February 2020 Imaging Case of the Month: An Emerging Cause for Infiltrative Lung Abnormalities

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Clinical History: A 25-year-old man with no previous medical history presented to the Emergency Room with complaints of worsening non-productive cough and fever to 102°F over the previous 7 days. The patient also complained of some nausea, vomiting, and generalized muscle aches. The patient denies rhinorrhea, sore throat, congestion, and diarrhea. The patient also illicit drug use, and drinks alcohol only occasionally. He said he previously smoked 1-2 packs-per day, having quit 6 months earlier.

The patient's physical examination showed normal vital signs, although his respiration rate was approximately 18/minute. The physical examination showed some mild basilar crackles bilaterally, but was otherwise entirely within normal limits.

Basic laboratory data showed a white blood cell count near the upper of normal= 10.3×10^9 / L (normal, $4–10.8 \times 10^9$/L) with a normal platelet count and no evidence of anemia, normal serum chemistries and renal function parameters, and normal liver function tests. The patient was referred for chest radiography (Figure 1).
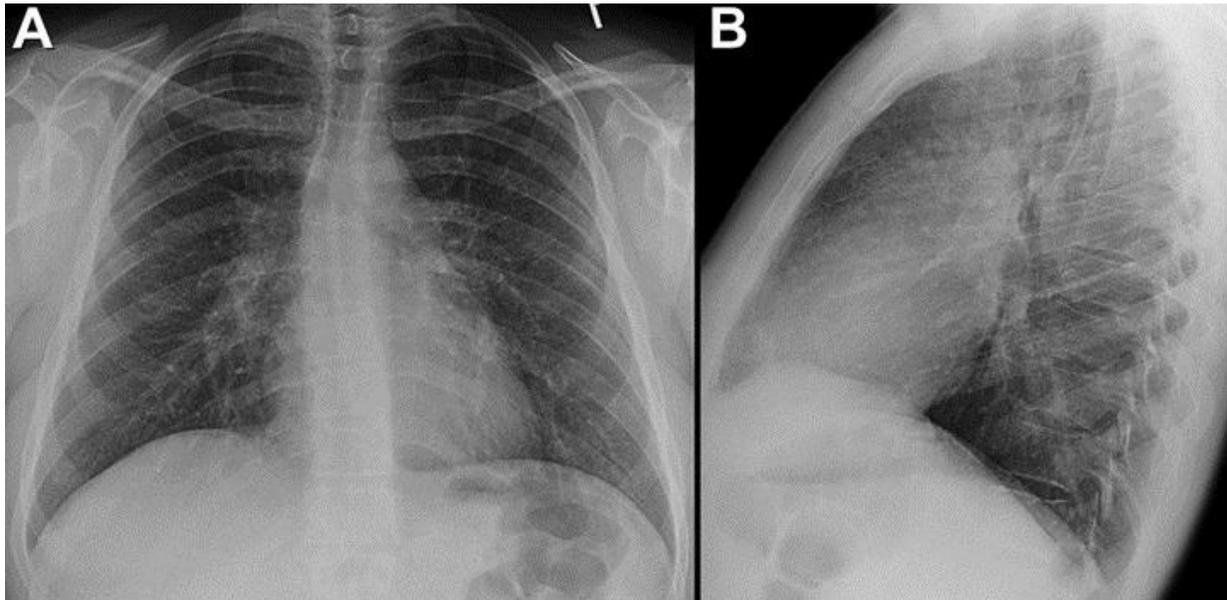

Figure 1. Frontal (A) and lateral (B) chest radiography at presentation.

Which of the following statements regarding the chest radiograph is ***most accurate***?

1. The chest radiograph shows bilateral consolidation
2. The chest radiograph shows findings suggesting increased pressure pulmonary edema
3. The chest radiograph shows mediastinal and peribronchial lymph node enlargement
4. The chest radiograph shows mild perihilar infiltration
5. The chest radiograph shows normal findings

Correct!
4. The chest radiograph shows mild perihilar infiltration

Frontal and lateral chest radiography shows mild increased linear opacities radiating from the hila centrally, bilaterally, consistent with "perihilar infiltration." The findings are subtle and non-specific. Occasionally increased pressure pulmonary edema can appear fairly similar, but typically peripheral interlobular septal thickening- Kerley "B" lines- are also evident in such patients. Furthermore, there may be pleural effusions and the heart size may be increased when increased pressure pulmonary edema is present, and these findings are lacking in this young patient. No consolidation is seen, nor is clear evidence of peribronchial and mediastinal lymphadenopathy.

Which of the following courses of action is the **_most appropriate next step_** for the management of this patient?

1. [18]FDG-PET scanning
2. Bronchoscopy with transbronchial biopsy
3. Cardiac MRI
4. Conservative management
5. CT pulmonary angiography

Correct!
4. Conservative management

Given the patient's young age and absence of apparent co-morbidity or complicating factors, conservative management with clinical follow-up is appropriate. [18]FDG-PET scanning is premature at this point, and the results of [18]FDG-PET are unlikely to alter the approach to the patient's management. Furthermore, typically, results from [18]FDG-PET scanning are interpreted in the context of the imaging findings at chest CT and the latter has yet to be performed. Invasive diagnostic testing is also premature at this point, and the patient's presenting complaints are not suggestive of acute pulmonary embolism, nor were risk factors for such identified. No features to suggest cardiac disease are present in the patient's history, physical examination, laboratory data, or at chest radiography to suggest a need for cardiac MRI.

The patient's chest radiograph was interpreted as normal. He was discharged from the emergency room with a prescription for broad-spectrum antibiotics. Subsequently he returned to the Emergency Room 3 days later with complaints similar to his initial presentation. Repeat laboratory data showed slight elevation in the white blood cell count, now abnormal at 12.4×10^9 / L (normal, 4-10.8 $\times 10^9$ / L). Repeat chest radiography (Figure 2) was performed.
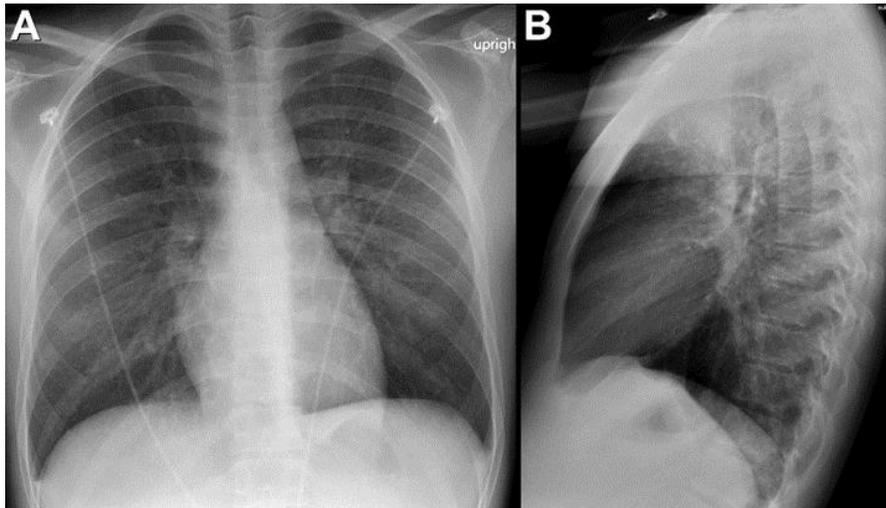

Figure 2. Frontal (A) and lateral (B) chest radiography at re-presentation.

Which of the following statements regarding the repeat chest radiograph is ***most accurate***?

1. The chest radiograph appears relatively unchanged
2. The chest radiograph shows new areas of consolidation
3. The chest radiograph shows new small pleural effusions
4. The chest radiograph shows normal findings
5. The chest radiograph shows worsening of the previous findings of perihilar infiltration

Correct!
1. The chest radiograph appears relatively unchanged

The repeat chest radiograph appears relatively unchanged. Mild perihilar infiltration may again be present, although even more difficult to appreciate on the repeat radiograph as the lung volumes are improved compared with the presentation chest radiograph (Figure 1); the repeat chest radiograph is arguably normal. No areas of consolidation are present and no pleural effusion is seen. The heart and mediastinal contours appear normal.

The patient was slightly more tachypneic (respiratory rate = 20 / minute) than his previous presentation, and he still complained of nausea and vomiting. The patient was admitted for presumed dehydration owing to his respiratory illness.

Which of the following courses of action is the **_most appropriate next step_** for the management of this patient?

1. Coccidioidomycosis testing
2. Pulse oximetry
3. Respiratory virus panel
4. Urinary Legionella antigen testing
5. All of the above

Correct!
5. All of the above

The patient's presentation appears consistent with an acute respiratory illness and, given his young age and absence of any complicating history, is very likely infectious in nature. Therefore, testing for respiratory pathogens as well as assessing his oxygenation is appropriate.

Testing for a number of respiratory viruses, including influenza A and B, various coronaviruses, human metapneumovirus, adenovirus, various parainfluenza viral strains, *Bordetella pertussis* and *parapertussis*, *Chlamydophilia pneumoniae* and *Mycoplasma pneumoniae* were all negative. Coccidioidomycosis testing as also unrevealing- both IgM and IgG were negative. HIV testing was also negative.

Which of the following courses of action is the ***most appropriate next step*** for the management of this patient?

1. Bronchoscopy
2. Chest CT
3. Chest MRI
4. Echocardiography
5. Repeat chest radiography

Correct!
2. Chest CT

Chest CT is reasonable as the patient appears to have a respiratory illness, but with few, and very-nonspecific, chest radiographic findings, and no clinical data to indicate an etiology. Chest MRI can be useful in selected circumstances, such as characterization of thymic lesions, but has little value for lung parenchymal assessment. Echocardiography is not unreasonable, but probably unnecessary as the patient is young and is not displaying features that suggest myocarditis or cardiac failure. Repeat chest radiography is unlikely to yield additional information to that already known through the 2 previous chest radiographs. Bronchoscopy may play a role in this patient's assessment, but is premature at this point; chest CT may provide information to direct any tissue sampling procedures and should be performed first.

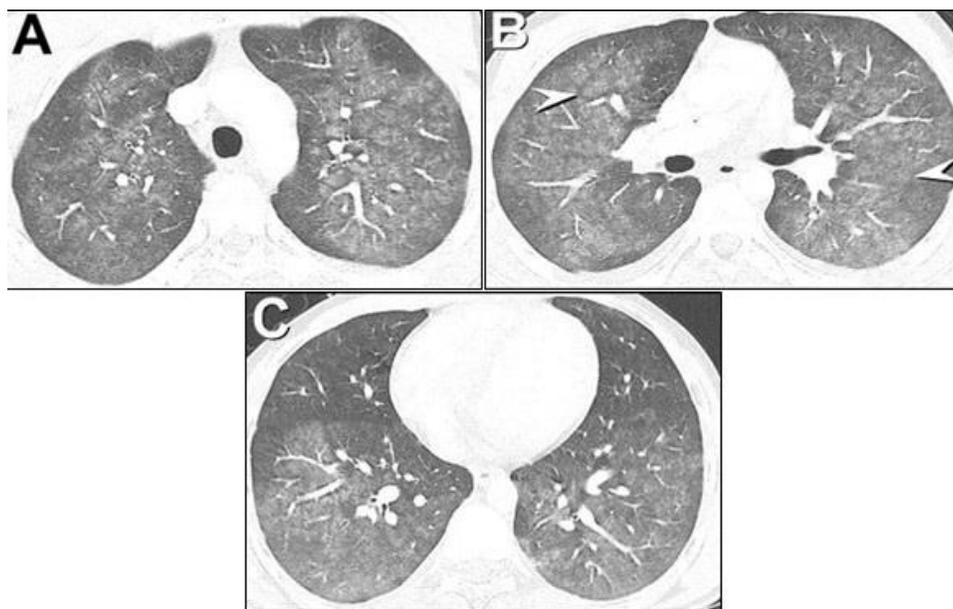Clinical Course: Chest CT (Figure 3) was performed.

Figure 3. Representative images from axial unenhanced chest CT displayed in lung windows.

Which of the following statements regarding the chest CT is ***most accurate***?

1. The chest CT shows bilateral ground-glass opacity associated with smooth interlobular septal thickening
2. The chest CT shows multifocal peripheral ground-glass opacity and faintly nodular opacities
3. The chest CT shows numerous small pulmonary cavities
4. The chest CT shows pleural effusion
5. The chest CT shows traction bronchiectasis, reticulation, and honeycombing consistent with fibrotic lung disease

Correct!
2. The chest CT shows multifocal peripheral ground-glass opacity and faintly nodular opacities

The chest CT shows multifocal bilateral areas of ground-glass opacity, in some areas with a faintly centrilobular nodular appearance. No consolidation or pleural effusion is present. Note the small rim of relatively "spared" lung around the lobular areas of ground-glass opacity (arrowheads). There are no features to suggest fibrotic lung disease, such as reticulation, traction bronchiectasis, or honeycombing. While ground-glass opacity is present, it is not associated with interlobular septal thickening.

The patient's fever and shortness of breath persisted despite broad spectrum antibiotic therapy.

Which of the following courses of action is the ***most appropriate next step*** for the management of this patient?

1. Chest CT
2. Echocardiography
3. Surgical lung biopsy
4. Upper endoscopy
5. Urinalysis

Correct!
1. Chest CT

Among the choices listed, given the persistence of as yet unexplained symptoms, a repeat chest CT is reasonable and is the most appropriate among the listed choices. Echocardiography is probably of little value given the patient's young age, lack of findings on imaging or laboratory data suggesting a cardiac etiology for the patient's complaints, although it certainly would not be wrong to obtain cardiac functional evaluation in this setting. Upper endoscopy, however, is probably of little benefit as none of the patient's symptoms or imaging findings have not been suggestive of a gastrointestinal abnormality. Surgical lung biopsy would certainly be of great help in determining the cause of the patient's infiltrative lung abnormalities, but is needlessly invasive at this point as bronchoscopy has yet to be performed.

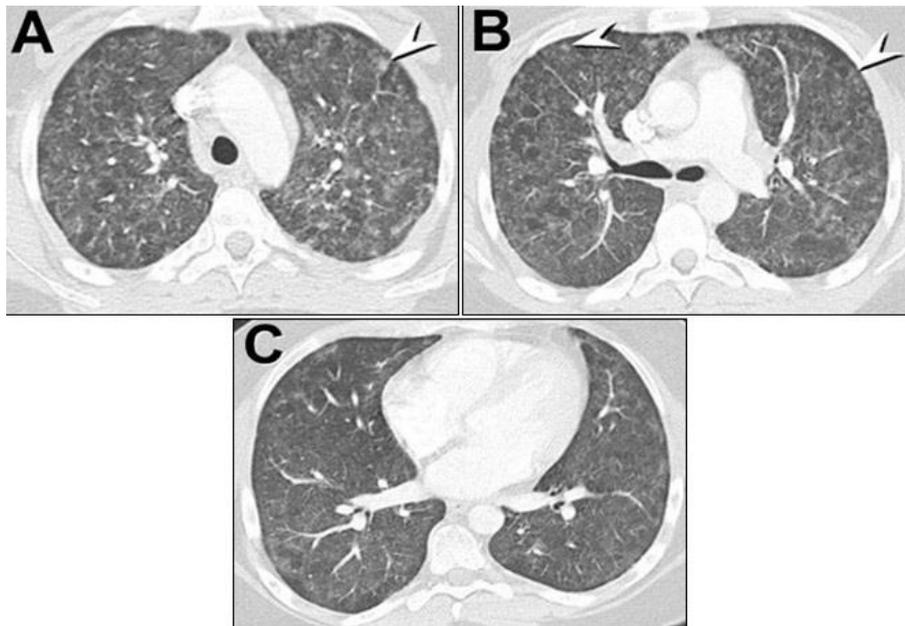The chest CT was repeated (Figure 4).

Figure 4. Representative images from repeat axial unenhanced chest CT displayed in lung windows.

Regarding the follow up chest CT (Figure 4), which of the following statements is ***most accurate***?

1. The chest CT shows multifocal areas of ground-glass opacity with areas of lobular low attenuation
2. The chest CT shows new areas of cavitation
3. The chest CT shows new areas of consolidation
4. The chest CT shows progression of the previous bilateral pulmonary ground-glass opacity
5. The chest CT shows resolution of the previous abnormalities and is now normal

Correct!
1. The chest CT shows multifocal areas of ground-glass opacity with areas of lobular low attenuation

The chest CT shows multifocal ground-glass opacity in some areas now with a more centrilobular nodular appearance (arrowheads). The CT is very similar to previous, perhaps even slightly regressed in the bases. However, areas of lobular low attenuation are now more conspicuous, suggesting some element of small airway obstruction. No new consolidation or cavitation is evident.

The patient underwent additional testing, including anti-nuclear antibody, cytoplasmic anti-neutrophil cytoplasmic antibodies, and HIV testing, all of which were negative.

Based on these data and the appearance of the most recent chest CT, which of the following is the **_most likely_** diagnosis for this patient?

1. Diffuse alveolar hemorrhage
2. Hypersensitivity pneumonitis
3. Opportunistic infection
4. Organizing pneumonia
5. Sarcoidosis

Correct!
2. Hypersensitivity pneumonitis

The presence of multifocal ground-glass opacity with features of small airway obstruction is a pattern associated with, though not absolutely specific for, hypersensitivity pneumonitis; this pattern of infiltrative and obstructive pulmonary abnormalities on the same inspiratory scan image has been referred to as the "headcheese" sign. Diffuse alveolar hemorrhage is also a consideration for multifocal ground-glass opacity, but would not explain the conspicuous feature of lobular low attenuation, which suggests small airway obstruction. The imaging appearance is not suggestive of sarcoidosis, which more commonly presents with symmetric peribronchial and mediastinal lymph node enlargement, perilymphatic nodules, and/or upper lobe fibrotic disease/opportunistic infection can present with multifocal ground-glass opacity-particularly *Pneumocystis jirovecii* pneumonia- but the patient is not immunocompromised, which makes this infection, and other opportunistic infections, very unlikely. Organizing pneumonia is a consideration, but typically manifests as multifocal consolidation, possibly some ground-glass opacity, distributed in the peripheral or frankly subpleural regions of lung or along the bronchovascular bundles; additionally, organizing pneumonia may present with the "atoll" or "reverse [ground-glass] halo" sign. In this case, however, the opacities are multifocal, or nearly diffuse, in distribution, and do not show a peripheral or peribronchial distribution, and are therefore not directly suggestive of organizing pneumonia.

At this point, which of the following courses of action is the ***most appropriate next step*** for the management of this patient?

1. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy
2. Cryobiopsy
3. Open surgical lung biopsy
4. Video-assisted thoracoscopic surgical lung biopsy
5. More than one of the above

Correct!
1. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy

Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy is arguably the most appropriate choice among those listed, but both cryobiopsy and video-assisted thoracoscopic surgical lung biopsy are appropriate choices as well. Open surgical lung biopsy is not a good choice as the desired information can be obtained through more than one of the other methods listed with less expense and morbidity.).

The patient underwent bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. The lavage fluid was clear, showing 35% neutrophils, 21% lymphocytes, and 39% alveolar macrophages with no features of current or previous hemorrhage. The lavage fluid did not show evidence of eosinophilia (5%). The transbronchial biopsy fragments were small, showing a mixed interstitial cellular infiltrate and intra-alveolar fibrin.

Which of the following courses of action is the ***most appropriate next step*** for the management of this patient?

1. ^{18}FDG-PET scanning biopsy
2. Open surgical lung biopsy
3. Repeat bronchoscopy with bronchoalveolar lavage and transbronchial
4. Repeat chest CT
5. Video-assisted thoracoscopic surgical lung biopsy

Correct!
5. Video-assisted thoracoscopic surgical lung biopsy

A larger pulmonary tissue sampling procedure capable of providing histopathological analysis, such as video-assisted thoracoscopic lung biopsy, is the next most appropriate step. Cryobiopsy could be considered here as well but was not offered as a choice. ^{18}FDG-PET scanning would add little management-altering information to this situation because whether or not the pulmonary opacities show elevated tracer utilization is irrelevant- a tissue sampling procedure is required for diagnosis at this point. Furthermore, ^{18}FDG-PET scanning is typically employed for staging known or suspected malignancies or for characterization of indeterminate lung nodules, and neither situation is the case here. Open surgical lung biopsy is not a good choice as the desired information can be obtained through video-assisted thoracoscopic lung biopsy with less expense and morbidity. Repeating either the chest CT or bronchoscopy is unlikely to add new or management-altering information at this juncture.

The patient underwent video-assisted thoracoscopic lung biopsy which showed acute and organizing lung injury with interstitial edema, type II pneumocyte hyperplasia, intra-alveolar fibrin deposition, acute fibrinous pneumonitis, lipid-laden macrophages, and foci of organizing pneumonia, associated with an inflamamtory cellular infiltrate composed of neurtrophils and lymphocytes. Finely vacuoloated foamy macrophages with similar foamy change in the cytoplasm of type II pneumocytes were also present.

At this point, which of the following represents **_most likely_** diagnosis for this patient?

1. Acute eosinophilic pneumonia
2. Acute interstitial pneumonia
3. E-cigarette / vaping-associated lung injury
4. Lipoid pneumonia
5. Undeclared connective tissue disorder

Correct!
3. E-cigarette / vaping-associated lung injury

While it is difficult to completely exclude a pulmonary manifestation of an as-yet undeclared connective tissue disorder, the patient's symptoms are not particularly suggestive of such- he has not complained of joint pain or stiffness or other similar rheumatological complaints, not is there clinical or laboratory evidence of such. The lack of eosinophilia on bronchoalveolar lavage and at lung biopsy excludes the diagnosis of acute eosinophilic pneumonia. Acute interstitial pneumonia is technically possible, but no evidence of hyaline membrane formation was seen at lung biopsy. The diagnosis of lipoid pneumonia can be made when foci of macroscopic fat are seen within areas of ground-glass opacity or consolidation at chest CT (not the case for this patient), or when pulmonary tissue sampling shows variably-sized fat droplets associated with a foreign body giant cell reaction; lipid-laden macrophages, however are, by themselves, very non-specific, and can be seen in lung biopsies of patients with patients with infections, drug reactions, and autoimmune disorders. Therefore, the diagnosis of lipoid pneumonia should not be suggested solely on the basis of the presence of lipid-laden macrophages at lung biopsy. However, at lung biopsy, the presence of foamy macrophages and similar foamy change in type II pneumocytes in the presence of acute lung injury has been considered suggestive of e-cigarette / vaping-associated lung injury.

With the biopsy information in hand, the patient was questioned regarding e-cigarette use / vaping. He admitted to vaping tetrahydrocannabinol containing "pods" over the previous 6 months in an effort to quit combustible tobacco smoking. In the month prior to presentation he had accelerated his vaping to stave off cigarette cravings. The patient's antibiotic therapy was withdrawn and corticosteroids were begun. After 2-3 days, the patient's symptoms improved and chest radiography (Figure 5) was repeated.
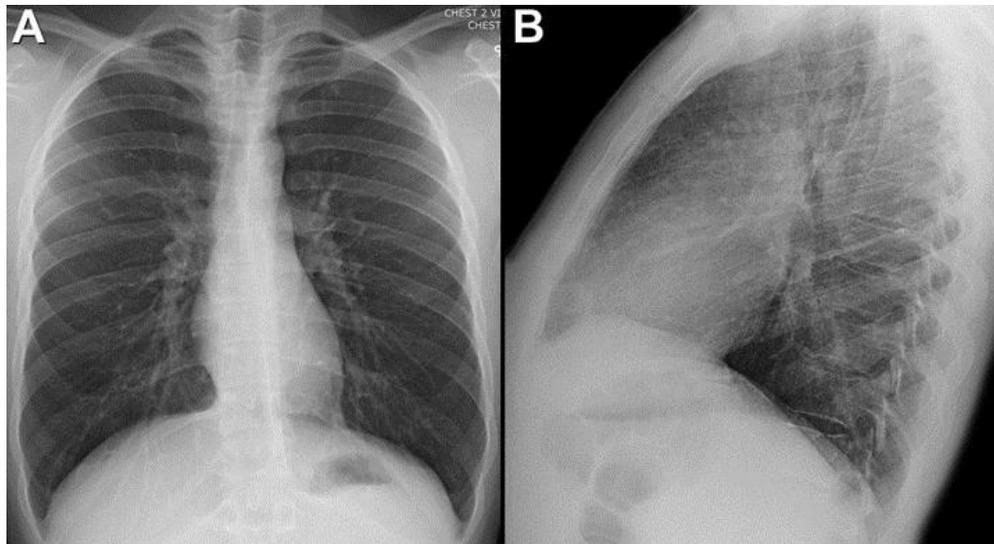

Figure 5. Frontal (A) and lateral (B) chest radiography performed just over a week following initial presentation.

Regarding the follow up chest radiograph (Figure 5), which of the following statements is **_most accurate_**?

1. The chest radiograph appears relatively unchanged
2. The chest radiograph shows new areas of consolidation
3. The chest radiograph shows new small pleural effusions
4. The chest radiograph shows normal findings
5. The chest radiograph shows worsening of the previous findings of perihilar infiltration

Correct!
4. The chest radiograph shows normal findings

The chest radiograph now appears clear. The previous abnormal findings have entirely resolved.

Diagnosis: e-cigarette or vaping associated acute lung injury

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