DIAGNOSTIC CHALLENGES OF EVALI: A REVIEW OF RADIOLOGICAL AND TOMOGRAPHIC FINDINGS IN E-CIGARETTE USERS

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ABSTRACT
This study aims to examine the specific outcomes of imaging tests, such as radiographs and computed tomography (CT), in patients with E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI). The use of electronic cigarettes (EC), also known as vaporizers, has increased significantly in recent years, particularly among young individuals and adults, due to the perception of them as safer alternatives to traditional cigarettes. However, growing evidence suggests potential lung damage, leading to the recognition of EVALI as a respiratory condition. This pathology has a significant diagnostic challenge due to the wide range of clinical and imaging findings that often resemble other respiratory conditions. In view of this scenario, a comprehensive review of clinical cases and studies published in the CAPES and PubMed Journal Portal database was carried out in order to identify specific patterns and characteristics in radiographs and CT, providing a more comprehensive understanding of the symptoms of EVALI and contributing to the early diagnosis and treatment of these patients.

Keywords: Electronic Cigarette. Image. Lung Injury. Medicine.

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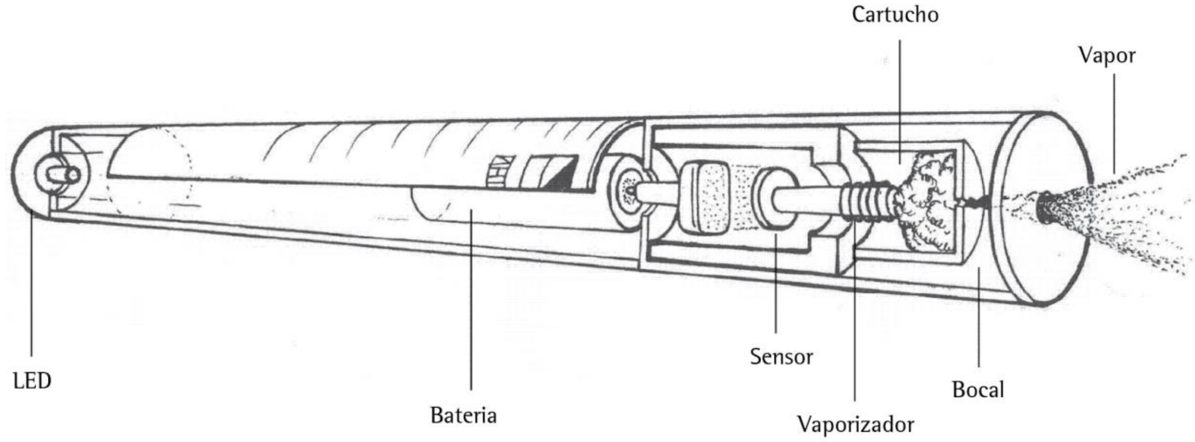
INTRODUCTION

In recent years, the use of electronic cigarettes (EC), also called vaporizers, has grown exponentially, particularly among young people and adults (Grana *et al*., 2014). It consists of three main components, a battery, an atomizer, and a cartridge containing nicotine (Figure 1), providing its users with doses of nicotine and other aerosolized additives (Knorst *et al.,* 2014).

Figure 1: Components of the electronic cigarette.



Source: Knorst *et al.,* 2014 (Adapted). The image illustrates the inner workings of an e-cigarette, highlighting its main components, liquid cartridge, sensor, and the battery.

This increase in the use of ECs is suggested by the widespread perception that they are a safer option compared to conventional cigarettes (Meo *et al*., 2014). However, growing evidence and recent literature underscore that the impacts of these devices on lung health are much more complex and specific than initially assumed (Shields *et al*., 2020). This increase in use has resulted in the emergence of a new serious clinical condition, the so-called Lung Injury Associated with Electronic Cigarette Use (EVALI).

EVALI presents a major diagnostic challenge, as its clinical signs and symptoms are nonspecific, often resembling other respiratory conditions, such as viral infections, atypical pneumonias, and even autoimmune diseases, such as sarcoidosis and hypersensitivity pneumonitis (Stimson *et al*., 2020). The condition can manifest with varied symptoms, such as fever, nausea, dyspnea, chest pain, and even gastrointestinal symptoms, making it difficult to make a differential diagnosis without the use of imaging tests (Morais *et al*., 2020). Since EVALI's initial recognition, researchers and health entities, such as the *Centers for Disease Control and Prevention* (CDC), have made efforts to identify the toxic components present in EC fluids and the mechanisms that cause lung injury. In response to the increase in these cases, the Brazilian Thoracic Association (SBPT) advised pulmonologists to adopt the diagnostic criteria established by the CDC (Chart 1), which include specific imaging findings, such as consolidations on X-rays and ground-glass opacities on chest computed tomography (CT).

Considering the relevance of imaging studies in the evaluation and management of EVALI, it is essential to identify the specific and frequent patterns that can help differentiate this condition from other lung diseases.

Chest X-rays are widely used as an initial examination, especially due to their wide availability and relatively low cost. Although less sensitive, x-ray may indicate diffuse or localized lung opacities, which are suggestive of EVALI in some cases (Kalininskiy *et al*., 2019). CT is the choice when seeking a more thorough condition assessment as it offers a more accurate picture of inspection patterns, including areas of ground-glass opacity and consolidations. In addition, it aids in the differential diagnosis to exclude infectious and autoimmune causes of pulmonary involvement (Helfgott *et al*., 2022).

In this context, this study aims to review the scientific literature on the radiological and tomographic findings of EVALI, gathering available data on the imaging characteristics typical of this condition. The search was carried out in the CAPES and PubMed databases. The analysis focused on detecting typical imaging patterns and describing specific and frequent signs, to facilitate early and accurate diagnosis. By consolidating and systematizing these findings, this study aims to contribute to a deeper understanding of the radiological and tomographic manifestations of EVALI, offering practical assistance to health professionals in the detection and management of the condition, promoting safer and more efficient diagnostic practices.

Table 1 – EVALI diagnostic criteria

Confirmed	Probable
Use of CE in the last 90 days;	Use of CE in the last 90 days;
Consolidations on X-ray or ground-glass CT chest CT;	Consolidations on X-ray or ground-glass CT chest CT;
Absence of alternative diagnoses, such as: Cardialogical, rheumatological, neoplastic diseases, etc. Infectious diseases – make at least a negative viral panel and influenza PCR (if indicated). Other tests (antigens, cultures, HIV), when indicated, must be negative.	Absence of non-infectious alternative diagnoses;
	Identification of infection through culture or PCR, but attending physicians do not believe that this is the only cause of respiratory disease.

Legend: CE = Electronic cigarette; CT = Computed tomography; PCR = Polymerase Chain Reaction; HIV = Human immunodeficiency virus (SBPT, 2019). (Adapted).

METHODOLOGY

The research was carried out through a summarized descriptive analysis of scientific articles published on the PubMed and CAPES Journal Portal platforms in the last five years on the subject. The search was standardized using the descriptors: "EVALI", "diagnostic", "MRI" (*Magnetic Resonance Imaging*), "*computed tomography*" and "x-ray", along with the Boolean operator "And" among the terms.

The selected articles underwent an inclusion metric through *the Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) tool. The inclusion criteria were: a) Studies in which imaging exams were evaluated: radiography and CT; b) Focus of imaging exams on the respiratory system; c) Analysis of individuals who used CE; d) Types of studies with clear and retrospective methodological criteria; e) Studies available free of charge in full; f) Studies published in the last 5 years; g) Studies with a number of patients equal to or greater than 10.

Articles that did not fit the inclusion criteria and proposed publication period were excluded, in order to bring more reliability to the theme studied. In the end, only the studies available in Tables 1 and 2 remained.

RESULTS AND DISCUSSION

Analysis of the studies revealed a broad spectrum of lung anomalies. CT images frequently showed ground-glass opacities, consolidations, and, in some cases, pleural effusions. These findings are consistent with the patterns described in the literature, which relate such anomalies to severe pulmonary inflammation and alveolar lesions caused by substances found in FB fluids (Christiani *et al.*, 2020). The radiographs showed bilateral diffuse opacities, often indistinguishable from those seen in conditions such as viral pneumonia and interstitial lung diseases (Leyden *et al.*, 2020). This overlapping of results shows the complexity of the differential diagnosis of EVALI, highlighting the importance of a careful clinical approach and a detailed history of EC use.

In addition to imaging characteristics, the studies indicated a strong correlation between the severity of the radiological findings and the clinical symptoms reported by the patients. People with more extensive opacities on CT generally had more severe respiratory symptoms, such as severe dyspnea and hypoxemia, reinforcing the importance of imaging as diagnostic and prognostic tools. These findings show the importance of improved diagnostic protocols that include detailed imaging analysis and constant surveillance of clinical symptoms for efficient management of EVALI cases. Tables 1 and 2 below summarize the main CT and X-ray findings in the patients analyzed, respectively.

Table 1 - Analysis of studies that take into account Computed Tomography.

Author	N	Objective	Conclusion
Aberegg *et al.*, 2020.	26	Describe the clinical features, bronchoscopic findings, imaging patterns, and results of EVALI.	- Organizing pneumonia (100%); - Hypersensitivity pneumonitis (19%); - Acute eosinophilic pneumonia (4%); - Subpleural consolidation (39%); - Airway thickening (81%). (Appendix 1)
Artunduaga *et al.*, 2020.	14	To evaluate the chest radiographic and tomographic findings of EVALI in the pediatric population.	- Ground-glass opacity (100%); - Consolidations (64%); - Interlobular septal thickening (14%); - Bilateral abnormalities (100%) - Abnormalities in the lower lobe (50%); - Subpleural preservation (79%).
Kligerman *et al.*, 2021.	160	What are the frequencies of imaging findings and CT patterns in EVALI and what is the relationship to vaporization behavior.	- Ground-glass opacity (81.2%); - Septal thickening (50.6%); - Linfadenopatia (63,1%); - Centrilobular nodule (36.3%); - Pneumonia in parenchymal organization (55.6%); - Pneumonyin airway-centered organization (8.8%); - Pneumonia in mixed organization (20%); - Acute eosinophilic pneumonia (3.8%); - Dano diffuse alveolar (5.6%); - Pulmonary hemorragia (3.8%).
Kalininskiy *et al.*, 2019.	11	Symptoms and Diagnostic Approach at EVALI.	- Bilateral ground-glass opacification (100%); - Subpleural preservation (64%); - Derrame pleural (9%); - Linfadenopatia mediastinal (27%);
Rao *et al.*, 2020.	13	To show the clinical characteristics of lung injury associated with the use of electronic cigarettes or vaping in adolescents.	- Ground-glass opacities (100%); - Lung bases greater than pulmonary apex (46%); - Thickening of the interlobular septa (15%); - Pneumomediastino (15%).
Panse *et al.*, 2020.	24	To characterize the CT appearance of lung injury associated with the use of e-cigarette or vaping product (EVALI) in a cohort with histopathologic evidence of this disorder.	- Ground-glass opacity (96%); - Consolidations (42%); - Interlobular septal thickening (29%); - Low lobular attenuation (46.1%); - Multifocal findings (54%); - Peripheral findings (17%); - Central findings (8%); - Centrilobular ground-glass opacity nodules similar to hypersensitivity pneumonitis (33%); - Organizing pneumonia (13%). (Appendix 1)

Werner *et al.*, 2020.	47	We compared the characteristics of patients with fatal cases of EVALI with non-fatal cases to improve the ability to identify patients at increased risk of death from the disease.	- Ground-glass opacities (100%); - Opacities (64%); - Diffuse infiltrate (30%); - Pneumonia (34%); - Consolidations (23%); - Edema (19%); - Pneumonite (15%); - Adenopatia (hilar ou mediastinal)(19%); - Pneumothorax (2%).

Caption: Appendix 1 states that Aberegg *et al.* (2020) and Panse *et al.* (2020) considered in their study. N=Number of participants.

Table 2 - Analysis of studies that take into account Radiography.

Author	N	Objective	Conclusion
Artunduaga *et al.*, 2020	14	To evaluate the chest radiographic and tomographic findings of EVALI in the pediatric population.	- Ground-glass opacity (100%); - Consolidations (57%); - Bilateral abnormalities (100%); - Symmetrical abnormalities (93%); - Extent of abnormality greater than 75% (29%); - Extent of abnormality between 50%–75% (36%); - Extent of abnormality 25%–50% (29%); - Extent of abnormality less than 25% (7%); - Pneumomediastino (7%); - Bilateral pleural spills (7%).
Chidambaram *et al.*, 2020.	11	To present clinical and imaging findings in adolescents with pulmonary symptoms of suspected EVALI.	- Ground-glass opacities (100%); - Bilateral opacities (45%); - Baseline predominance of abnormalities (82%); - Alveolar opacities (45%).
Kalininskiy *et al.*, 2020.	11	Symptoms and Diagnostic Approach at EVALI.	- Bilateral ground-glass opacification (100%); - Derrame pleural (9%); - Fibrotic characteristics
Werner *et al.*, 2020.	56	To compare the characteristics of patients with fatal cases of	- Opacities (59%); - Ground-glass opacities (11%); - Diffuse infiltrate (52%); - Pneumonia (29%);
		EVALI with non-fatal cases to improve the ability to identify patients at increased risk of death.	- Consolidations (20%); - Edema (32%); - Pneumonite (4%); - Pneumothorax (2%).
Rao *et al.*, 2020.	13	Clinical characteristics of lung injury associated with e-cigarette use or vaping in adolescents.	- Ground-glass opacities (100%), - Radiograph with subtle findings that showed markedly abnormal pulmonary findings on chest computed tomography (15%).

Legend: N=Numbers of participants

Comparison between the studies reveals differences and similarities in imaging findings. CT allows for greater detail, with a high prevalence of ground-glass opacities, ranging from 81.2% to 100% of cases (Aberegg *et al.*, 2020; Layden *et al.*, 2020; Kligerman *et al.*, 2021). CT also allows the identification of specific features, such as interlobular septal thickening and subtle centrilobular nodules, associated with organizing pneumonia, hypersensitivity pneumonitis, and other inflammatory patterns (Artunduaga *et al.*, 2020; Panse *et al.*, 2020). In addition, less common complications, such as pulmonary hemorrhage and diffuse alveolar damage, have been documented in some studies that obtained CT, highlighting the sensitivity of this method to identify discrete and different changes at each stage of the disease.

Regarding chest X-rays, although it presents less detail compared to CT, it is still effective for identifying ground-glass opacities, especially in more advanced and bilateral presentations, as reported by Kalininskiy *et al.* (2020) and Werner *et al.* (2020). The findings are more general, such as bilateral opacities, consolidations, and diffuse infiltrates, with a lower frequency of specific and subtle findings (Artunduaga *et al.*, 2020). Comparing CT with radiography, the reduced ability to visualize discrete or specific alterations, such as centrilobular nodules and interlobular septal thickening, which were better detected by CT, is evident.

A highlight among the studies is the variability in the identification of serious complications. While CT scans show complications such as pneumothorax and pneumomediastinum in detail, X-rays may not show abnormal pulmonary findings, as noted by Rao *et al.* (2020), who reports that 15% of patients with subtle chest X-ray findings had marked pulmonary findings on CT.

As weaknesses found, we observed the difference in the sample between the studies and the variation in the methods of analysis, since radiography and CT are interpretative exams. The need for future investigations with larger cohorts and longitudinal analyses, additional studies can further assess the progression of lesions and response to treatment.

In short, CT is more sensitive to detect the diversity of EVALI findings and variations, providing a more complete assessment of lesions and their distributions. Although useful as an initial examination, radiography has limitations, especially for milder manifestations, due to its availability. This comparison underscores the importance of using CT in suspected cases of EVALI, where radiography does not provide a conclusive diagnosis.

CONCLUSION

This study analyzed the scientific literature on the radiological and tomographic findings of EVALI, with the objective of recognizing common and frequent imaging patterns that may contribute to the diagnosis of this condition. The analysis revealed that the most frequent CT findings are ground-glass opacities and interlobular septal thickening, and the data revealed the important role of CT in identifying pulmonary alterations, due to its high sensitivity. Regarding radiography, CT offers a more accurate and detailed view of pulmonary irregularities, being more accurate and efficient.

Radiography, despite being useful as an initial examination, especially to identify consolidations and more evident opacities, has limitations in the detection of more discrete and specific alterations. Therefore, for an accurate and efficient diagnosis, the use of CT is recommended, especially in complex clinical situations. These findings highlight the importance of imaging tests in the diagnosis of EVALI and other respiratory conditions, such as viral pneumonia and interstitial lung diseases.

Thus, it is worth emphasizing the need for more improved diagnostic protocols, which include both detailed imaging tests and the complete clinical history of patients. It is crucial to conduct future studies with more extensive bases, randomized controlled trials, and longitudinal analyses, to assess lesion progression and response to treatment, contributing to a deeper diagnostic understanding of EVALI, as well as improving diagnostic and therapeutic practices.

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APPENDIX

APPENDIX 1

Appendix 1 - CT classification scheme used by Aberegg *et al.,* 2020 and Panse *et al.,* 2020.

Standard Classification Method	Classification method
Organizing Pneumonia	irregular, peripheral, or perilobular bilateral UFOs or consolidation; reverse halo sign;
Hypersensitivity Pneumonitis	OVFs predominant in the upper or middle lung; centrilobular nodules; air trapping
Acute eosinophilic pneumonia	bilateral and symmetric UFOs or consolidation; pleural effusions; septal thickening;
Acute Lung Injury	Acute phase - heterogeneous consolidation; OVFs; dependent on disorganized paving;
	Organization phase - development of reticulation and traction bronchiectasis;
Hemorragia Alveolar Difusa	Centrilobular nodules; OVFs; consolidation; subpleural preservation;
Lipoid Pneumonia, Exogenous	Dependent distribution; OVFs; consolidation; disorganized paving; Fat attenuation macroscópica, ≤30 HU;
Interstitial Giant Cell Pneumonia	OVFs; architectural distortion; peribronchiolar linear opacities;
Thickening of the airway wall	Qualitative visual analysis.

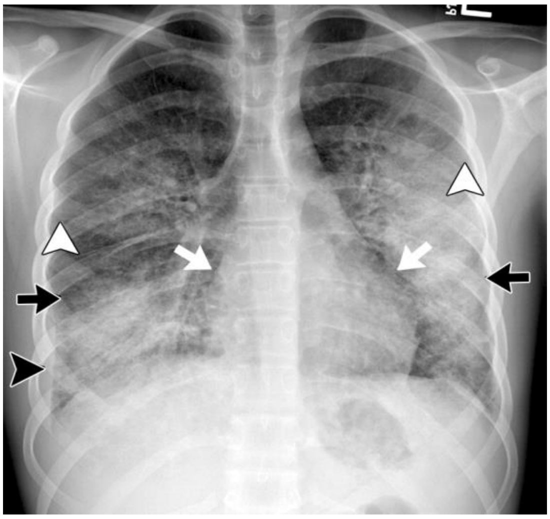
Legend: OVF= Ground-Glass Opacities; HU=Hounsfield units (Aberegg *et al.*, 2020) - Translated (adapted).

APPENDIX 2

Clinical case examples of evali with ct and radiography:

Case 1: The images show an 18-year-old man with EVALI. A pattern of organizing pneumonia is observed.

Image A1: Posteroanterior radiograph shows consolidation and opacity of the middle and lower lung bilaterally. Small right pleural effusion (black arrowhead) and septal thickening (white arrowhead) are seen. There is preservation of the cardiac borders (white arrows) as well as subpleural portions of the lung (black arrows).



B1 and C1 images: Coronal B1 and sagittal oblique C1 CT images illustrate the radiographic findings with light ground-glass opacity predominant in the lower lung with few areas of consolidation. There is prominent subpleural and perilobular preservation (black arrows). In addition, there is preservation of the peribronchovascular interstitium, best illustrated around the arteries and larger pulmonary veins (white arrows). Centrilobular nodules predominantly ground-glass in the upper lobe are present bilaterally (white arrowheads). Apart from the thickening of the interlobular septa, there are few areas with thickening of the intralobular septa creating a "mosaic pavement" pattern (black arrowheads).

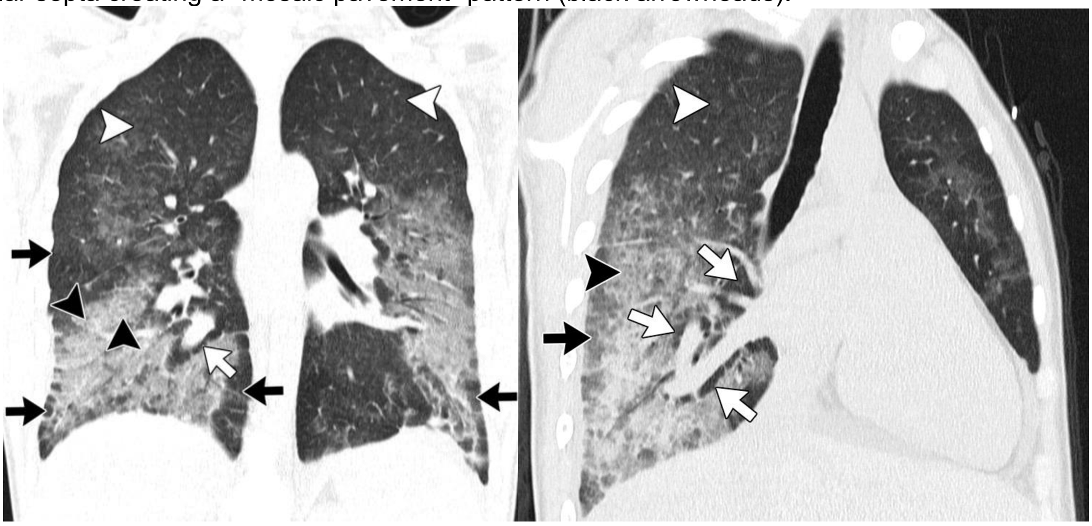


Image D1: Chest X-ray three days after the start of corticosteroids, the patient showed dramatic clinical and radiographic improvement.

Case 2: Images show EVALI with a pattern of organizing pneumonia in an 18-year-old man who vaporized nicotine and tetrahydrocannabinol with a fever of 39.4°C, vomiting for 3 days, and negative tests for infection and rheumatologic disease.

Image A2: Posteroanterior radiograph shows a predominant perihilar cloudy opacity with preservation of the edge of the heart (white arrows) and periphery (black arrows). Septal thickening is present (arrowhead).

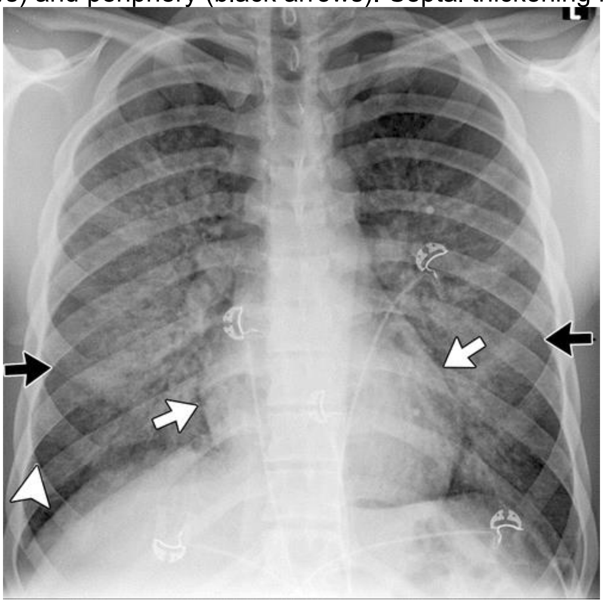
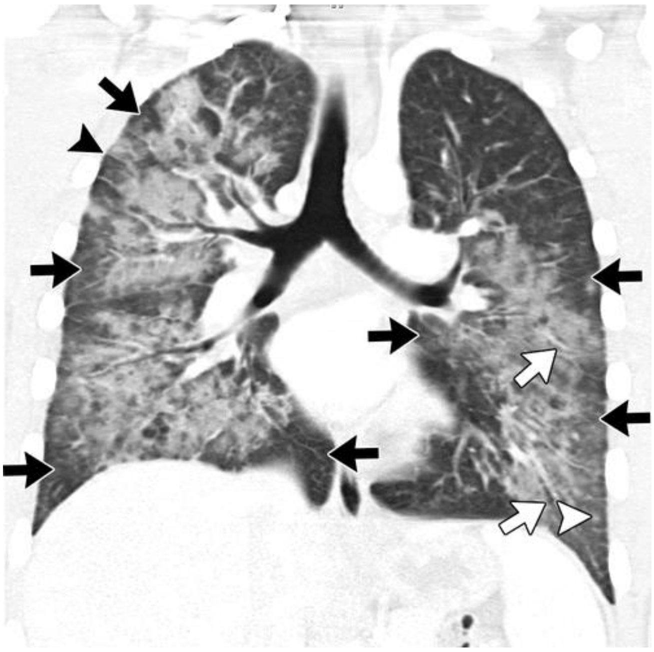


Image B2: CT image shows perihilar predominant ground-glass opacity with prominent preservation of the subpleural interstitium both peripherally and centrally (black arrows) with interspersed areas of lobular preservation. The peribronchovascular interstitium (white arrows) is preserved. Septal thickening (black arrowhead) and scattered centrilobular nodules are present (white arrowhead). The patient improved rapidly after administration of corticosteroids.



Case 3: Images show lung injury associated with the use of e-cigarettes or vaping products in a 37-year-old man with a history of daily vaping of tetrahydrocannabinol products.

Image A3: Coronal CT image shows diffuse ground-glass opacity with subpleural preservation (arrows) and interlobular and intralobular septal thickening creating a "mosaic pavement" pattern (arrowhead). On this initial CT scan, it is unclear whether this represents organizing pneumonia or an initial exudative phase of diffuse alveolar damage. The patient's condition worsened dramatically with progressive consolidation and loss of volume, requiring intubation.

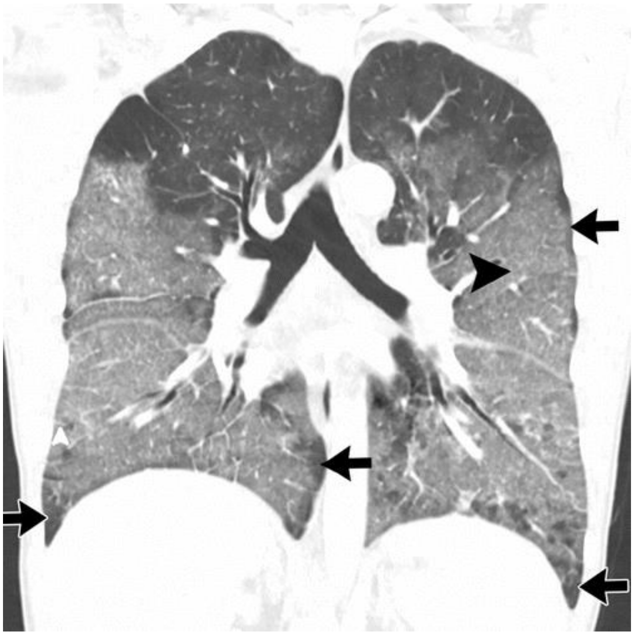
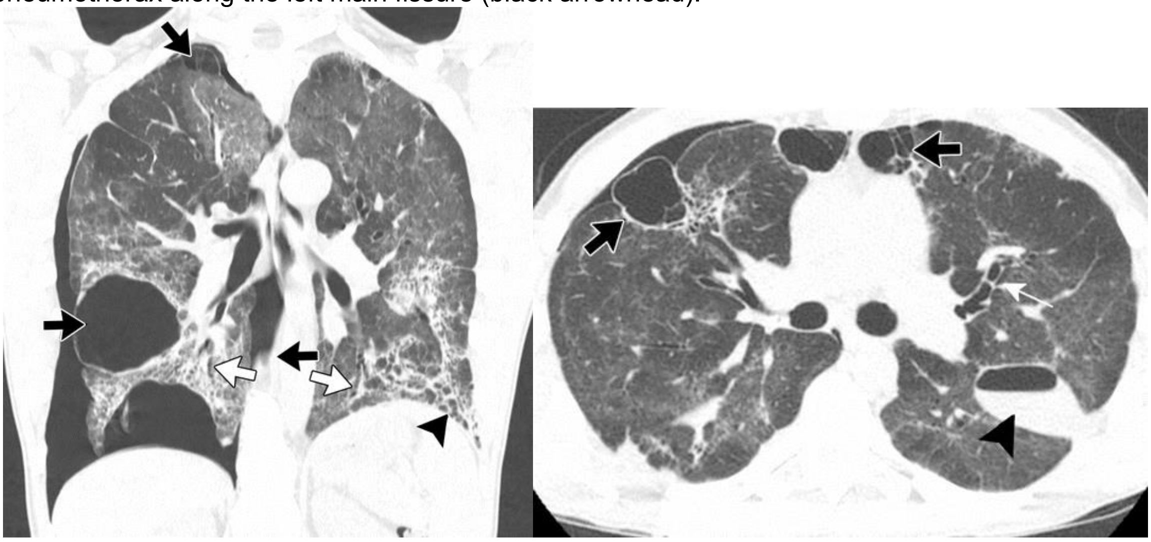


Image B3 and C3: Coronal B3 and axial C3 CT scan, 14 days after image A, showing improvement in ground-glass opacity with development of fibrosis predominant in the lower lobe with reticulation (black arrowhead in B3), bronchiectasis (white arrows), and loss of volume. In addition, there was the development of numerous blisters of varying sizes bilaterally (black arrows), moderately sized right pneumothorax, and loculated hydropneumothorax along the left main fissure (black arrowhead).



Case 4: Images show EVALI with acute eosinophilic pneumonia in a 21-year-old man who was vaping nicotine and tetrahydrocannabinol products daily.

Image A4: Posteroanterior radiograph 2 days after admission, showing extensive consolidation.

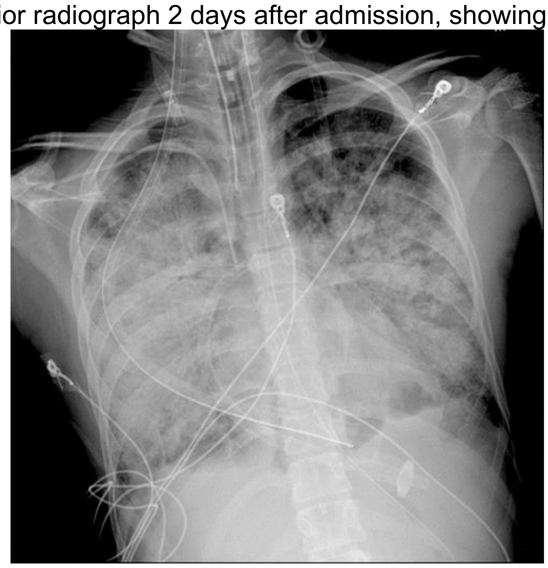


Image B4: Presence of extensive consolidation with areas of lobular and subpleural preservation (black arrowhead), with diffuse alveolar damage, septal thickening (white arrow), moderate to large bilateral pleural effusions, and normal-appearing left ventricle (black arrow), showing acute eosinophilic pneumonia. The patient's clinical condition and radiographic image (Image A4) continued to worsen, and he was subsequently intubated. The patient underwent bronchoscopy, which showed a large percentage of eosinophils.

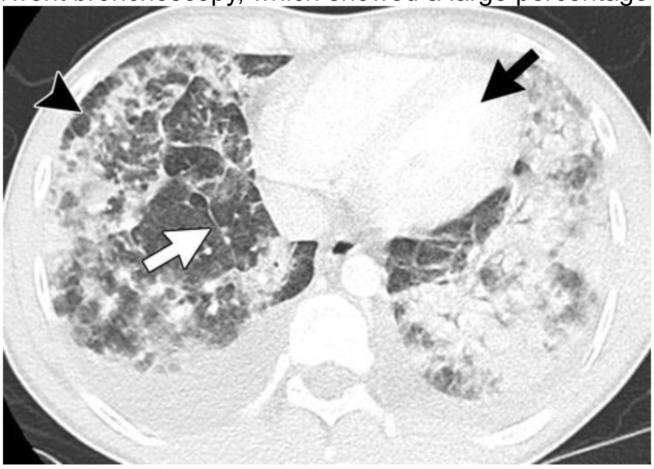
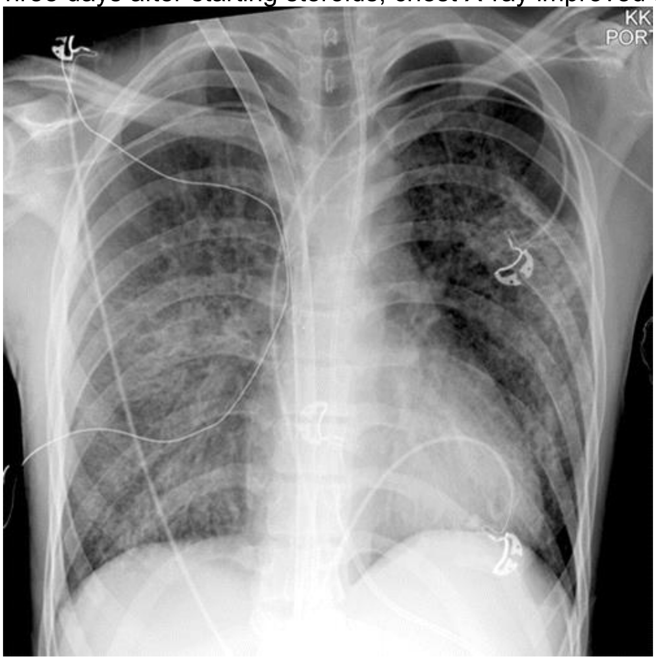


Image C4: Three days after starting steroids, chest X-ray improved significantly.



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