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Case 25-2020: A 47-Year-Old Woman with a Lung Mass

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PRESENTATION OF CASE

Dr. Jonathan E. Eisen: A 47-year-old woman presented to this hospital early during the pandemic of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), because of cough and shortness of breath.

The patient had been well until 2 months before this evaluation, when intermittent nonproductive cough and wheezing developed. She had no fever, chills, or shortness of breath. Two days before this evaluation, the cough worsened in frequency and severity and new shortness of breath developed. The patient was evaluated by her primary care physician by telephone call. Humidification, fluticasone nasal spray, and fexofenadine were recommended, as was a follow-up telephone call in 2 weeks.

However, the next day, the patient sought evaluation at the emergency department of this hospital because of worsening shortness of breath with ambulation. A review of systems was notable for rhinorrhea, myalgias, and dizziness. She had no fever, chills, sore throat, chest pain, nausea, vomiting, abdominal pain, diarrhea, leg swelling, or weight loss.

The patient had a history of eczema and gestational diabetes. Medications included azelastine nasal spray, fluocinonide cream, folate, and ferrous sulfate; she had not yet begun to use the fluticasone nasal spray and fexofenadine that had been newly recommended by her primary care physician. There were no known drug allergies. The patient was originally from the equatorial region of South America and had moved to the United States 20 years earlier; she had not traveled outside the United States in many years. She lived in an apartment in an urban area of New England with her husband and five children. She did not drink alcohol, smoke tobacco, or use illicit drugs. Her mother had had diabetes and melanoma.

On examination, the temperature was 38.0°C, the heart rate 100 beats per min-

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ute, the blood pressure 124/64 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. She appeared to be well and was breathing comfortably. The lungs were clear on auscultation. The white-cell count was 4430 per microliter (reference range, 4500 to 11,000); the lymphocyte count was 550 per microliter (reference range, 1000 to 4800). Blood levels of electrolytes and results of liver- and renal-function tests were normal. Nucleic acid testing of a nasopharyngeal swab for influenza A and B viruses and respiratory syncytial virus was negative.

Dr. Jo-Anne O. Shepard: Posteroanterior and lateral radiography of the chest revealed a 4-cm rounded mass in the right lower lobe (Fig. 1A and 1B). Computed tomography (CT) of the chest, performed after the administration of intravenous contrast material, revealed a rounded mass in the right lower lobe with ground-glass attenuation and a rim of higher attenuation at the periphery of the mass, findings that represent the reversed halo sign (Fig. 1C). In addition, there were smaller ground-glass nodules at the periphery of the right middle lobe and left upper lobe, with associated right hilar lymphadenopathy (Fig. 1C, 1D, and 1E). These findings are most consistent with viral pneumonia, although primary cancer of the lung cannot be ruled out.

Dr. Eisen: Intravenous fluids were administered, and the dizziness abated. Because there was an initial concern about the possibility of lung cancer, a telephone oncology consultation was requested. The patient was discharged from the emergency department. Self-quarantine at home and additional outpatient imaging studies were recommended.

RADIOLOGIC DIFFERENTIAL DIAGNOSIS

Dr. Amita Sharma: This 47-year-old, previously healthy woman presented for an evaluation of cough and shortness of breath early during the Covid-19 pandemic. A CT scan of the chest obtained during evaluation in the emergency department was notable for a rounded mass in the right lower lobe, which initially raised concern about the possibility of cancer. However, the peripheral lesions with ground-glass attenuation and the reversed halo sign may provide addi-

Figure 1 (facing page). Imaging Studies of the Chest.

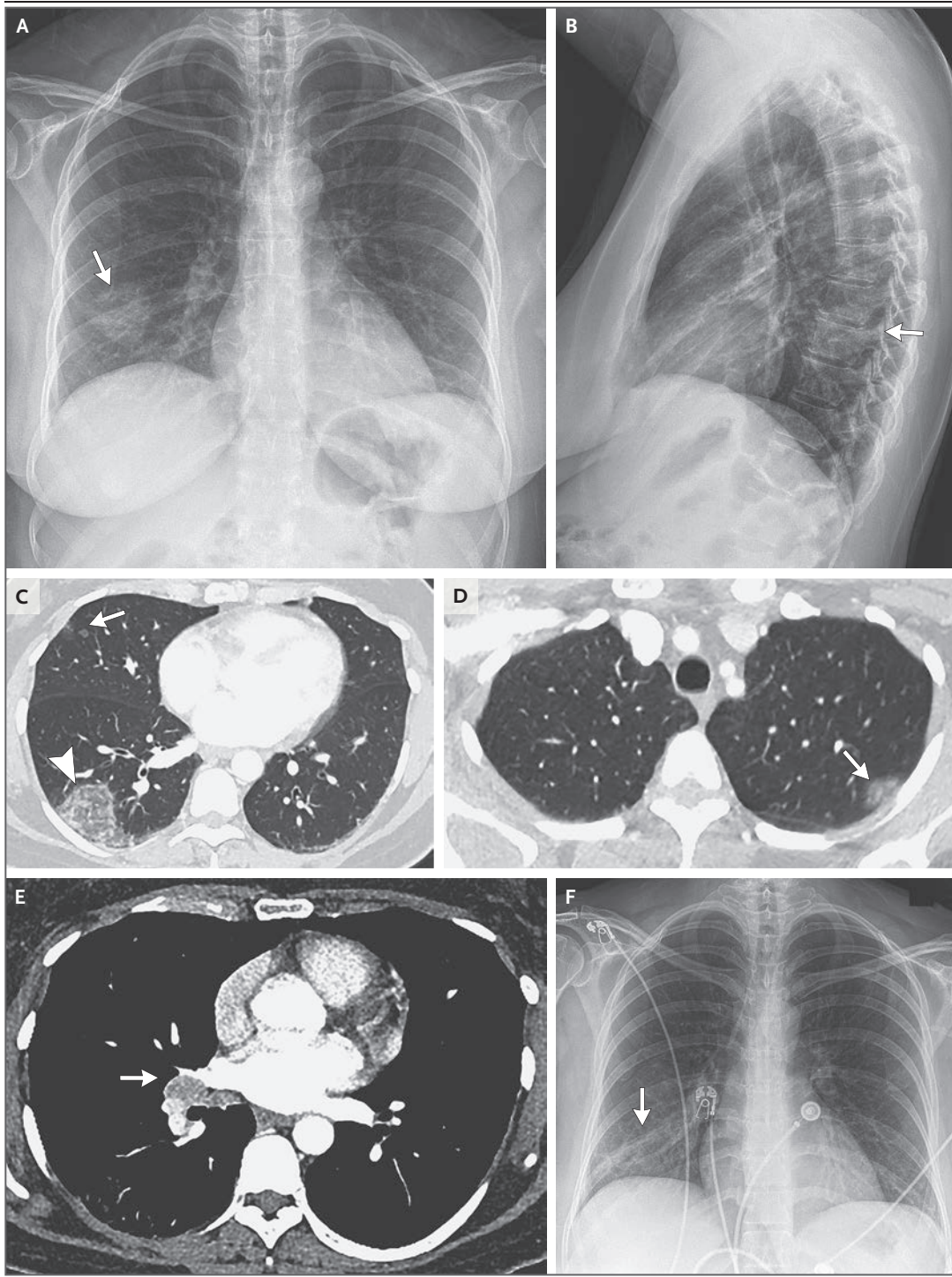
Imaging studies were obtained on the patient's initial presentation to the emergency department. Posteroanterior and lateral radiographs of the chest (Panels A and B, respectively) show a rounded mass in the right lower lobe (arrows). Computed tomographic (CT) images of the chest (Panels C, D, and E), obtained after the administration of intravenous contrast material, show a rounded mass in the right lower lobe with ground-glass attenuation and a rim of higher attenuation at the periphery of the mass, findings that represent the reversed halo sign (Panel C, arrowhead). Additional, smaller ground-glass nodules are present at the periphery of the right middle lobe (Panel C, arrow) and left upper lobe (Panel D, arrow). There is associated right hilar lymphadenopathy (Panel E, arrow). Additional imaging studies were obtained 3 days later, during the patient's hospitalization. A portable chest radiograph (Panel F) shows that the discrete mass has evolved into faint patchy opacities in the right lower lobe (arrow).

tional clues in this case. The first step in building a differential diagnosis based on imaging findings would be to compare the current CT scan with a previous study to determine the chronicity of the lesions; however, a CT scan of the chest had not been obtained previously for this patient.

GROUND-GLASS OPACITY

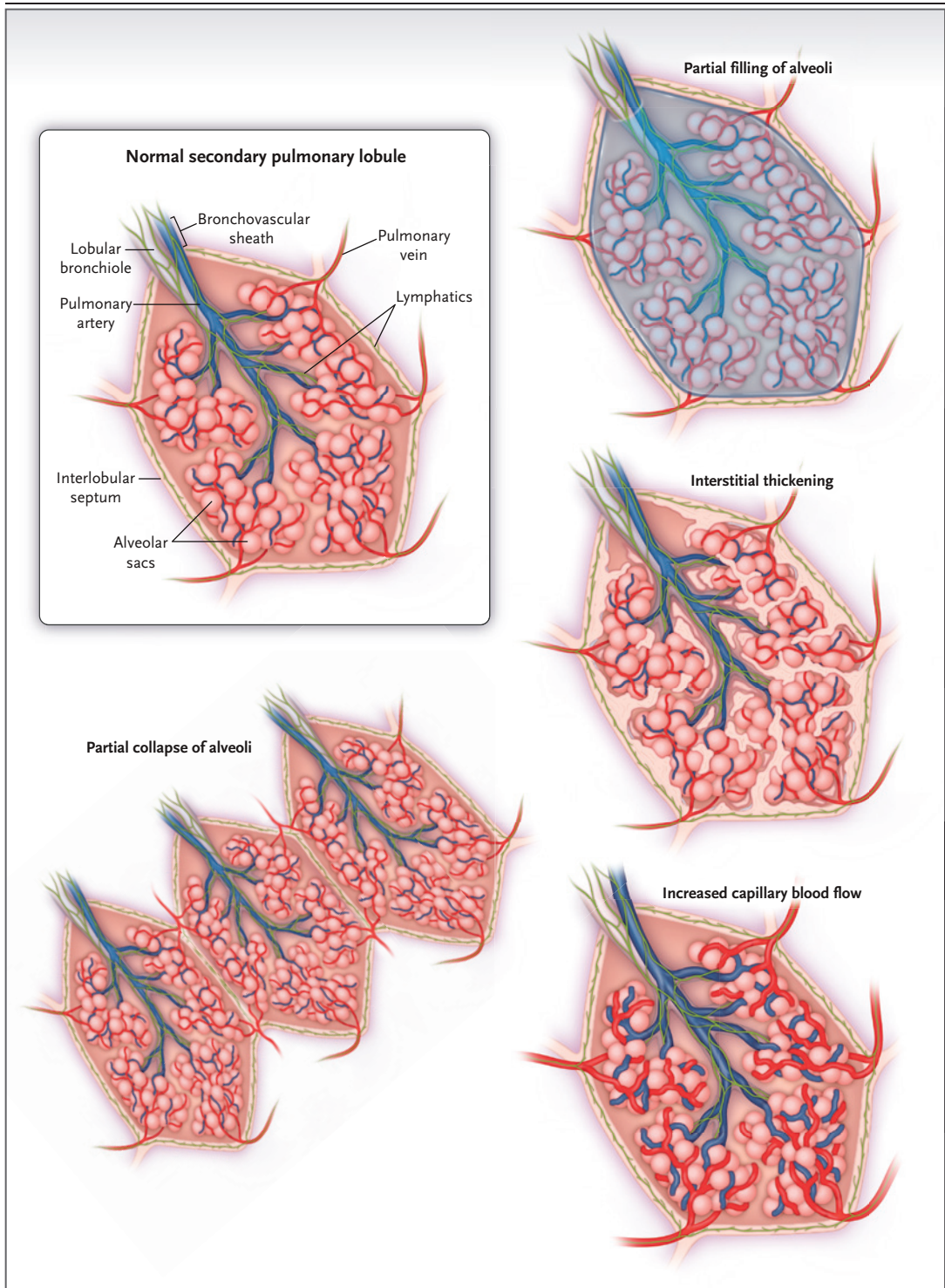
Ground-glass opacity is defined as hazy opacity of the lung with preservation of bronchovascular margins.² It occurs when displacement of air from the alveolar spaces increases the attenuation of the lung (Fig. 2). Fluid, atelectasis, interstitial thickening, and increased blood flow within the lung parenchyma can cause ground-glass opacity.

Ground-glass opacity can be caused by many physiologic and pathologic conditions, and the differential diagnosis of this finding is influenced by the rate of development and distribution of the finding, the patient's immune status, and additional CT features.² If the CT image is obtained during expiration, which causes a relative decrease in lung aeration, this physiologic (normal) condition may result in diffuse ground-glass opacity. Dependent atelectasis can cause ground-glass opacity in the posterior subpleural lung that may be mistaken for an abnormality such as early interstitial lung disease; a CT image obtained with the patient in the prone position would show clearing of dependent density from the posterior lung.³



Partial filling of the airspaces may occur when air is displaced by fluid, which occurs in the context of edema, hemorrhage, infection, inflammation, or cancer. Ground-glass opacity may be diffuse, focal, or multifocal. When it is diffuse, it may have a central, peripheral, or

random distribution.⁴⁻⁶ Edema, hemorrhage, and pneumonitis usually cause diffuse and central or geographic opacity, rather than the focal and peripheral lesions seen in this patient. These conditions are associated with the presence of septal and intralobular lines, but these findings



were not observed in this case. The ground-glass opacity seen in this patient was focal and mass-like and was associated with smaller bilateral ground-glass nodules.

Viral infections typically cause ground-glass opacities. Most infections are associated with multiple bilateral opacities that may be rounded. Opacity may be focal or multifocal and may have

Figure 2 (facing page). Causes of Ground-Glass Opacity on Chest CT.

The inset shows a normal secondary pulmonary lobule, which is defined by Miller³ as a functional unit of lung surrounded by an interlobular septum. The lobular branch of the bronchus and the pulmonary artery divide to supply several acini in the center of the secondary pulmonary lobule. Oxygenated blood returns to the heart through branches of the pulmonary veins that lie, together with lymphatics, in the interlobular septa. Lymphatics also surround the bronchovascular sheath. Ground-glass opacity is seen on chest CT when the air within the acini in the center of the secondary pulmonary lobule is partially displaced, which can be caused by partial filling due to replacement of air by fluid; thickening of the intraalveolar interstitium; increased capillary blood flow; or partial collapse of the alveoli, which leads to a relative loss of aeration.

a central or peripheral distribution. Peribronchovascular peripheral ground-glass opacities may reflect a pattern of organizing pneumonia resulting from infection or associated lung injury.⁷ The viral cause of pneumonia cannot be identified on the basis of CT features alone; there is substantial overlap of imaging findings among the possible causes.

PERIPHERAL DISTRIBUTION OF GROUND-GLASS OPACITY

Causes of peripheral ground-glass opacity include organizing pneumonia, chronic eosinophilic pneumonia, pulmonary infarction, contusion, sarcoidosis, lymphoma, and lung cancer. Adenocarcinoma of the lung can manifest as peripheral ground-glass opacity with or without consolidation. Pure ground-glass nodules can occur with certain histologic subtypes of adenocarcinoma, including atypical adenomatous hyperplasia, adenocarcinoma in situ, and minimally invasive adenocarcinoma. However, the lesions associated with these subtypes are not as large as the dominant mass in this patient, which measured more than 4 cm in greatest dimension. Lepidic-predominant adenocarcinoma may manifest as a ground-glass mass and should be included in the differential diagnosis in this case.^{8,9} The multiple bilateral ground-glass nodules seen in this patient could represent metastatic cancer in the context of adenocarcinoma or represent multiple tumors in the context of multifocal lung cancer. However, in these scenarios, the additional nodules are not usually exclusively subpleural.

REVERSED HALO SIGN

The reversed halo sign is a focal rounded area of ground-glass opacity surrounded by a ring of consolidation.² It is also known as the “atoll sign” because it resembles an atoll, an island that consists of a ring-shaped coral reef surrounding a lagoon.¹⁰ This sign was first described as a finding on high-resolution CT that is specific for cryptogenic organizing pneumonia.^{11,12} Since its initial description, the reversed halo sign has been reported in association with a wide range of pulmonary diseases, including secondary organizing pneumonia, pulmonary infarction, infections (e.g., community-acquired pneumonia, tuberculosis, invasive fungal infections, paracoccidioidomycosis, histoplasmosis, cryptococcosis, and pneumocystis pneumonia), lung cancer, metastatic disease, lymphomatoid granulomatosis, granulomatosis with polyangiitis, and sarcoidosis.¹³

The differential diagnosis related to the reversed halo sign depends on the patient’s immune status, travel history, drug history, and rate of disease development. This patient was immunocompetent and did not have a history of trauma, known exposure to tuberculosis, or recent travel. She was originally from South America, where paracoccidioides is endemic, but she had not traveled there for many years. The CT scan showed no evidence of a pulmonary embolus or features indicative of granulomatous disease. Central reticulation and lucencies within the reversed halo sign have been described with infarction and invasive fungal infections. Nodularity of the peripheral rim or within the central ground-glass opacity has been reported with granulomatous diseases.¹³ These features were not present in this patient. A helpful clue in this case is the isolated right hilar lymphadenopathy, which is suggestive of pulmonary infection or cancer.

CLINICAL COURSE

Dr. Eisen: Three days after the patient’s discharge from the emergency department, fever persisted despite the administration of acetaminophen, and she returned to the hospital for further evaluation. She reported that the cough had become productive of yellow-green sputum, and she also reported dizziness, weakness, nausea, and an episode of vomiting. The temperature was

38.1°C, the heart rate 95 beats per minute, the blood pressure 131/72 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. There were crackles in the right middle lobe. Testing for *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae* antigens in the urine was negative. Additional imaging studies were performed.

Dr. Shepard: Portable radiography of the chest revealed increased faint patchy opacities in the right lower lobe (Fig. 1F). The discrete mass was no longer apparent.

Dr. Eisen: Ceftriaxone, azithromycin, dextromethorphan, and intravenous fluids were administered. The patient was admitted to the hospital, and a diagnosis was made.

CLINICAL IMPRESSION

Dr. Eisen: I cared for the patient during this admission, when she presented shortly after discharge with evolving symptoms. Initial findings on CT of the chest had suggested a possible diagnosis of cancer, in particular lung adenocarcinoma or lymphoma. Although she had some epidemiologic factors (e.g., female sex and non-smoker status) that may be more prevalent among patients with lung adenocarcinoma than among patients with other types of cancer, she was Hispanic and relatively young and did not have a family history of lung cancer, and these factors favored a low pretest probability for lung adenocarcinoma. Furthermore, as the patient's fevers and sputum production persisted and similar symptoms were identified in several family members in her home, the suspected underlying cause shifted from cancer toward an infectious process. A nasopharyngeal swab tested positive for SARS-CoV-2 RNA.

IMAGING FINDINGS IN COVID-19 PNEUMONIA

Dr. Brent P. Little: Radiography is often used for the primary evaluation of patients with a suspected respiratory infection, such as Covid-19. This approach can confirm the presence of a disease, as well as provide information about the severity and morphologic features of the disease. Moreover, it can reveal the presence of an alternative condition or of superimposed acute or chronic conditions.¹⁴

RADIOGRAPHY

Covid-19 pneumonia has a variety of appearances on chest radiography. One common appearance is bilateral hazy opacities, with or without consolidation, that predominantly involve the lower lung (Fig. 3A and 3B). This pattern, which is not unique to this infection, may be indicative of the frequent occurrence of organizing lung injury in the disease, as was suggested by the reversed halo sign seen on CT in this patient. Opacities with a peripheral distribution have been seen in cases of organizing lung injury due to many other causes, such as other viral infections, drug reactions, connective-tissue diseases, or cryptogenic organizing pneumonia. In Covid-19, the time course for the development of radiographic abnormalities is variable. Opacities often appear within the first several days of the disease, and then they often worsen and become more confluent, reaching peak severity at approximately 10 to 12 days.¹⁵ For example, in this patient, the discrete mass in the right lower lobe evolved into faint patchy opacities.

Given that the radiographic features of Covid-19 can be quite variable, opacities that are considered to have a typical distribution — in the peripheral lower lung bilaterally — may be seen in only half the cases with radiographic abnormalities (Fig. 3A and 3B). Opacities that are asymmetric, unilateral, located in the upper or middle lung, or solitary have been observed, and in some cases, focal subsegmental atelectasis is the only finding (Fig. 3C). Approximately 30 to 50% of patients with Covid-19 may have normal results on radiography, especially in early or mild disease (Fig. 3D).^{15,16} For patients who have one or a few peripheral opacities that are nodular or masslike, cancer is included in the differential diagnosis, as it was for this patient during her first presentation to this hospital.

Certain radiographic findings — including pleural effusions, interstitial thickening, and lobar consolidation — are considered to be atypical of Covid-19 and suggest other conditions, such as pulmonary edema or other types of pneumonia. However, more than one disease process can be present in patients with Covid-19. For example, cardiogenic pulmonary edema may occur after an exacerbation of heart failure, and cases of acute myocarditis with resulting cardiac dysfunction have been reported.¹⁷

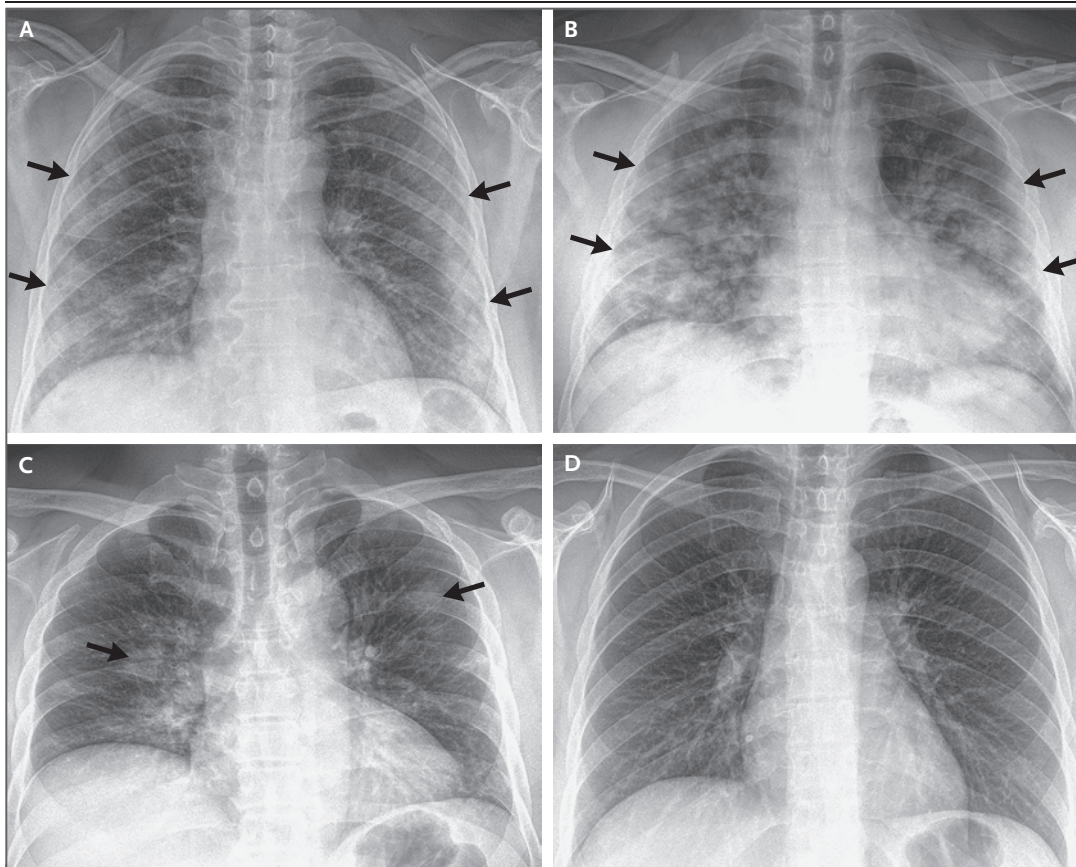


Figure 3. Radiographic Findings in Patients with Covid-19.

Posteroanterior radiographs obtained from patients with Covid-19 are shown. Images from a 64-year-old woman and a 37-year-old man (Panels A and B, respectively) show typical radiographic findings of Covid-19, including opacities that predominantly involve the peripheral lower lung (Panel A, arrows), which is a pattern that can be seen in organizing lung injury, and extensive bilateral opacities with an overall peripheral predominance (Panel B, arrows). An image from a 41-year-old man (Panel C) shows less common radiographic findings of Covid-19, including bilateral asymmetric opacities without a definite peripheral or lower-lung predominance; the opacities are rounded bilaterally (arrows). An image from a 31-year-old woman (Panel D) is normal, with clear lungs and no evidence of pneumonia.

COMPUTED TOMOGRAPHY

Dr. Little: CT is more sensitive than radiography for the detection of pulmonary abnormalities in patients with Covid-19 and also can better depict the morphologic features of opacities. Commonly reported CT findings of Covid-19 pneumonia include bilateral pulmonary opacities distributed in the peripheral lower lung (Fig. 4A and 4B).¹⁹ In typical cases, bilateral ground-glass opacities, sometimes with areas of consolidation, are present, and they can have an appearance suggestive of organizing pneumonia.¹⁸ The opacities can be multifocal, are often rounded, and can have the reversed halo sign (Fig. 4B). Many patients with Covid-19 pneumonia have some but not all of the features of the classic or typical CT appearance. For example, the ground-glass opacities

may be peripheral and rounded but unilateral rather than bilateral, or the opacities may be peripheral but located in the upper or middle lung rather than the lower lung.²⁰ In rare cases, a single ground-glass opacity with or without consolidation may be the only finding. These appearances can be confusing and mistaken for other disease processes.

Several additional CT appearances of Covid-19 overlap broadly with findings in other viral infections. These appearances are classified as indeterminate for Covid-19 according to some grading systems, including the Radiological Society of North America (RSNA) consensus guidelines.¹⁸ Diffuse ground-glass opacities with or without consolidation, patchy opacities without a clear peripheral distribution, or a few scattered

nonrounded opacities are nonspecific appearances that can be seen with a wide variety of infections and with some noninfectious conditions, such as pulmonary hemorrhage or edema (Fig. 4C). These appearances are unlikely to raise concern for cancer.

Certain CT findings are uncommonly seen in patients with Covid-19 pneumonia and are much more commonly seen in patients with other disease processes.¹⁸ Findings that are atypical of Covid-19 include lobar or segmental consolidation or posterior confluent consolidation, which is more commonly seen in bacterial infection or aspiration pneumonitis; discrete small pulmonary nodules, which are sometimes seen in viral, fungal, or mycobacterial infection; and cavitation, which is suggestive of necrotizing bacterial, myco-

bacterial, or fungal infection (Fig. 4D). In addition, interstitial thickening and pleural effusions are atypical of Covid-19 and are suggestive of pulmonary edema. All these findings are uncommon in Covid-19 alone but could occur as a manifestation of associated superimposed infections or complications. These findings were not observed in this patient.

It is important to note that, although CT is more sensitive than radiography for the detection of Covid-19 pneumonia, it cannot replace SARS-CoV-2 nucleic acid testing as the standard diagnostic test. A negative CT scan can be seen in some patients with Covid-19, especially those with early or mild pulmonary involvement. In one study, 56% of patients with early infection had a negative CT scan.²⁰ Similarly, in a study

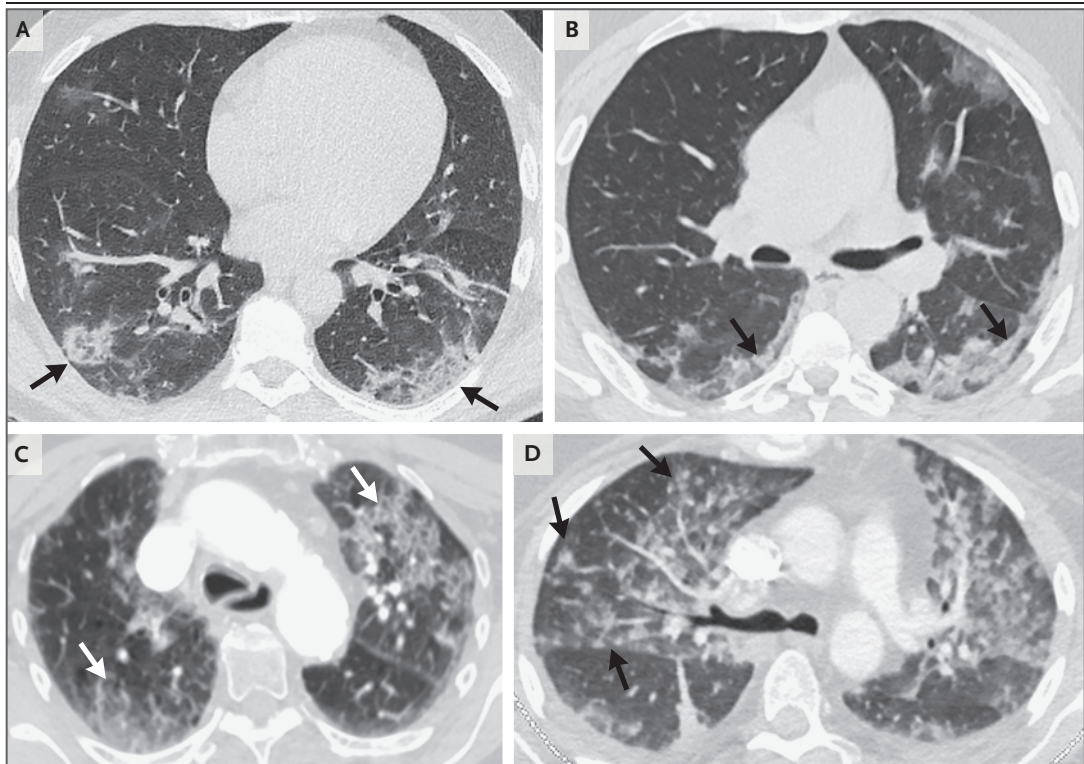


Figure 4. Patterns of CT Findings in Patients with Suspected Covid-19.

Axial CT images obtained from patients with suspected Covid-19 are shown. An image from a 50-year-old man with SARS-CoV-2 infection (Panel A) shows findings that are classified as typical of Covid-19, including bilateral peripheral ground-glass opacities and consolidation, with reversed halo signs (arrows). An image from a 40-year-old man with SARS-CoV-2 infection (Panel B) also shows bilateral peripheral ground-glass opacities and consolidation; some of the peripheral opacities have a linear and perilobular distribution (arrows). An image from an 88-year-old woman with SARS-CoV-2 infection (Panel C) shows findings that are classified as indeterminate for Covid-19, including bilateral patchy ground-glass opacities without a clear distribution in the axial plane (arrows). An image from a 32-year-old woman who tested negative for SARS-CoV-2 but tested positive for rhinovirus (Panel D) shows findings that are classified as atypical of Covid-19, including bilateral ground-glass opacities with clustered, well-defined centrilobular nodules in a tree-in-bud pattern (arrows). The classifications follow the expert consensus reporting guideline of the Radiological Society of North America, endorsed by the American College of Radiology and the Society of Thoracic Radiology.¹⁸

that involved patients who had acquired SARS-CoV-2 on the cruise ship *Diamond Princess*, 21% of symptomatic passengers and 46% of asymptomatic passengers were found to have negative chest CT scans.²¹

RADIOLOGY DURING A PANDEMIC

ROLE OF COMPUTED TOMOGRAPHY

Dr. Adam Bernheim: In China, the emergence of Covid-19 was met with aggressive use of chest CT for the purposes of diagnosis and disease management in patients with suspected infection. In fact, the National Health Commission of China explicitly recommended that the diagnosis of Covid-19 be based on clinical and chest CT findings alone; at one point in February 2020, the number of cases in China increased by 15,000 in a single day when criteria for the diagnosis of Covid-19 were changed, allowing the diagnosis to be based on CT findings in the absence of a positive nucleic acid test for SARS-CoV-2.²²

However, with subsequent global spread of the disease, most North American and European countries advocated for a more conservative approach, reserving chest CT to be performed in limited scenarios. Some investigators and policymakers suggest that the value of CT in effecting diagnostic and management decisions is limited (or minimal when results of portable chest radiography are available) for the following reasons: frequent performance of CT increases the potential for infection transmission to other patients and health care staff, the diagnosis of Covid-19 hinges on nucleic acid testing, the CT appearance in some patients can be nonspecific or even normal, and CT results do not alter disease management in a large percentage of cases.

Guidelines from the American College of Radiology advised radiologists to avoid the use of CT for screening and as a first-line test for diagnosis; to use CT sparingly in hospitalized, symptomatic patients with specific clinical indications; and to use discretion in performing CT to inform decisions regarding whether to test, admit, or treat patients with suspected infection.²³ The Society of Thoracic Radiology and the American Society of Emergency Radiology issued a joint position statement that advised against routine CT screening for the diagnosis of Covid-19 and proposed restricting the use of CT to patients who have tested positive for the

disease and in whom complicating features such as abscess formation are suspected.²⁴ The European Society of Radiology, the European Society of Thoracic Imaging, and the Fleischner Society all issued guidelines, as well. The Fleischner Society was more accepting of imaging; although the society conceded that imaging was not routinely indicated as a screening test for Covid-19 in asymptomatic patients, it endorsed the use of imaging in patients with moderate-to-severe features of Covid-19 regardless of nucleic acid test results, and it also supported the use of imaging in patients with worsening respiratory status.^{25,26}

Ultimately, the decision to perform chest CT in patients with suspected Covid-19 revolves around multiple factors — including many individual case-specific clinical considerations, as well as the disease prevalence in a specific place and at a specific time — and the appropriate approach for any given patient with a dominant masslike opacity may vary from one institution or country to another. In this patient, in whom an initial radiograph showed a rounded mass, CT was performed because the differential diagnosis included possibilities other than Covid-19, such as lung cancer, and further evaluation was warranted.

REPORTING GUIDANCE FOR RADIOLOGISTS

Dr. Bernheim: In early spring 2020, globally increasing rates of Covid-19 necessitated the formulation of an organized, systematic, and reproducible approach for radiologists to implement in their reports that would aid in consistency of reporting and in communication with clinicians. An expert consensus panel assembled by the RSNA issued guidance that proposed structured reporting and grouping of findings into the following four categories, which are based on the radiologist's degree of confidence that the finding corresponds to Covid-19 pneumonia: typical appearance, indeterminate appearance, atypical appearance, and negative for pneumonia.¹⁸ Moreover, a Dutch group offered the Covid-19 Reporting and Data System (CO-RADS), a system that reflects the rationale used in many other currently available standardized reporting systems in radiology.²⁷ The findings in this patient may be categorized as CO-RADS 4 — which is defined by CT features that are highly suspicious for Covid-19 but have some overlap with other causes — owing to the presence of multiple

typical features of Covid-19 (bilateral ground-glass opacities in the lower lung and a reversed halo sign), as well as a somewhat atypical feature (a masslike dominant lesion).

follow-up telephone call with her primary care physician, the patient reported that the symptoms had resolved.

FOLLOW-UP

Dr. Eisen: On the third hospital day, when symptoms abated, the patient was discharged home to complete a course of cefpodoxime and azithromycin. Self-quarantine was recommended. In a

FINAL DIAGNOSIS

Pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Presented as a tabletop exercise during the Covid-19 pandemic. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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