A Comparison of Clinical and Chest CT Findings in Patients With Influenza A (H1N1) Virus Infection and Coronavirus Disease (COVID-19)

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OBJECTIVE. The purpose of this study was to compare clinical and chest CT findings in patients with influenza A (H1N1) pneumonia and coronavirus disease (COVID-19) pneumonia.

MATERIALS AND METHODS. Thirty patients with diagnosed influenza A (H1N1) virus infection (group A) and 30 patients with diagnosed COVID-19 (group B) were retrospectively enrolled in the present study. The clinical characteristics and chest CT findings of the two groups were compared.

RESULTS. Fever, cough, expectoration, and dyspnea were the main symptoms in both groups with viral pneumonia, with cough and expectoration more frequently found in group A. Lymphopenia, an elevated C-reactive protein level, and an increased erythrocyte sedimentation rate were common laboratory test findings in the two groups. The median time from symptom onset to CT in group A and group B was 6 and 15 days, respectively, and the median total CT score of the pulmonary lobes involved was 6 and 13, respectively. Linear opacification, crazy-paving sign, vascular enlargement, were more common in group B. In contrast, bronchiectasis and pleural effusion were more common in group A. Other common CT features, including peripheral or peribronchovascular distribution, ground-glass opacities (GGOs), consolidation, subpleural line, air bronchogram, and bronchial distortion, did not show statistical significance.

CONCLUSION. On CT, the significant differences between influenza A (H1N1) pneumonia and COVID-19 pneumonia were findings of linear opacification, crazy-paving sign, vascular enlargement, pleural thickening, and pleural effusion, which were more common in patients with COVID-19 pneumonia, and bronchiectasis and pleural effusion, which were more common in patients with influenza A (H1N1) pneumonia. Other imaging findings, including peripheral or peribronchovascular distribution, ground-glass opacities (GGO), consolidation, subpleural line, air bronchogram, and bronchial distortion, were not significantly different between the two patient groups.

Keywords: coronavirus disease, COVID-19, CT, influenza A (H1N1) virus, pneumonia, viral pneumonia

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Influenza virus infections are prevalent and cause substantial morbidity and mortality worldwide [1, 2]. According to a recent study, approximately 291,243 to 645,832 deaths due to infection with influenza viruses occur annually worldwide [1]. Influenza viruses are grouped into four types (A, B, C, and D), with seasonal flu epidemics attributed to influenza A and B viruses [3]. H1N1 is a subtype of influenza A virus that leads to respiratory infections and that has caused two pandemics over the past 102 years [4, 5]. In 1918, a novel H1N1 influenza virus rapidly erupted and spread across Europe, North America, and Asia, infecting 500 million people and killing more than 50 million [6]. The most recent pandemic due to H1N1 influenza virus occurred in 2009 and affected 60.8 million people, resulting in 284,000 deaths worldwide [7, 8].

In December 2019, a group of patients had viral pneumonia of unknown cause, with most of these patients having been exposed to the Huanan Seafood Market in Wuhan, China [9]. A novel coronavirus was detected on January 6, 2020, and was termed "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). This novel coronavirus has led to more than 80,000 confirmed cases of coronavirus disease (COVID-19) in China. Many reports of the clinical and imaging findings of COVID-19 pneumonia have emerged [10–12]. Considering the contemporary influenza epidemics (especially those in areas including the United States) and the

pandemic nature of COVID-19, it is essential to clarify the differences between the two infectious diseases on the basis of laboratory test and imaging findings because their clinical symptoms are similar. In the present study, we attempted to compare the differences between the clinical and high-resolution CT features of two types of viral pneumonia: that related to influenza A (H1N1) virus infection and that related to COVID-19.

Materials and Methods

Patients

The present study was approved by the ethics committees at our institutions. The requirement for informed consent was waived because this study was retrospective and therefore posed no potential risk to patients.

We searched the hospital information system at the Second Xiangya Hospital to identify patients with influenza A (H1N1) virus infection (group A) seen from December 2018 to February 2019, by use of the search terms "influenza A" and "H1N1." Forty-eight patients with influenza A (H1N1) virus infection were identified. Eighteen patients who had evidence of coinfection or who had insufficient data were excluded. Therefore, a total of 30 patients were included in group A. A total of 136 patients with COVID-19 who were seen at Tongji Hospital from February 7 to February 14, 2020, were identified. From this group of 136 patients, a matched sample of 30 patients (group B) was randomly selected to avoid selection bias. Patients who had clinical or laboratory evidence of coinfection, including infection with influenza A virus, influenza B virus, parainfluenza, adenovirus, respiratory syncytial virus, *Legionella pneumophila*, *Mycoplasma* species, and *Chlamydia* species, were excluded. All cases were confirmed by reverse transcription–polymerase chain reaction (RT-PCR) testing of pharyngeal swab specimens. High-resolution CT scans were obtained from the hospital's PACS. Clinical data were obtained from electronic medical records.

CT Images

CT was conducted using 64-MDCT scanners (Revolution [GE Healthcare] and Somatom Force [Siemens Healthineers]), with the use of standard tube voltage and tube current settings. While in the supine position, patients underwent CT performed without IV contrast medium but with suspended end-inspiration. After contiguous 8- or 10-mm chest CT sections were obtained, images were reconstructed with a slice thickness of 1.00 or 1.25 mm. All images were photographed at window levels appropriate for the lung parenchyma (width, 1200 HU; level, −600 HU) and the mediastinum (width, 360 HU; level, 55 HU).

Chest CT Image Review

CT images were evaluated independently in random order by two chest radiologists, each of whom had 5 years of experience in chest CT interpretation. For cases for which the decisions of the two radiologists were discordant, a final decision was reached by consensus or by a senior radiologist. CT findings were recorded as present or absent on images with a slice thickness of 1.00 or 1.25 mm. The imaging findings that we evaluated included nodular appearance, ground-glass opacity (GGO),, consolidation, linear opacification, subpleural line, crazy-paving sign, peripheral (involving mainly the outer one-third of the lung) or peribronchovascular distribution, vascular enlargement [13], bronchial wall thickening, bronchiectasis, air bronchogram, bronchial distortion, lymphadenopathy (short-axis diameter > 1 cm), pleural thickening, pleural effusion, and pericardial effusion [14].

A CT scoring system was adopted to quantitatively evaluate lung involvement (assessing five lobes, with a score of 0–5 possible for each lobe). The specific definition of lobe involvement used was as follows: a score of 0 indicated no involved area and scores of 1, 2, 3, 4, and 5 denoted involvement in 0% to < 5%, 5% to < 25%, 25% to < 50%, 50% to < 75%, and 75–100% of the area, respectively. The total CT score was the sum of the scores for each lobe.

Statistical Analysis

SPSS software (version 22.0, SPSS) was used for the statistical analysis. The count data were expressed as a percentage, and measurement data were expressed as median values and quartiles (25th and 75th percentiles). The Mann-Whitney test was used to compare the differences between the two groups for continuous variables. The Fisher exact test was used to compare the categoric variables of the two groups. A two-tailed $p < 0.05$ was considered to indicate a statistically significant difference.

TABLE 1: Demographic and Clinical Characteristics of Patients With Influenza A (H1N1) Pneumonia (Group A) and Patients With Coronavirus Disease (COVID-19) Pneumonia (Group B)

Characteristic	Group A (*n* = 30)	Group B (*n* = 30)	*p*
Age (y), mean ± SD	53.6 ± 18.7	52.7 ± 15.1	0.701
Sex			
Male	18	19	1.000
Female	12	11	
Comorbidity			
Chronic respiratory disease	4	0	0.112
Diabetes	3	4	1.000
Cardiovascular disease	3	2	1.000
Hypertension	6	8	0.761
Malignancy	6	0	0.024[a]
Renal transplant	1	1	1.000
Symptom			
Fever	21	24	0.552
Cough	29	22	0.026[a]
Expectoration	24	13	0.007[a]
Dyspnea	15	13	0.796
Rhinorrhea	5	0	0.052
Sore throat	5	0	0.052
Headache	3	5	0.707
Chest pain	2	1	1.000
Myalgia	1	4	0.353
Fatigue	3	8	0.181
Nausea	2	4	0.671
Vomiting	3	1	0.612
Diarrhea	0	5	0.052

(Table 1 continues on next page)

TABLE 1: Demographic and Clinical Characteristics of Patients With Influenza A (H1N1) Pneumonia (Group A) and Patients With Coronavirus Disease (COVID-19) Pneumonia (Group B) (continued)

Characteristic	Group A (*n* = 30)	Group B (*n* = 30)	*p*
Routine blood test finding, median (25th to 75th percentile)			
WBC count (× 10^9 cells/L)	6.0 (4.8–8.5)	4.9 (4.2–6.4)	0.063
Neutrophil count (× 10^9 cells/L)	4.75 (3.15–7.00)	3.57 (2.72–4.92)	0.037[a]
Lymphocyte count (× 10^9 cells/L)	0.83 (0.58–1.60)	0.92 (0.72–1.10)	0.873
Lymphopenia	17	24	0.238
Monocyte (× 10^9 cells/L)	0.34 (0.19–0.51)	0.40 (0.30–0.55)	0.207
RBC count (× 10^{12} cells/L)	4.1 (3.8–4.7)	4.4 (4.0–4.8)	0.148
Hemoglobin level (g/L)	126 (111–145)	135.0 (126.3–144.5)	0.098
Platelet count (× 10^9 cells/L)	192 (142–270)	192.5 (145.0–245.0)	0.987
Infection-related biomarker, median (25th to 75th percentile)			
C-reactive protein level (mg/L)	41.7 (10.0–105.0)	36.1 (11.0–62.7)	0.446
Erythrocyte sedimentation rate (mm/h)	20.0 (12.0–62.0)	33.5 (15.0–59.0)	0.460
Procalcitonin level (ng/mL)	0.11 (0.09–0.37)	0.04 (0.03–0.09)	0.002[a]

Note—Except where otherwise indicated, data are number of patients.
[a]Statistically significant.

TABLE 2: Comparisons of the CT Characteristics of Patients With Influenza A (H1N1) Pneumonia (Group A) and Patients With Coronavirus Disease (COVID-19) Pneumonia (Group B)

CT Finding	Group A (*n* = 30)	Group B (*n* = 30)	*p*
Time from symptom onset to CT (d), median (25th to 75th percentile)	6 (0–14)	15 (12–17)	< 0.001
Total CT score of lobe involvement, median (25th to 75th percentile)	6 (2–12)	13 (7–21)	0.007[a]
Distribution of pulmonary lesions			
Peripheral	27	28	1.000
Peribronchovascular	20	16	0.430
CT characteristic			
Nodular appearance	1	4	0.353
Ground-glass opacities	22	27	0.181
Consolidation	26	29	0.353
Linear opacification	15	27	0.002[a]
Subpleural line	10	18	0.069
Crazy-paving sign	9	18	0.037[a]
Vascular enlargement	20	28	0.021[a]
Bronchial wall thickening	6	3	0.472
Bronchiectasis	9	1	0.012[a]
Air bronchogram	19	15	0.435
Bronchial distortion	10	10	1.000
Lymphadenopathy	9	3	0.104
Pleural thickening	19	27	0.030[a]
Pleural effusion	16	4	0.002[a]
Pericardial effusion	6	3	0.472

Note—Except where otherwise indicated, data are number of patients.
[a]Statistically significant.

Results

Clinical Findings

The demographic and clinical characteristics of patients in group A and group B are presented in Table 1. Fever, cough, expectoration, and dyspnea were the main symptoms in both group A and group B, with cough (29 vs 22 patients, respectively; p = 0.026) and expectoration (24 vs 13 patients, respectively; p = 0.007) more common in group A. Less common symptoms included rhinorrhea, sore throat, headache, chest pain, myalgia, fatigue, nausea, vomiting, and diarrhea, with no statistical difference observed between the two groups.

For comparison of the results of routine blood tests, three patients in group A who had hematologic malignancy were excluded. All routine blood test parameters were in the normal range, except for the lymphocyte count (median, 0.83 × 10^9 cells/L [25th to 75th percentile, 0.58–1.60 × 10^9 cells/L] for group A vs 0.92 × 10^9 cells/L [25th to 75th percentile, 0.72–1.10 × 10^9 cells/L] for group B; p = 0.88), which decreased in both group A and group B (17 of 27 vs 24 of 30 patients, respectively; p = 0.238). Both group A and group B showed increases in the C-reactive protein level (median, 41.7 mg/L [25th to 75th percentile, 10.0–105.0 mg/L] vs 36.1 mg/L [25th to 75th percentile, 11.0–62.7 mg/L], respectively) and the erythrocyte sedimentation rate (median, 20.0 mm/h [25th to 75th percentile, 12.0–62.0 mm/h] vs 33.5 mm/h [25th to 75th percentile, 15.0–59.0 mm/h], respectively), with no significant difference observed between groups. The procalcitonin level in the two groups was in the normal range.

CT Findings

Comparisons of the CT characteristics of influenza A (H1N1) pneumonia and COVID-19 pneumonia are presented in Table 2. The median time from symptom onset to CT in group A and group B was 6 days (25th to 75th percentile, 0–14 days) and 15 days (25th to 75th percentile, (12–17 days), respectively. The median total CT score of the pulmonary lobes involved in group A and group B was 6 (25th to 75th percentile, 2–12) and 13 (25th to 75th percentile, 7–21), respectively. There was no significant difference between the two groups with regard to distribution pattern, nodular appearance, GGO, consolidation, subpleural line, bronchial wall thickening, air bronchogram, bronchial distortion, lymphadenopathy, and pericardial effusion (Figs. 1 and 2). The following findings did reach statistical significance in group A and group B: bronchiectasis (nine

patients vs one patient, respectively; p = 0.012), pleural effusion (16 vs four patients, respectively; p = 0.002) (Figs. 1 and 3), linear opacification (15 vs 27 patients, respectively; p = 0.002), crazy-paving sign (nine vs 18 patients, respectively; p = 0.021), vascular enlargement (20 vs 28 patients, respectively; p = 0.037), and pleural thickening (19 vs 27 patients, respectively; p = 0.030) (Fig. 4).

Discussion

The results of the present study showed that bronchiectasis and pleural effusion were more common among patients with influenza A (H1N1) pneumonia, whereas linear opacification, crazy-paving sign, vascular enlargement, and pleural thickening were more common among patients with COVID-19 pneumonia. Other CT features, including distribution pattern, nodular appearance, GGO, consolidation, subpleural line, bronchial wall thickening, air bronchogram, bronchial distortion, lymphadenopathy, and pericardial effusion, did not differ between the patients with influenza A (H1N1) pneumonia and patients with COVID-19 pneumonia.

The reported typical CT findings of influenza A (H1N1) pneumonia were diffuse or patchy GGO with or without focal areas of consolidation and were usually located in the lower lobes [15]. Obscure patchy or diffuse areas of GGO or consolidation would become rapidly confluent and were absorbed approximately 3 weeks later [16]. Another recent study reported that although GGO, consolidation, and bronchial thickening were common CT findings of influenza A (H1N1) pneumonia, septal interlobular thickening and lymphadenopathy were not found [17]. As for COVID-19 pneumonia, some studies reported that the most common CT findings were the presence of extensive GGO and consolidation with or without vascular enlargement, interlobular septal thickening, air bronchography, reticular pattern, fibrotic stripe, subpleural line, and tractive bronchiectasis [12, 18–20]. In the present study, we found the crazy-paving sign, defined as interlobular septal thickening with superimposed GGO, was more common in patients with COVID-19 pneumonia, which might be a clue in the differential diagnosis. Observation of the microvascular dilation sign on CT (observed in 45.2% of patients in a study by Zhou et al. [13] and in 71.3% of patients in a study by Zhao et al. [20]) was proven to be a different finding more common in patients with COVID-19 pneumonia in our study. Linear opacification and pleural thickening, although reported to be less common CT findings in patients with COVID-19 pneumonia [21], were found to be of differential significance in the diagnosis of COVID-19 pneumonia and and influenza A (H1N1) pneumonia in the present study. In contrast, bronchiectasis and pleural effusion, which were uncommon in patients with COVID-19 pneumonia, were observed in a slightly higher proportion of patients with influenza A (H1N1) pneumonia. The differences in these imaging features might provide some hints.

In a study comparing the imaging characteristics of pneumonia caused by SARS-CoV-2 with those of other types of viral pneumonia, Bai et al. [22] showed that imaging characteristics had a high specificity but moderate sensitivity in differentiating COVID-19 pneumonia from pneumonia not caused by COVID-19 [22]. In that study, COVID-19 pneumonia more commonly manifested as peripheral distribution, GGO, fine reticular opacity, and vascular thickening, whereas central and peripheral distribution, pleural effusion, and lymphadenopathy were less commonly observed. Similar to their study, our study found that influenza A (H1N1) pneumonia and COVID-19 pneumonia were sometimes difficult to identify, with both showing GGO and consolidation on chest CT, although some signs differed statistically. However, unlike the study by Bai and colleagues, our study found that peripheral and peribronchovascular distribution was common both in patients with COVID-19 pneumonia and in patients with influenza A (H1N1) pneumonia, and we found that different signs could help identify these two entities. Further study of the sensitivity and specificity of diagnosing COVID-19 pneumonia and influenza A (H1N1) pneumonia on the basis of our findings is required.

In the present study, the median total CT score of the involved pulmonary lobes in group B was 13, which was higher than the median total CT score of 6 for group A. Possible reasons for this finding might be the long interval from symptom onset to CT, which may have led to the extent of lung involvement progressing over time [23], or an increased virulence of SARS-CoV-2 compared with the influenza A (H1N1) virus.

With regard to clinical characteristics, the respiratory symptoms commonly observed in both study groups included fever, cough, expectoration, and dyspnea. Cough and expectoration were more frequent in group A. Of note, five patients in group B had diarrhea as an initial symptom; this symptom that has been reported elsewhere [24], and increasing clinical evidence has confirmed that the digestive system might serve as an alternative route of infection [11], with this possibly being clinically unique to COVID-19. Based on findings from our study, laboratory test findings, including results of routine blood tests and measurements of inflammatory markers, failed to distinguish between the two diseases because both were characterized by decreased lymphocyte counts and increased C-reactive protein levels and erythrocyte sedimentation rates.

The present study has some limitations. First, the number of cases included was relatively small. Second, the CT images were obtained from two hospitals, and the scanning parameters and image quality were different, which might have affected the interpretation of certain imaging details. Third, the cases might have represented different stages of disease, resulting in differences in the appearance of radiologic signs. Fourth, only influenza A (H1N1) pneumonia was compared with COVID-19, so differences between individuals with COVID-19 and individuals with other infections or coinfections may need to be considered.

In summary, to potentially aid in distinguishing between influenza A (H1N1) pneumonia and COVID-19 pneumonia, radiologists may use findings of bronchiectasis and pleural effusion to identify patients with influenza A (H1N1) pneumonia and findings of linear opacification, crazy-paving sign, vascular enlargement, and pleural thickening to identify patents with COVID-19 pneumonia. Nevertheless, a definitive diagnosis needs to be combined with etiologic testing because the distribution pattern and findings of GGO, consolidation, a subpleural line, and air bronchogram are basically similar for the two diseases.

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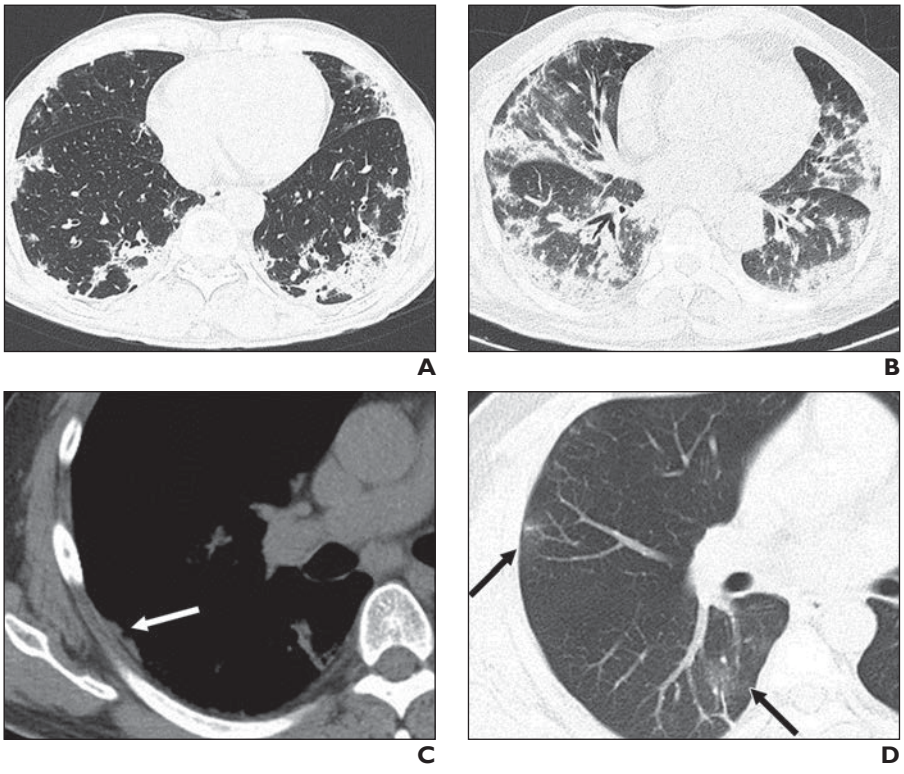

Fig. 1—Patients with diagnosed influenza A (H1N1) pneumonia.
A, 61-year-old man with fever, cough, and expectoration of 5 days' duration. Axial CT image shows consolidation in both lungs. Lesions are mainly peripherally distributed.
B and **C,** 53-year-old man who presented with cough and expectoration of 1 month's duration and fever of 10 days' duration. Axial CT images show consolidation and linear opacification in both lungs and peripheral and peribronchovascular distribution (**B**) as well as pleural thickening (*arrow*, **C**).
D, 30-year-old man with cough and fever of 7 days' duration. Axial CT image shows ground-glass opacities (*arrows*) in right upper and lower lobes.

(Fig. 1 continues on next page)

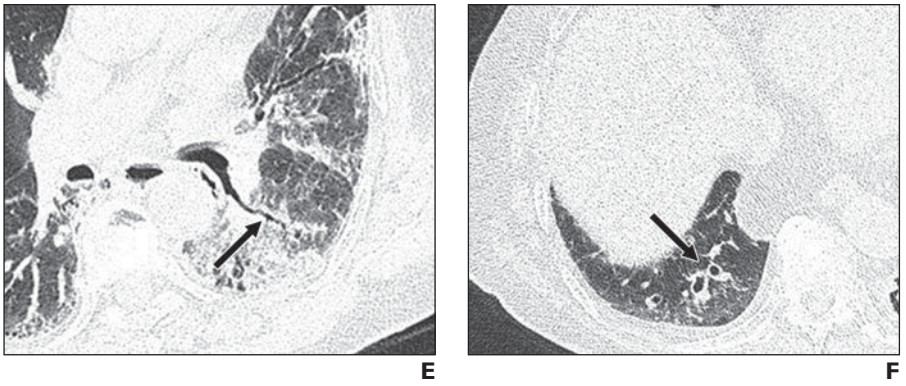

Fig. 1 (continued)—Patients with diagnosed influenza A (H1N1) pneumonia.
E, 75-year-old woman with cough and fever of 20 days' duration. Axial CT image shows consolidation accompanied by air bronchogram and bronchial distortion (*arrow*) in left lower lobe.
F, 89-year-old man with cough and expectoration of 3 days' duration. Axial CT image shows bronchiectasis and bronchial wall thickening (*arrow*) in bilateral lower lobes.

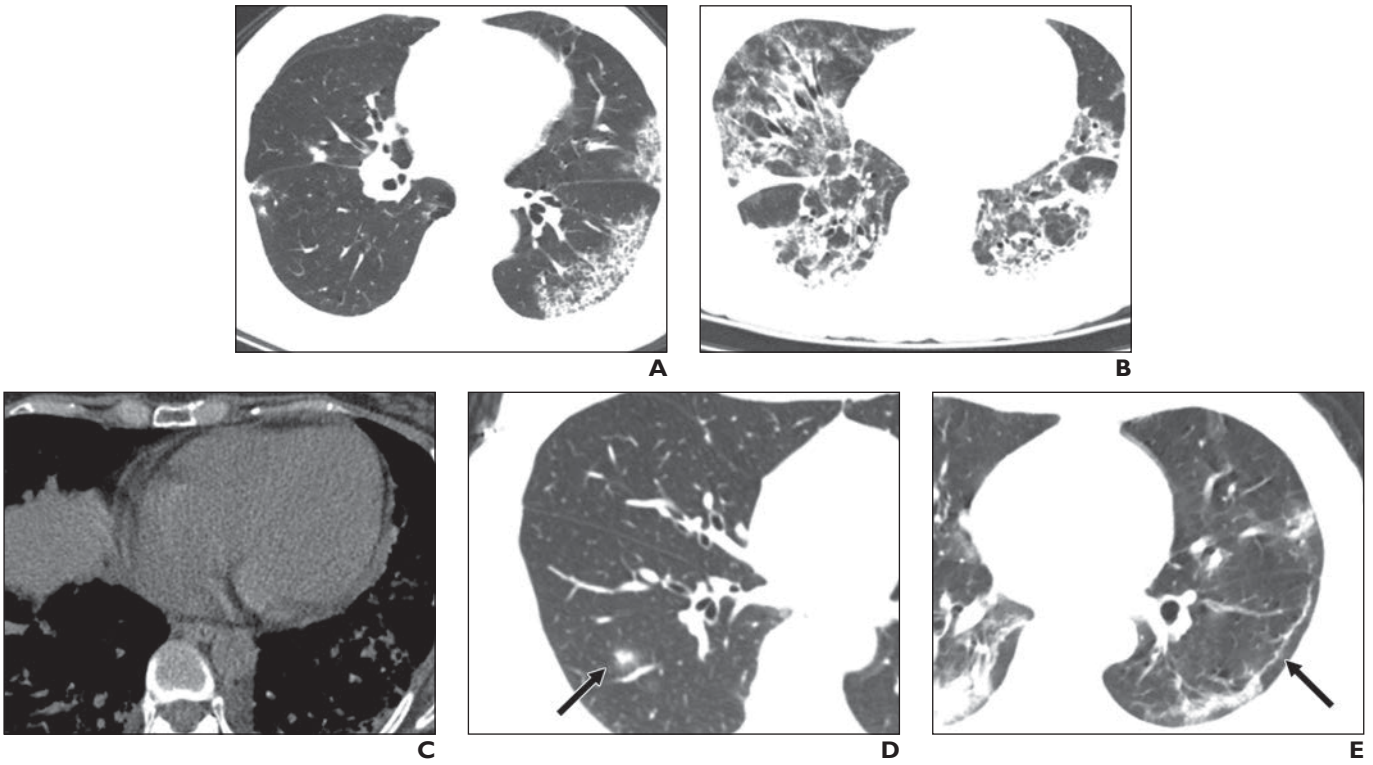

Fig. 2—Patients with confirmed coronavirus disease (COVID-19) pneumonia.
A, 64-year-old man with fever of 8 days' duration. Axial CT image shows crazy-paving sign and focal consolidation. Lesions are mainly peripherally distributed.
B and **C,** 39-year-old woman. Axial CT images obtained 8 days after onset of fever and fatigue show peribronchovascular distribution of consolidation, ground-glass opacities, and linear opacification (**B**) and small amount of pericardial effusion (**C**).
D, 32-year-old woman with fever of 5 days' duration. Axial CT image shows node with halo sign (*arrow*) in right lower lobe.
E, 50-year-old woman with fever of 12 days' duration. Axial CT image shows subpleural line (*arrow*) in left lower lobe.

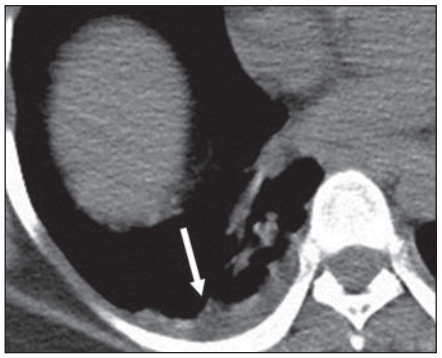

Fig. 3—29-year-old woman with influenza A (H1N1) pneumonia diagnosed after cough of 1 day's duration. Axial CT image shows small amount of right-sided pleural effusion (*arrow*).

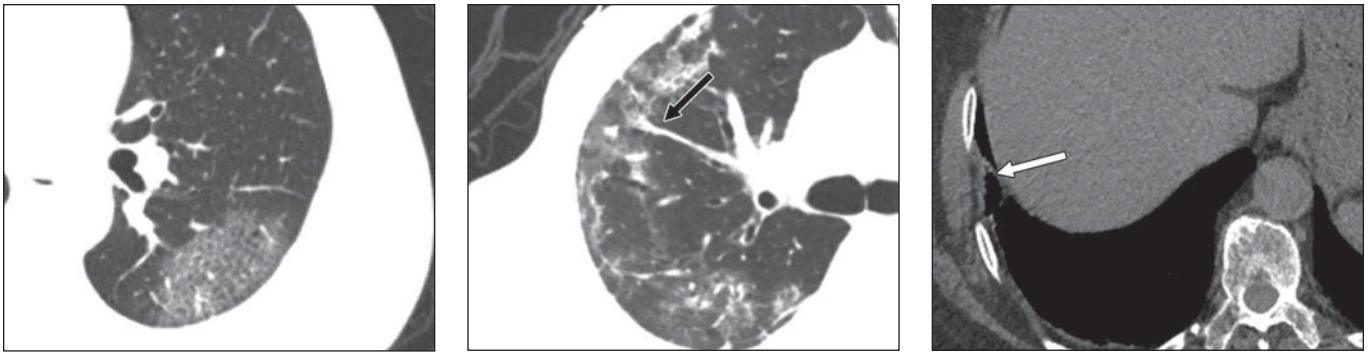

Fig. 4—Patients with confirmed coronavirus disease (COVID-19) pneumonia.
A, 56-year-old man who had fever of 12 days' duration. Axial CT image shows crazy-paving sign in left lower lobe.
B, 67-year-old man who had fever of 8 days' duration. Axial CT image shows vascular enlargement (*arrow*) in right middle lobe.
C, 74-year-old woman who presented with fever of 10 days' duration and fatigue of 4 days' duration. Axial CT image shows pleural thickening (*arrow*).