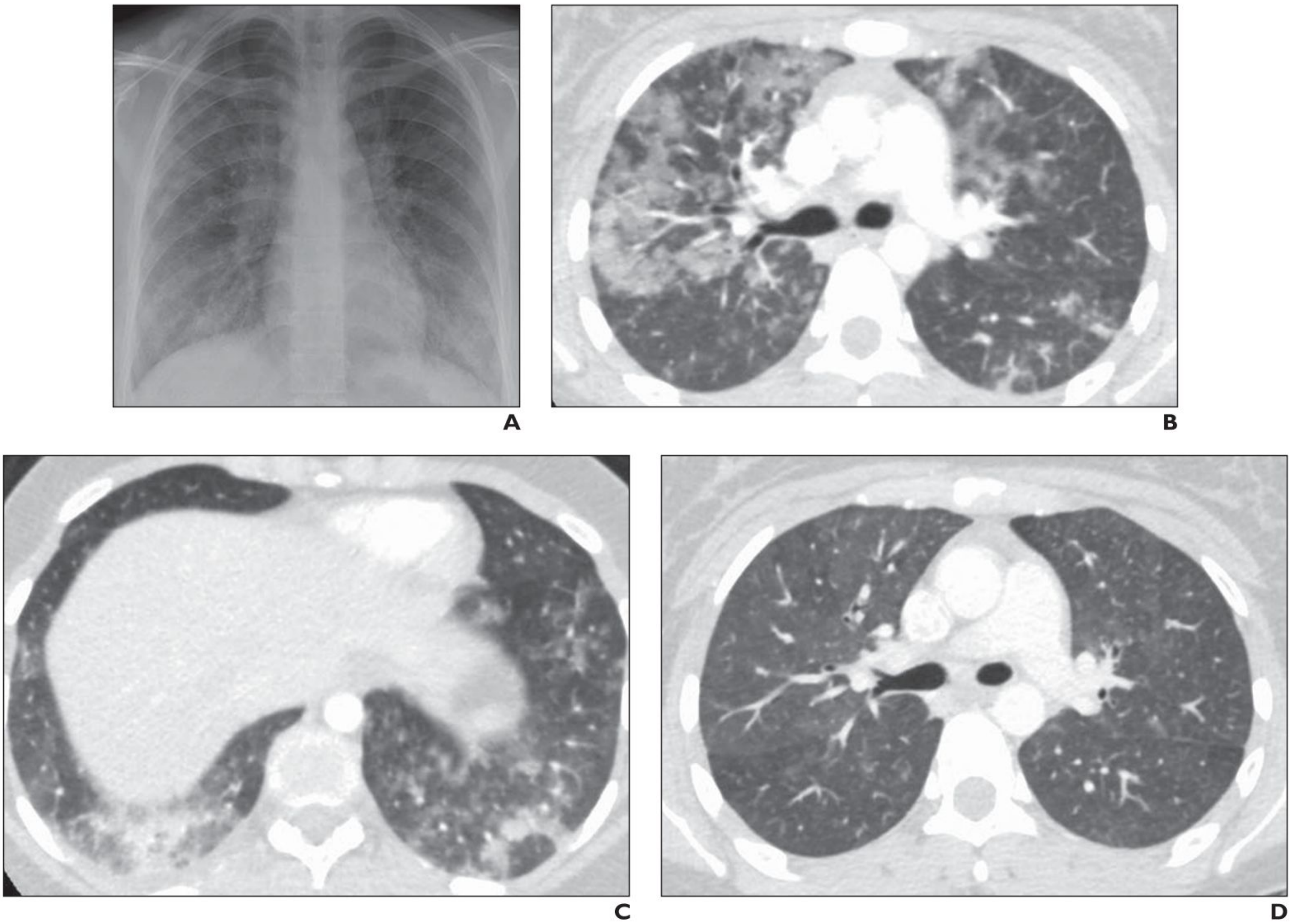

Fig. 5—19-year-old woman with acute eosinophilic pneumonia from vaping cannabidiol oil. Patient had history of asthma and presented with recent onset of severe dyspnea refractory to inhaler treatment. At presentation, she was febrile and required 15 L of high-flow nasal cannula oxygen to maintain saturation above 90%.
A, Chest radiograph shows bilateral hazy multifocal, multilobar opacities.
B and **C,** Axial pulmonary CT angiography images show patchy bilateral ground-glass opacity, dependent consolidation, and small right pleural effusion. Results of workup were notable for peripheral WBC count of 16,000/µL with 36% eosinophils.
D, Patient's symptoms promptly improved with high-dose corticosteroid therapy. Repeat CT image obtained 3 days after **A**–**C** shows near resolution of opacities.

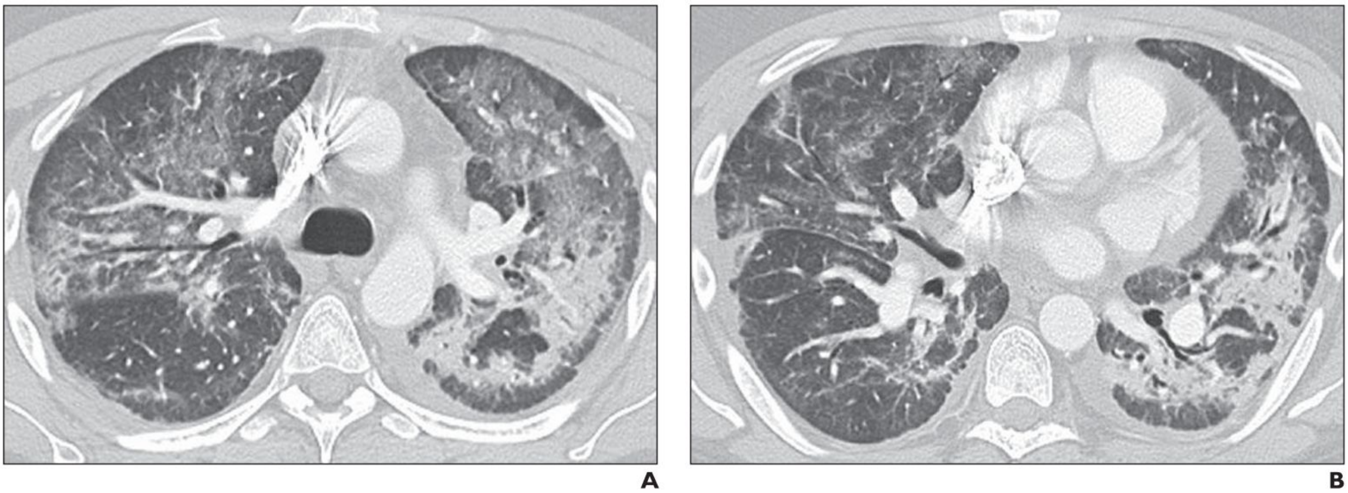

Fig. 6—28-year-old man with increasing shortness of breath after vaping cannabis oil.
A and **B,** Axial CT images show relatively symmetric peribronchiolar ground-glass opacity and consolidation with subpleural sparing in pattern suggestive of organizing pneumonia. Patient was treated with steroids. Radiograph (not shown) obtained on day 8 revealed significant improvement in lung opacities.

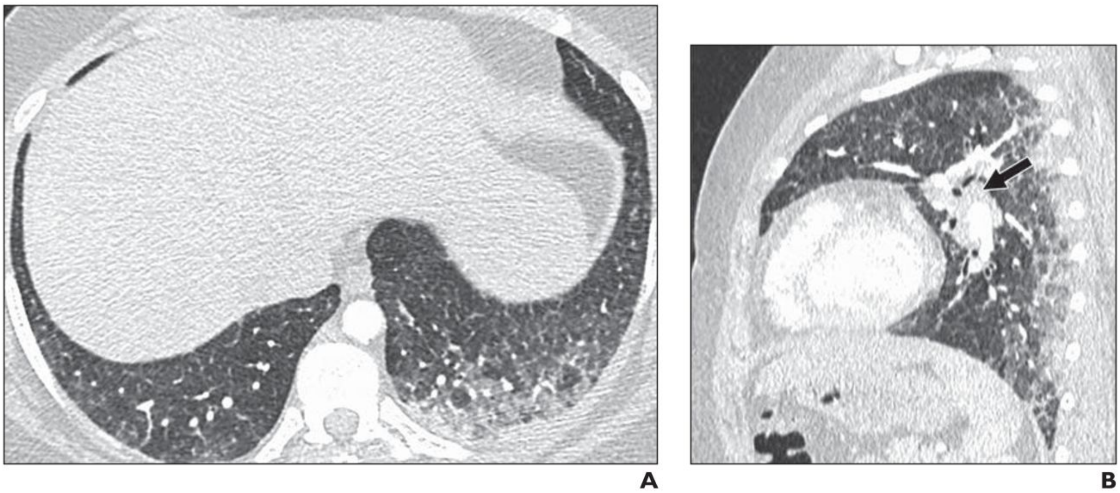

Fig. 7—25-year-old woman with lipoid pneumonia from vaping. Patient presented with several months' history of intermittent shortness of breath, subjective fever, chills, and night sweats.
A and **B,** Axial (**A**) and sagittal (**B**) reformat images from pulmonary CT angiography show mild diffuse ground-glass opacity and more dependent consolidation in distribution typical of lipoid pneumonia. Sagittal image also shows reactive left hilar lymph node enlargement (*arrow*, **B**). Bronchoalveolar lavage revealed high proportion of macrophages that stained positive (oil red O stain) for lipid material.

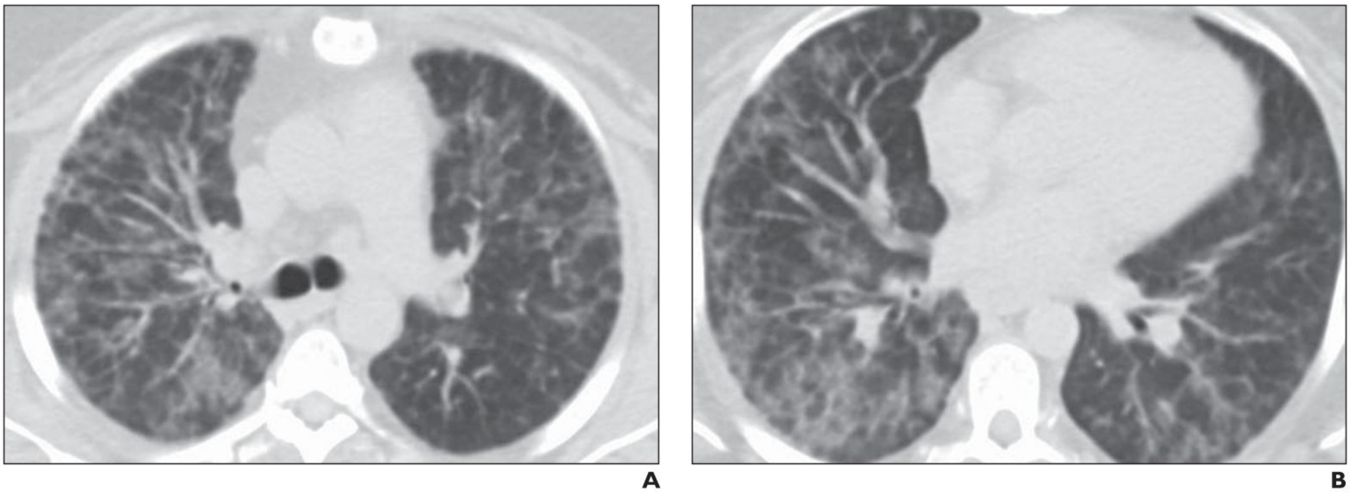

Fig. 8—Giant cell interstitial pneumonia (GIP) attributed to vaping in 49-year-old woman who presented with 1–2 years of worsening dyspnea.
A and **B,** Axial CT images show relatively symmetric ground-glass opacity and perilobular opacities involving all lobes, findings that can be seen in GIP. Subsequent surgical lung biopsy results were consistent with GIP. When asked about exposures, patient said that she had begun vaping tetrahydrocannabinol mixture around time that her symptoms started. She had no other occupational exposures to heavy metals, and her vape pen was found to have traces of cobalt on subsequent analysis.

ing-induced lung injury because cessation of vaping is an important step in treatment.

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