



E-cigarette, or vaping, product use-associated lung injury in adolescents: a review of imaging features

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Abstract

Background There has been a recent increase in recognition of lung disease related to the use of electronic cigarettes (called “vaping”). These patients present with acute respiratory illness following exposure to vaporized cannabis or nicotine products and sometimes require hospitalization and intensive care. We describe the imaging findings of this disease entity in the pediatric population.

Objective To describe the radiologic findings of lung injury associated with electronic cigarette use (vaping) in the adolescent pediatric population.

Materials and methods We identified all adolescents with acute respiratory illness and a history of electronic cigarette use who presented at our institution within a 3-month period (June 2019 through August 2019). We excluded adolescents with potential intercurrent pulmonary disease. We reviewed the charts for symptomatology and laboratory and pathology data. In addition, we reviewed the chest radiographs and chest CTs of these adolescents.

Results The review group consisted of 12 teenage pediatric patients (10 boys and 2 girls; mean age 16.9 years, range 16.0–17.7 years) with acute respiratory illness found to have a temporal association with electronic cigarette use for cannabis products, nicotine, or both. Other etiologies for illness in these adolescents had been excluded by clinical and laboratory evaluation. All of the adolescents were admitted to the hospital for treatment. The clinical presentations included dyspnea, abdominal pain and constitutional symptoms. Pulmonary function testing that was performed in all patients during admission or follow-up demonstrated reduced diffusion capacity in 4/12 (33%), an obstructive ventilatory pattern in 4/12 (33%), a restrictive pattern in 1/12 (8%), and a mixed obstructive and restrictive pattern in 2/12 (17%) adolescents. Bronchoalveolar lavage studies, performed in 9 of the 12 adolescents, revealed inflammatory cells and lipid-laden macrophages. All of the patients underwent CT of the chest; the findings were notable for centrilobular ground-glass nodules (11/12; 92%) and confluent ground-glass opacities (12/12; 100%), with frequent subpleural sparing (9/12; 75%). Additionally, 6/12 (50%) adolescents demonstrated small pleural effusions; 6/12 (50%) had mild bronchial wall thickening; 9/12 (75%) had enlarged hilar or mediastinal lymph nodes; and 2/12 (17%) had a small pericardial effusion.

Conclusion As seen in our teenage population, e-cigarette, or vaping, product use-associated lung injury (EVALI) is characterized by centrilobular ground-glass nodules and ground-glass opacities with subpleural sparing. The imaging findings are most consistent with acute lung injury resulting from toxic inhalation. Because adolescent pediatric patients might not be forthcoming with their history of electronic cigarette use, it is important for the pediatric radiologist to be aware of the imaging patterns of this disease.

Keywords Adolescents · Computed tomography · EVALI (e-cigarette or vaping product use-associated lung injury) · Inhalation injury · Interstitial lung disease · Lungs · Radiography · Vaping · Vaping-associated lung injury

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Introduction

There has been a recent increase in recognition of respiratory illness related to the use of electronic cigarettes (vaping) [1, 2]. This e-cigarette or vaping product use-associated lung injury, or EVALI, has been identified across the United States, with the first and largest regional cluster in adolescent pediatric patients occurring in the Midwest [3]. These children have sustained varying degrees of acute respiratory illness

following exposure to vaporized cannabis or nicotine products, and many have required hospitalization, including intensive care [4].

In this relatively new entity, definitive pathological diagnostic criteria have not been established. Imaging plays a key role in the diagnosis of the disease. Other entities are excluded through the use of careful histories and laboratory evaluations, and a temporal association with the use of electronic cigarettes must be present [3].

The purpose of our review was to identify the radiologic findings of lung injury associated with vaping in the adolescent pediatric population. Our goal is to increase recognition of this emerging disease process to allow for accurate diagnosis in the teenage population.

Materials and methods

This retrospective review complied with the Health Insurance Portability and Accountability Act and was approved by the human research protection program of our institution. From a pulmonology database and our radiology archive, we identified all adolescents diagnosed with e-cigarette, or vaping, use-associated lung injury at our tertiary-care pediatric hospital over a 3-month period (June 2019 through August 2019). The final clinical diagnosis was based on a temporal association with electronic cigarette use, imaging evidence of pulmonary injury, and exclusion of other causes by careful history and investigations. We excluded adolescents with potential intercurrent pulmonary disease and those older than 17.9 years.

We reviewed the teenagers' electronic medical records for demographic data, symptomatology, laboratory and pathology evaluations, and treatment regimens. The evaluated clinical findings included dyspnea, hypoxia, chest and abdominal pain, and constitutional symptoms. Information regarding the frequency and duration of vaping and the substance inhaled was recorded when available. The chest CT studies and radiographs were retrospectively reviewed by two pediatric radiologists with 4 years and 2 years of experience (P.D.T., S.S.K.) to identify the pertinent imaging findings in the lungs, pleura, mediastinum and lymph nodes. Disagreement between the reviewers was resolved by arbitration by a third pediatric radiologist with 7 years of experience (K.P.B.). Descriptive statistics were calculated to evaluate the imaging findings.

Results

Fourteen adolescents were diagnosed with EVALI over a 3-month period. One adolescent additionally had a diagnosis of latent tuberculosis infection but was not found to have clinical evidence of active disease. Another adolescent had a history

of bronchogenic cyst resection 5 months prior, with persistent postsurgical chest pain prior to the onset of her acute respiratory illness. Both adolescents were excluded from this review, given the potential for intercurrent pulmonary disease to account for their symptoms. Twelve teenage patients comprised the final review group (10 boys and 2 girls; ages 16.0–17.7 years [mean 16.9 years] at presentation).

The most common presenting symptoms were dyspnea ($n=9$), nausea or vomiting ($n=11$), cough ($n=9$), chest pain ($n=6$) and abdominal pain ($n=5$). Constitutional symptoms such as fevers, chills, night sweats, fatigue, weakness, myalgias and malaise were seen in 11 of the 12 adolescents, and 7 of the 12 reported unintentional weight loss in conjunction with the other symptoms.

Five adolescents reported using electronic cigarettes for nicotine only, two reported electronic cigarette use for cannabis (tetrahydrocannabinol, or THC) only, and five adolescents reported vaping both nicotine and THC products. All five of the adolescents who reported vaping only nicotine also reported cannabis use in some other form (edible or combustible). Eleven of the adolescents acknowledged using electronic cigarettes within 3 months prior to presentation. Of those, nine said they had vaped within 1 week prior to admission. One adolescent reported that most recent use was 2–3 weeks prior to admission but that onset of symptoms was 1 month prior to admission. One adolescent indicated that most recent use was within 2 months prior to admission but that onset of symptoms was 1 month prior to admission; of note, this adolescent's self-reported vaping history varied over the course of several clinical encounters. A single adolescent reported cessation of electronic cigarette use 5 months prior to admission and onset of symptoms 2 months prior to admission. A summary of the teenagers' reported substance use patterns can be found in Table 1.

Physical examination of the lungs was normal in two adolescents. Four adolescents were clear to auscultation but were hypoxic or tachypneic, or demonstrated accessory muscle use. Three adolescents had diminished breath sounds and three had wheezing, crackles or rhonchi.

Laboratory evaluation revealed leukocytosis in 9 of 11 patients (blood count was not performed in 1 patient), an elevated lactate dehydrogenase level in the 10/10 adolescents in whom it was performed, and an elevated C-reactive protein level in 12 of 12 adolescents. Bronchoalveolar lavage was performed in 9 of the 12 patients. In all nine, increased neutrophils were identified in the lavage. Bronchoalveolar lavage also identified lipid-laden macrophages in all adolescents, ranging from scant to moderate.

Pulmonary function tests were performed in 10 of the 12 adolescents during admission. The findings were normal in four. Three of 10 adolescents had reduced diffusion capacity. Two had an obstructive ventilatory pattern, one had a restrictive pattern, and two had a mixed obstructive and restrictive

Table 1 Demographics and substance use patterns in 12 adolescents with e-cigarette, or vaping, product use-associated lung injury (EVALI)

Patient	Age (years)	Gender	Substance used for vaping	Timing	Non-vaping marijuana use
1	16.6	Male	Nicotine and THC	Unknown duration; most recent use within 2 months PTA	No
2	16.5	Male	Nicotine	Began use 6–8 months PTA; daily use for several weeks PTA	Yes
3	17.0	Male	Nicotine	3–5 days/week; unknown duration	Yes
4	17.0	Female	Nicotine and THC	Multiple times daily for unknown duration; most recent use 2–3 weeks PTA	Yes
5	16.1	Male	Nicotine and THC	THC multiple times daily qod for 6–12 months; nicotine 1–2 times/week for 1 year	Yes
6	17.7	Male	Nicotine	Daily use for 2–3 months with most recent use 5 months PTA	Yes
7	17.5	Male	Nicotine	Daily use; unknown duration	Yes
8	17.7	Male	Nicotine	Daily use for 4 months	Yes
9	17.0	Male	THC	Unknown duration; most recent use 3 days prior to onset of symptoms	Yes
10	16.0	Male	Nicotine and THC	Daily use of either nicotine or THC for 10 months	No
11	16.6	Female	Nicotine and THC	Daily use of nicotine and nightly use of THC for 2 years	No
12	17.0	Male	THC	At least once per week; unknown duration	No

PTA prior to admission, qod every other day, THC tetrahydrocannabinol

pattern. The two remaining adolescents underwent pulmonary function testing 6 weeks after discharge. Both of these adolescents had obstructive patterns, and one demonstrated reduced diffusion capacity.

Ten adolescents had chest radiographs at initial presentation. The chest radiographic findings ranged from normal to nodular opacities, patchy alveolar opacities, or mixed interstitial and alveolar opacities with central and lower lung predominance (Fig. 1). No pleural effusion or lymphadenopathy was detected by chest radiography.

Chest CTs were performed in all of the adolescents; one of the studies was performed as a chest/abdomen/pelvis CT. Intravenous contrast agent was administered in 10 of the 12. Pulmonary imaging findings included confluent ground-glass opacities in all 12 adolescents, centrilobular ground-glass nodules in 11, reticular interstitial opacities in 6, and bronchial wall thickening in 6 (Fig. 2). In 9 of the 12 adolescents,

subpleural sparing of the ground-glass opacities was present (Figs. 1 and 2). Extrapulmonary imaging findings consisted of enlarged mediastinal or hilar lymph nodes in nine adolescents, small pleural effusions in six and small pericardial effusions in two (Figs. 3 and 4). The chest CT findings are summarized in Table 2. The two radiologists evaluating the chest CTs agreed regarding the presence of confluent ground-glass opacities, subpleural sparing, interstitial septal thickening and extrapulmonary findings in all adolescents. The radiologists disagreed about the presence of bronchial wall thickening in six adolescents and the presence of centrilobular ground-glass nodules in four. Disagreement between the initial radiologists was resolved by arbitration by a third pediatric radiologist.

All 12 adolescents were admitted to the hospital. Two required higher-level care in the intensive care unit. Following diagnosis of EVALI, all 12 adolescents received high-dose steroids for treatment of the acute pulmonary inflammation.

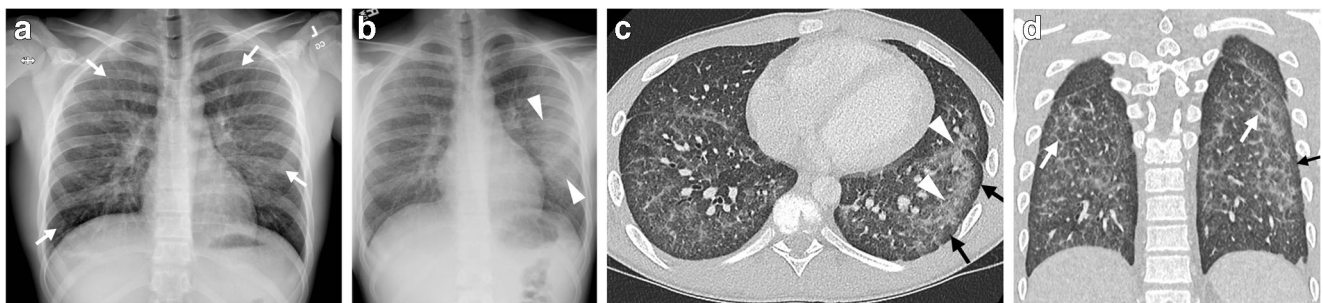


Fig. 1 E-cigarette, or vaping, product use-associated lung injury in a 16-year-old boy who presented with chest pain, shortness of breath, and cough for 1 month (Patient 1). **a** Posteroanterior (PA) radiograph of the chest demonstrates faint nodular opacities in both lungs (arrows) with diffusely increased interstitial markings. **b** PA radiograph of the chest obtained 2 days later demonstrates progression of the nodular opacities into confluent opacities in the left mid lung (arrowheads). **c, d** Axial (**c**)

and coronal (**d**) chest CT images in lung windows (slice thickness 0.63 mm, kVp 100, mAs 61–106) obtained 4 days after the initial chest radiograph demonstrate centrilobular ground-glass nodules in both lungs and confluent ground-glass opacities in the left lower lobe (arrowheads) with subpleural sparing (black arrows) and interstitial septal thickening (white arrows)

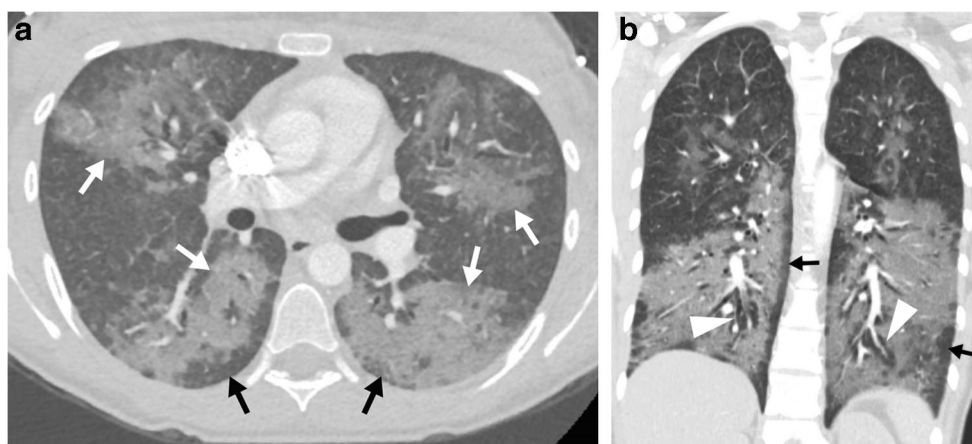


Fig. 2 E-cigarette, or vaping, product use-associated lung injury in a 17-year-old girl who presented with chest pain, nausea, vomiting, abdominal pain, cough and weight loss for 1 month (Patient 4). **a, b** Axial (**a**) and coronal (**b**) chest CT images in lung windows (slice thickness 5 mm for axial images and 3 mm for coronal reconstructions, kVp 120, mAs 30.5–

34.5) obtained at presentation demonstrate lower lobe predominant confluent ground-glass opacities in both lungs (*white arrows*) with areas of subpleural sparing (*black arrows*) and peribronchovascular sparing (*arrowheads*)

Discussion

Electronic cigarettes have been available and in use for 15 years [5]. They have been marketed as a safer alternative to traditional cigarettes, purported to contain and deliver fewer carcinogens than combustible cigarettes [6]. However, with the growing use of electronic cigarettes, increasing accounts of associated illnesses have been described [1]. Prior reports have suggested higher incidences of asthma and bronchitic symptoms in adolescent electronic cigarette users [7, 8]. Individual case reports from 2018 and early 2019 detail instances of hypersensitivity pneumonitis, acute respiratory distress syndrome, diffuse alveolar hemorrhage, eosinophilic pneumonia and lipid pneumonia seen in association with vaping [9–13]. In the summer months of 2019, nearly 300 cases of EVALI were reported across the country, including one vaping-related death, such that the United States Centers

for Disease Control and Prevention (CDC) issued an emergency alert to physicians regarding the illness and its signs and symptoms [1]. Over the same period, 14 adolescents from southeastern Wisconsin were seen at our institution for e-cigarette use-associated lung injury. As of Oct. 15, 2019, 1,479 people with EVALI had been identified across the United States, and there had been 33 reported deaths [14]. Approximately 15% of people with EVALI are in the pediatric age group [14].

The spectrum of pulmonary diseases associated with combustible cigarette smoking is well-established and includes a variety of lung injury patterns, with insidious onset typically resulting from chronic cigarette use. Many of these entities fall into the category of interstitial lung disease, manifesting as dyspnea and restricted lung function with impaired gas exchange [15]. The actual imaging findings vary with each disease pattern, but as the name implies, these diseases tend to

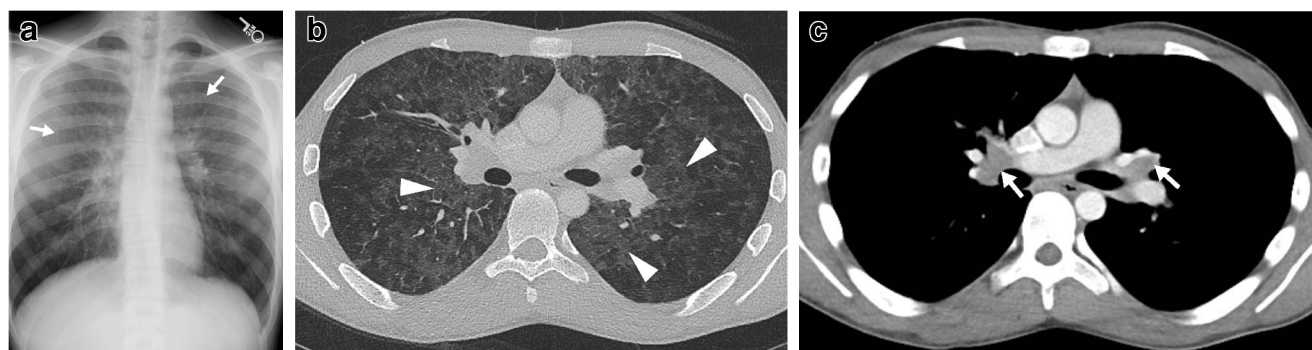


Fig. 3 E-cigarette, or vaping, product use-associated lung injury in a 17-year-old boy who presented with anorexia, weight loss, progressive dyspnea, chest pain, cough, fatigue and nausea for 1 month (Patient 6). **a** Posteroanterior radiograph of the chest obtained at presentation demonstrates numerous faint nodular opacities in both lungs (*arrows*). **b, c** Axial chest CT images in lung (**b**) and soft-tissue (**c**) windows (slice

thickness 0.6 mm for lung window image and 5 mm for soft-tissue window image, kVp 100, mAs 32.0–319.5) obtained the same day demonstrate confluent ground-glass opacities (*arrowheads*) in both lungs causing mosaic attenuation and bilateral hilar lymphadenopathy (*arrows*)

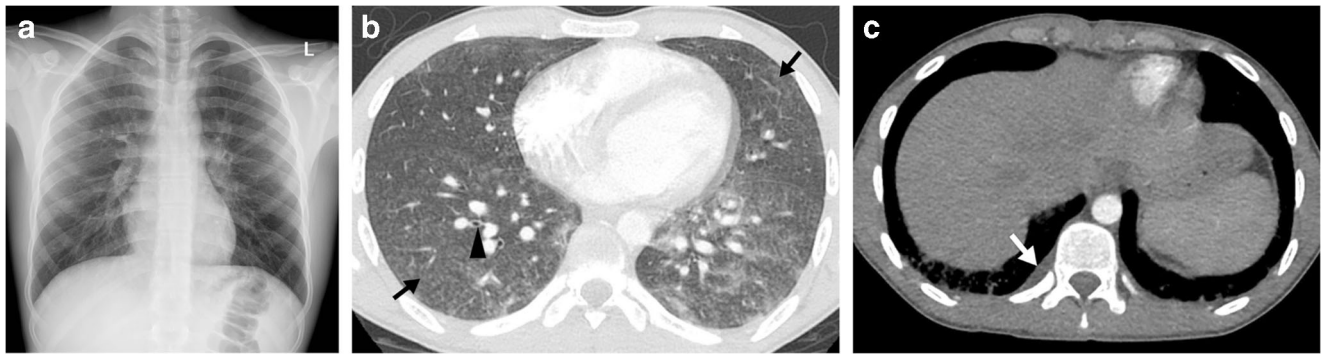


Fig. 4 E-cigarette, or vaping, product use-associated lung injury in a 17-year-old boy who presented with chest pain, myalgias, chills, fever, fatigue, nausea, vomiting and diarrhea for 6 days (Patient 7). **a** Posteroanterior radiograph of the chest obtained at presentation is normal. **b, c** Axial chest CT images in lung (**b**) and soft-tissue (**c**)

windows (slice thickness 2 mm, kVp 120, mAs 50) obtained 3 days after the radiograph demonstrate diffuse centrilobular ground-glass nodules in both lungs (*black arrows*), mild bronchial wall thickening (*arrowhead*) and small right pleural effusion (*white arrows*)

involve the pulmonary interstitium and have varying degrees of airway and alveolar fibrosis [16].

The patterns of lung disease described with electronic cigarette use are distinct from those seen with combustible cigarette use [17]. Prior reports in the adult population have described individual patients with hypersensitivity pneumonitis, diffuse alveolar hemorrhage, acute lung injury, acute eosinophilic pneumonia, organizing pneumonia, lipid pneumonia, and giant cell interstitial pneumonia manifesting clinically with respiratory symptoms [17]. In our experience in the adolescent pediatric population, these patients present with systemic symptoms, including nausea and vomiting, fever, myalgias and fatigue, in addition to respiratory symptoms such as dyspnea.

Laboratory evaluation in our patients revealed leukocytosis, elevated inflammatory markers and elevated lactate dehydrogenase levels, the last indicating some form of tissue damage. Bronchoalveolar lavage, when performed, demonstrated increased neutrophils, compatible with acute inflammation.

Lipid-laden macrophages were also seen on each bronchoalveolar lavage performed in these adolescents, a finding that can be seen in the setting of bronchiolitis, hypersensitivity pneumonitis, drug toxicity and lipid pneumonia, among other etiologies [18]. It is uncertain in the setting of EVALI whether the presence of lipid-laden macrophages indicates toxicity or is merely a marker of exposure to vaporized substances [19]. Bronchoalveolar lavage in our patients did not identify increased eosinophils to suggest acute eosinophilic pneumonia, nor did it reveal findings of alveolar hemorrhage. This correlates with a recent preliminary report from histopathological examination of lung biopsy specimens from 17 people with EVALI [19].

Pulmonary function test results were normal in four of our patients (25%). Four adolescents (25%) had an obstructive ventilatory pattern, one (8%) had a restrictive ventilatory pattern and two (17%) had a mixed obstructive and restrictive pattern. In a study describing short-term effects of e-cigarette

Table 2 Chest CT findings in 12 adolescents with e-cigarette, or vaping, product use-associated lung injury (EVALI)

Patient	Reticular interstitial opacities	Centrilobular ground-glass nodules	Confluent ground-glass opacities	Subpleural sparing	Pleural effusions	Enlarged hilar and/or mediastinal lymph nodes	Bronchial wall thickening	Pericardial effusion
1	Yes	Yes	Yes	Yes	Yes	Yes	No	No
2	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
4	No	Yes	Yes	Yes	No	No	No	No
5	No	Yes	Yes	No	No	Yes	Yes	No
6	No	No	Yes	No	No	Yes	No	No
7	No	Yes	Yes	No	Yes	Yes	Yes	No
8	No	Yes	Yes	Yes	Yes	Yes	No	No
9	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	No	Yes	Yes	Yes	No	No	No	No
12	Yes	Yes	Yes	Yes	No	No	No	No

use on lung function in 10 otherwise healthy individuals, Stockley et al. [20] identified an increase in airway resistance after 5 min of vaping. Reduced diffusion capacity, seen in four of our patients (25%), might result from alveolar filling by exudates, decreased lung compliance, and small airway dysfunction, among other etiologies [21].

One adolescent had a normal chest radiograph at initial presentation. In nine others who had initial chest radiographs available for review, imaging findings consisted of perihilar patchy alveolar opacities, nodular opacities, or mixed alveolar and interstitial opacities. In a preliminary report regarding clinical and imaging findings in people with EVALI in Wisconsin and Illinois, 91% of people with EVALI had abnormalities on chest radiograph [3].

Of our 12 patients, all had patchy ground-glass pulmonary opacities on chest CT. In most of the adolescents, the airspace opacities spared the subpleural regions (9/12, 75%). Centrilobular ground-glass nodules were also a predominant finding, seen in 11 of 12 (92%) adolescents. CTs in six of our patients (50%) showed mild bronchial wall thickening, and reticular interstitial thickening was also seen in six patients (50%). Unlike with interstitial lung disease patterns seen with combustible cigarette use, fibrosis and air-trapping were not seen in any of our patients [15].

In addition, extrapulmonary findings were not infrequent. Six adolescents (50%) had associated pleural effusions, albeit small, and two (17%) had small pericardial effusions. Nine adolescents (75%) had enlarged mediastinal or hilar lymph nodes.

In contrast to the chronic pulmonary findings seen with combustible cigarette use, the clinical and imaging findings seen in our teenage patients with EVALI appeared more acute/subacute. Reports in the adult population have described many patterns of lung injury with EVALI, including hypersensitivity pneumonitis, diffuse alveolar hemorrhage, acute lung injury, acute eosinophilic pneumonia, organizing pneumonia, acute lipoid pneumonia and giant cell interstitial pneumonia [17]. The findings in our adolescent patients are most consistent with the acute lung injury/diffuse alveolar damage pattern, which manifests as bilateral ground-glass opacities with a gravitationally dependent gradient, interlobular septal thickening and pleural effusions. In our patient cohort, the ground-glass opacities frequently spared the subpleural region. This is in contrast to the subpleural predominance of abnormalities described with giant cell interstitial pneumonia [22]. Centrilobular ground-glass nodules, which can be seen in the setting of hypersensitivity pneumonitis, were identified in most of our patients. However, the predominantly lower-lung distribution of the ground-glass nodules in our patients is distinct from the upper- to mid-lung distribution of opacities typically seen in hypersensitivity pneumonitis [23].

Lipoid pneumonia is characterized by ground-glass opacities and consolidation in the dependent portions of the lower lungs [17, 24, 25]. Although we did identify

lower-lung predominance of ground-glass opacities in our patients, the nondependent portions of the lungs were involved as well. The CT findings in our patients were not characteristic of lipoid pneumonia. While preliminary reports have described pneumothoraces and pneumomediastinum in some people with EVALI, neither was seen in our patient cohort. In addition, extrapulmonary findings such as mediastinal and hilar lymph node enlargement and pleural effusions were prevalent in our teenage patients.

The CDC is testing pathology specimens from lung biopsies and autopsies of affected individuals [14]. Preliminary pathological findings in EVALI have been reported to include diffuse alveolar damage, bronchiolitis, organizing pneumonia and acute fibrinous pneumonitis [19]. Prior case reports have suggested hypersensitivity pneumonitis, diffuse alveolar hemorrhage, eosinophilic pneumonia, or lipoid pneumonia as the possible pathological basis of EVALI [9–12]. However, in a recent report of the biopsy findings in 17 patients, authors across four states found no evidence of lipoid pneumonia and opined that the histological changes in the lungs of affected individuals could be a result of chemical pneumonitis along the airways caused by toxic inhalational injury [19].

Despite vigilance in attempts at eliciting reliable substance use histories in our patients, the use of electronic cigarettes was often not known early in the course of our patients' illnesses. Our patients therefore frequently did not receive steroid therapy at presentation or while clinical and laboratory evaluations were being performed to exclude infection, connective tissue disorders and other potential causes. Chest CTs were performed in our patients to evaluate for etiologies such as pneumonia and pulmonary embolus and because of critical illness or clinical deterioration. The CDC now recommends obtaining a chest radiograph in any person with a history of electronic cigarette use who displays respiratory or gastrointestinal symptoms, especially when accompanied by hypoxemia [26]. If the clinical and radiographic findings are consistent with EVALI, a chest CT might not be needed. Chest CTs can be obtained when the radiographic findings are discordant with the clinical picture or when there is a need to evaluate severe or worsening disease [26].

Similarly, while nine of our patients underwent bronchoalveolar lavage, bronchoscopy is not necessary in all patients. Consultation with a pulmonologist might be needed for management of these patients, and the need for bronchoalveolar lavage to exclude other diagnoses should be made by reviewing the individual patient's presentation and illness [26].

The causative agent in EVALI has not been identified [14]. Numerous types of vaping devices are in use today, and users can add many different flavorings to these devices, complicating identification of the causative agent [17, 27]. Initial investigations link most of the cases to THC obtained from informal sources [14]. However, several patients, including some

in our case series, reported vaping only nicotine products [3]. It is worth noting that THC use is illegal in several of the affected states, and people might not feel comfortable revealing their history of THC use for fear of legal repercussions [3]. In the pediatric population, in particular, eliciting a history of any e-cigarette use can be difficult as a result of perceived legal or social ramifications.

Our review has a number of limitations, including small sample size. Several of our patients reported combustible cannabis use, potentially confounding our results. To minimize other confounding factors, we excluded two adolescents with EVALI who had potential intercurrent pulmonary illness. In addition, this was a retrospective review in which the radiologists were not blinded to the clinical information, potentially leading to observer bias.

Conclusion

In our Midwestern teenage population, the recently identified e-cigarette or vaping product use-associated lung injury (EVALI) has demonstrated imaging findings of centrilobular ground-glass nodules and confluent ground-glass opacities with subpleural sparing. The findings are most consistent with acute lung injury resulting from toxic inhalation. Because adolescents might not be forthcoming with their histories of electronic cigarette use, it is important for pediatric radiologists to recognize the imaging hallmarks of this disease entity.

Compliance with ethical standards

Conflicts of interest None

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