CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 18-2021: An 81-Year-Old Man with Cough, Fever, and Shortness of Breath

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PRESENTATION OF CASE

Dr. Matthew J. Emmett (Medicine): An 81-year-old man was admitted to this hospital with fever, cough, and shortness of breath during the pandemic of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The patient had been in his usual state of health until 3 days before this admission, when fever and cough developed. On the morning of admission, he noted an abrupt onset of shortness of breath at rest and dyspnea on exertion. There was also substernal chest pain on the left side that worsened with deep breaths and when he lay down. The patient's son called emergency medical services, and the patient was brought to the emergency department of this hospital for further evaluation.

On arrival at the emergency department, the patient described ongoing chest pain and shortness of breath. The son reported that the patient had fallen at home 2 days before admission, but the patient did not remember falling and the son was not able to provide details about the nature or circumstances of the fall. The patient reported no pain in his abdomen, arms, legs, or groin and no headache.

The patient had a history of hypertension. During a previous evaluation for cough, he was reportedly told that he had a lung disease that had "caused the lung tissue to harden." Before the onset of his most recent symptoms, he had walked outside on a daily basis without limitation from shortness of breath. He took an unknown medication for hypertension. The patient did not smoke tobacco, use illicit drugs, or drink alcohol. He lived in an apartment with his wife.

On examination, the temperature was 37.9°C, the blood pressure 157/95 mm Hg, the pulse 112 beats per minute, the respiratory rate 30 breaths per minute, and the oxygen saturation 91% while the patient was breathing ambient air. The respiratory rate decreased to 28 breaths per minute and the oxygen saturation improved to 96% with the administration of supplemental oxygen through a nasal cannula at a rate of 4 liters per minute. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 22.8. Retractions were noted in the supraclavicular areas. Inspiratory crackles could be heard at the lung

bases. The heart sounds were regular, with tachycardia but no murmur. There was no tenderness on palpation of the chest wall and no edema in the legs. Laboratory test results are shown in Table 1.

Dr. Reece J. Goiffon: A single-view portable anteroposterior radiograph of the chest showed bilateral patchy airspace opacities that were more extensive in the left lung than in the right lung, with predominance in the peripheral lower lung zones and with relative sparing of the perihilar regions (Fig. 1). These opacities were superimposed on mild apical and bibasilar bronchiectasis and bibasilar reticular opacities. A radiograph of the pelvis showed no fracture.

Dr. Emmett: An electrocardiogram showed sinus tachycardia. Blood samples were obtained for culture, and a nasopharyngeal swab was submitted to test for SARS-CoV-2 RNA. Azithromycin and ceftriaxone were administered, and the patient was admitted to the hospital.

On arrival at the medical floor, the patient was in respiratory distress, with a respiratory rate of 40 breaths per minute and an oxygen saturation of 86% while he was receiving supplemental oxygen through a nasal cannula at a rate of 4 liters per minute. The patient was restless and appeared uncomfortable, moving around in the bed and attempting to sit up; he reported severe pleuritic chest pain. The oxygen flow rate was adjusted to 5 liters per minute, and morphine was administered intravenously. A repeat electrocardiogram showed sinus tachycardia.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Kathryn A. Hibbert: This 81-year-old man with a history of hypertension and possible chronic lung disease presents with fever, cough, acute onset of shortness of breath, and focal pleuritic chest pain. His evaluation is notable for tachypnea, tachycardia, hypoxemia, and signs of increased work of breathing. Imaging studies show bilateral peripheral opacities. His clinical trajectory is also a concern, given the progression of hypoxemia and respiratory distress within hours after presentation to the hospital. Taken together, these features indicate that this patient presents with a rapidly worsening pneumonia syndrome, which will be the starting point for building a differential diagnosis.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission
Sodium (mmol/liter)	135–145	138
Potassium (mmol/liter)	3.4–4.8	3.8
Chloride (mmol/liter)	100–108	99
Carbon dioxide (mmol/liter)	23.0–31.9	18
Urea nitrogen (mg/dl)	8–25	17
Creatinine (mg/dl)	0.60–1.50	1.0
Glucose (mg/dl)	70–110	118
Lactic acid (mmol/liter)	0.5–2.0	3.5
Alanine aminotransferase (U/liter)	10–55	70
Aspartate aminotransferase (U/liter)	10–40	128
Alkaline phosphatase (U/liter)	45–115	128
Total bilirubin (mg/dl)	0.0–1.0	1.7
Direct bilirubin (mg/dl)	0.0–0.4	0.5
Albumin (g/dl)	3.3–5.0	3.5
Hematocrit (%)	36–46	44.5
Hemoglobin (g/dl)	12–16	15
White-cell count (per μl)	4500–11,000	11,920
Differential count (per μl)		
Neutrophils	1800–7700	10,100
Lymphocytes	1000–4800	850
Monocytes	200–1200	600
Eosinophils	0–900	40
Immature granulocytes	0–100	280
Platelet count (per μl)	150,000–400,000	179,000
Prothrombin time (sec)	11.5–14.5	14.7
Prothrombin-time international normalized ratio	0.9–1.1	1.2
D-dimer (ng/ml)	<500	>10,000
Fibrinogen (mg/dl)	150–400	679
Ferritin (μg/liter)	20–300	1760
Lactate dehydrogenase (U/liter)	110–210	1340
C-reactive protein (mg/liter)	<8	185
Erythrocyte sedimentation rate (mm/hr)	0–13	84
Creatine kinase (U/liter)	60–400	1607
N-terminal pro–B-type natriuretic peptide (pg/ml)	0–1800	495
High-sensitivity troponin T (ng/liter)	0–14	62

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

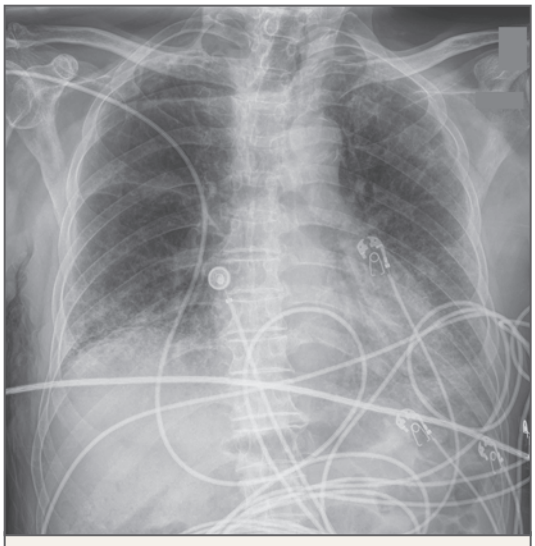

Figure 1. Chest Radiograph.

A portable anteroposterior chest radiograph shows bilateral patchy airspace opacities that are more extensive in the left lung than in the right lung. The opacities are mostly peripheral, with sparing of the perihilar region (the reverse batwing sign). Basilar reticular opacities are present, with mild basilar and apical bronchiectasis.

NONINFECTIOUS PNEUMONIA SYNDROMES

The causes of a pneumonia syndrome are not limited to infectious pneumonia and may include myriad other diseases, such as aspiration pneumonitis, cardiogenic pulmonary edema, cancer, vasculitis (with or without hemorrhage), diffuse alveolar hemorrhage, and the broad group of interstitial lung diseases.[1] Some of these disorders are particularly good mimics of an infectious process. However, this patient's clinical history and imaging findings make many of these causes of pneumonia syndrome unlikely.

Aspiration pneumonitis is always important to consider in patients with radiographic opacities and hypoxemia, particularly those who are elderly. However, in this case, no history is provided that would suggest dysphagia, clinically significant gastroesophageal reflux disease, or an episode of emesis and aspiration. In addition, the peripheral distribution of radiographic densities is not typical of aspiration, which frequently manifests as opacities in dependent areas of the lung.

Cardiogenic pulmonary edema is typically characterized by dyspnea, hypoxemia, and bilateral opacities. However, the infiltrates associated with cardiogenic pulmonary edema are usually perihilar and radiate outward. In addition, this patient did not report concomitant symptoms of weight gain, leg swelling, abdominal discomfort, orthopnea, or paroxysmal nocturnal dyspnea that are classic features of heart failure. His history of fever is also not consistent with cardiogenic pulmonary edema.

Rapidly growing cancers such as lymphoma can mimic infection with the presence of both systemic symptoms and focal opacities. Nonetheless, the tempo and acuteness of this patient's disease course, which occurred over a 3-day period, would be atypical for cancer, especially given that he reported no subacute symptoms such as unintentional weight loss.

Vasculitis and diffuse alveolar hemorrhage (inflammatory or bland) can mimic other alveolar filling processes such as edema and infectious pneumonia, are not always accompanied by hemoptysis, and can be accompanied by fever and other systemic symptoms. This patient has elevations in inflammatory markers, including the C-reactive protein level and the erythrocyte sedimentation rate, but otherwise does not have features in his history or presentation that would specifically suggest vasculitis or hemorrhage. Although it is important to consider noninfectious causes of pneumonia, the absence of specific suggestive features in this patient reduces the likelihood of these conditions. These possibilities should remain on the differential diagnosis if no other cause is identified.

INTERSTITIAL LUNG DISEASE

The patient describes having a history of a disease that "caused the lung tissue to harden," and therefore interstitial lung disease deserves special attention. There are many causes of interstitial lung disease, including diseases of unknown cause (idiopathic)[2] such as acute interstitial pneumonia and idiopathic pulmonary fibrosis, diseases associated with specific exposures such as hypersensitivity pneumonitis and drug-induced pneumonitis, and diseases associated with specific diagnoses such as sarcoidosis. Among the interstitial lung diseases, those most likely to be confused with acute infectious pneumonia include acute interstitial pneumonia (an idiopathic form of acute respiratory distress syndrome [ARDS]), cryptogenic organizing pneumonia (the idiopathic form of organizing pneumonia), and acute eosinophilic pneumonia. There are no

findings on imaging studies that would suggest a chronic fibrotic process, and the patient has no coexisting conditions such as rheumatologic disease that can be associated with nonspecific interstitial pneumonitis. Acute interstitial pneumonia and cryptogenic organizing pneumonia are diagnoses that are typically made only after infection has been ruled out, since their manifestations, and even their histologic patterns of diffuse alveolar damage and organizing pneumonia, are commonly seen with infection. Therefore, these two diagnoses should be considered only after an initial evaluation for infection has been performed. Acute eosinophilic pneumonia[3] can be manifested by peripheral patchy opacities, such as those that were seen on this patient's chest radiograph, and the diagnosis requires the finding of eosinophil predominance on bronchoalveolar lavage. However, the demographic features of patients with acute eosinophilic pneumonia do not match those of this patient; although this type of pneumonia is more commonly diagnosed in men than in women, it is also most frequently diagnosed in patients 20 to 40 years of age. Therefore, interstitial lung disease does not seem to be the most likely cause of this patient's acute pneumonia syndrome.

INFECTIOUS PNEUMONIA

All that being said, the most likely diagnosis in this patient is community-acquired pneumonia.[4] The differential diagnosis of community-acquired pneumonia is broad, and in many cases, a pathogen may not be identified. However, empirical treatment should target the most common pathogens, which include *Streptococcus pneumoniae*, and atypical pathogens such as *Mycoplasma pneumoniae*, legionella species, and *Chlamydia pneumoniae*. It is also vital to keep in mind the epidemiologic characteristics of respiratory viruses (e.g., seasonal influenza) in order to appropriately consider viral causes of pneumonia. This patient presented in Boston during the spring of 2020, when the Covid-19 pandemic had a substantial presence and the number of hospitalized patients was rapidly increasing.[5] He also has laboratory findings that have been commonly reported in patients with Covid-19, including lymphopenia and elevations in D-dimer, ferritin, and C-reactive protein levels and in the erythrocyte sedimentation rate. Together with the findings on the patient's chest radiograph — peripheral patchy opacities — SARS-CoV-2 is the most likely infectious pathogen.[6]

OTHER CONSIDERATIONS

In many ways, this patient's history and presentation reflect what we now recognize as classic features of Covid-19 — fever, cough, hypoxemia, patchy peripheral opacities, and common laboratory abnormalities. However, the description of an acute worsening of shortness of breath and the onset of focal pleuritic chest pain, although nonspecific, should arouse concern about acute pulmonary embolism in any clinical context.

If I am correct that this patient has pneumonia associated with Covid-19, the rapid progression of his hypoxemia suggests that ARDS may have developed as a complication of the Covid-19–related pneumonia.[7] The Berlin definition of ARDS includes both a ratio of partial pressure of arterial oxygen (Pao_2) to fraction of inspired oxygen (Fio_2) of 300 mm Hg or less and a positive end-expiratory pressure of at least 5 cm of water. However, the patient's worsening clinical trajectory is troubling, and his ratio of Pao_2 to Fio_2 suggests that he would meet this hypoxemia threshold if an arterial blood gas measurement were obtained.[8] Complicating this conclusion is the development of a likely pulmonary embolism, which would, in part, explain his hypoxemia. In fact, the mechanisms of hypoxemia for each of these pulmonary diseases are synergistic and are probably worsening his hypoxemia beyond the independent effect of each disease.

The mechanisms of hypoxemia associated with ARDS include shunt (the perfusion of nonventilated lung units) and low ventilation-to-perfusion ratios in certain regions of the lungs whereby the degree of perfusion is out of proportion to the degree of ventilation; both of these mechanisms result in a reduction in oxygenated pulmonary capillary blood, as well as systemic hypoxemia. The primary mechanism of hypoxemia in patients with clinically significant pulmonary embolism is also a low ventilation-to-perfusion ratio. When a clot obstructs blood flow to one portion of the lung, the nonperfused lung becomes so-called dead space (ventilation without perfusion), and the cardiac output is diverted to the remainder of the lung. Consequently, the nonaffected lung has a net increase in perfusion (with the assumption that no clini-

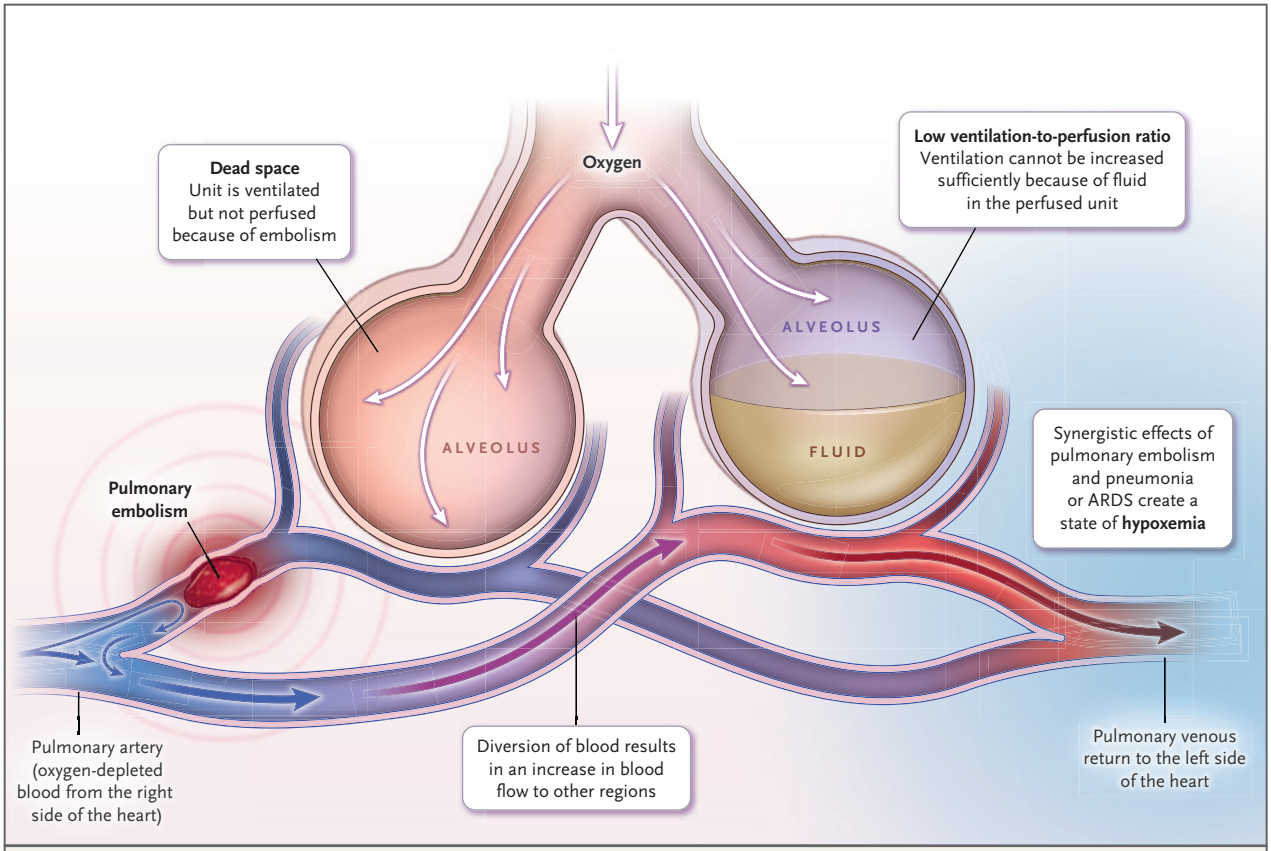

Figure 2. Synergistic Effects of Pulmonary Embolism and Acute Respiratory Distress Syndrome.

Occlusion of the pulmonary vasculature with a clot results in lung units that are ventilated but not perfused — so-called dead space. Dead space decreases the efficiency of minute ventilation but does not itself cause hypoxemia. However, when part of the pulmonary vascular tree is occluded and cardiac output is preserved, pulmonary arterial blood flow is diverted to the remaining lung units. To maintain a normal ventilation-to-perfusion ratio and therefore oxygenation, ventilation to these lung units must increase proportionally. If the patient is unable to sufficiently increase ventilation, particularly in the context of concomitant parenchymal disease such as pneumonia or acute respiratory distress syndrome (ARDS), this regional increase in blood flow results in ventilation–perfusion mismatch and hypoxemia.

cally significant right ventricular failure is present). If a patient is able to augment local ventilation to match this increase in perfusion, then hypoxemia does not occur. However, if a patient is unable to augment ventilation sufficiently, then hypoxemia develops. Hypoxemia may occur if the clot is large and if there is very high local perfusion of the preserved lung, but it can also occur when ventilation is impeded by a separate process. A complex cascade of pathophysiological processes, including the release of inflammatory mediators, that occurs in response to an acute pulmonary embolism can affect ventilation–perfusion mismatch by causing local bronchoconstriction, vasoconstriction, and surfactant dysfunction. In this patient, the pneumonia and evolving ARDS limit his ability to augment effective alveolar ventilation in the regions affected by the clot, and the clot may have caused ineffective perfusion in the regions of his lung that are spared by Covid-19 (Fig. 2).

Is there a relationship between Covid-19 and pulmonary embolism? Microvascular dysfunction is a well-known feature of ARDS, and up to 30% of patients with ARDS have pulmonary emboli.[9-11] These emboli are traditionally thought to be in situ vessel thromboses rather than true emboli associated with peripheral deep venous thrombosis. Another consideration in this patient is whether his clot is more directly related to Covid-19 than to ARDS, although there is no way to easily distinguish the two. The elegance

of a parsimonious diagnosis — one answer to explain all of a patient's ailments — is often invoked along with the principle of Ockham's razor, which states that, "Plurality ought never be posed without necessity."[12] However, in clinical medicine, patient presentations often do not fit these maxims, and this is one clinical situation in which a life-threatening diagnosis — acute pulmonary embolism — must be ruled out. Therefore, in addition to testing the patient's nasopharyngeal specimen for SARS-CoV-2 RNA to establish the diagnosis of Covid-19, I would recommend obtaining a computed tomographic (CT) pulmonary angiogram to identify pulmonary embolism.

DR. KATHRYN A. HIBBERT'S DIAGNOSIS

Pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and acute pulmonary embolism.

DIAGNOSTIC TESTING

Dr. Emmett: The first diagnostic test was nucleic acid testing of a nasopharyngeal swab for SARS-CoV-2 RNA; the specimen had been obtained while the patient was in the emergency department. Within a few hours after the specimen was submitted, the test showed a positive result for SARS-CoV-2 RNA, thus confirming the diagnosis of SARS-CoV-2 infection.

Dr. Goiffon: The second diagnostic test was dual-energy CT, which was performed after the administration of intravenous contrast material that was timed to maximally opacify the pulmonary arteries (Fig. 3). The imaging revealed multifocal ground-glass opacities and associated septal thickening in the periphery of both lungs that were more extensive in the left lung than in the right lung. Some of the ground-glass opacities abutted or surrounded smaller consolidations. Iodine map images showed decreased perfusion that was disproportionate to the density of the ground-glass opacities. Subocclusive filling defects were observed in the left main artery and segmental arteries of the left lower lobe, and an occlusive thrombus was noted in the lingular arteries. A four-chamber image showed that the ratio of the size of the right ventricle to the size of the left ventricle was approximately 1.1.

DISCUSSION OF MANAGEMENT

Dr. Annemarie E. Fogerty: In the 19th century, Rudolf Virchow identified three factors that contributed to pathologic venous thrombosis: increased blood coagulability, venous stasis, and vein damage. This patient had several features related to Virchow's triad. Although he did not have a known genetic mutation associated with thrombosis, cancer, or previous venous thromboembolism, his illness involved infection and inflammation, which are known hypercoagulable states. Venous stasis is another contributor in immobilized patients, particularly those in the intensive care unit (ICU). Endothelial injury is most commonly attributed to surgery or trauma, neither of which applied to this patient. However, endothelial inflammation (i.e., endotheliitis) is considered to be a major factor contributing to the risk of venous thromboembolism in patients with Covid-19 and thus merits special consideration.

The normal endothelium maintains an anticoagulant surface to permit smooth vascular blood flow. This is achieved through numerous processes, including the antiplatelet functions of nitric oxide and prostaglandins; the anticoagulant properties of heparins, thrombomodulin, and the protein C receptor pathway; and the fibrinolytic activity of tissue plasminogen activator. If the normal function of the endothelium is interrupted, as can occur with SARS-CoV-2 infection, the anticoagulant properties can be thwarted, which can result in a procoagulant state. Angiotensin-converting enzyme 2 (ACE2), which is abundantly expressed on the epithelia of the lung and small intestine and on the vascular endothelium, is the functional receptor of SARS-CoV-2.[13] Thus, this patient was vulnerable to thrombogenesis on the basis of SARS-CoV-2 infection leading to presumed endotheliitis.

Endothelial cell damage and direct invasion of SARS-CoV-2 within the endothelial cell membrane have been shown to result in a distorted microvascular and endothelial architecture of the infected lung.[14] Similar findings have been observed in the renal and small bowel endothelium of patients with Covid-19.[15] Endothelial inflammation is reflected in the many laboratory features that are now recognized as characteristic of SARS-CoV-2 infection, which were seen in this case: marked elevations in the levels of

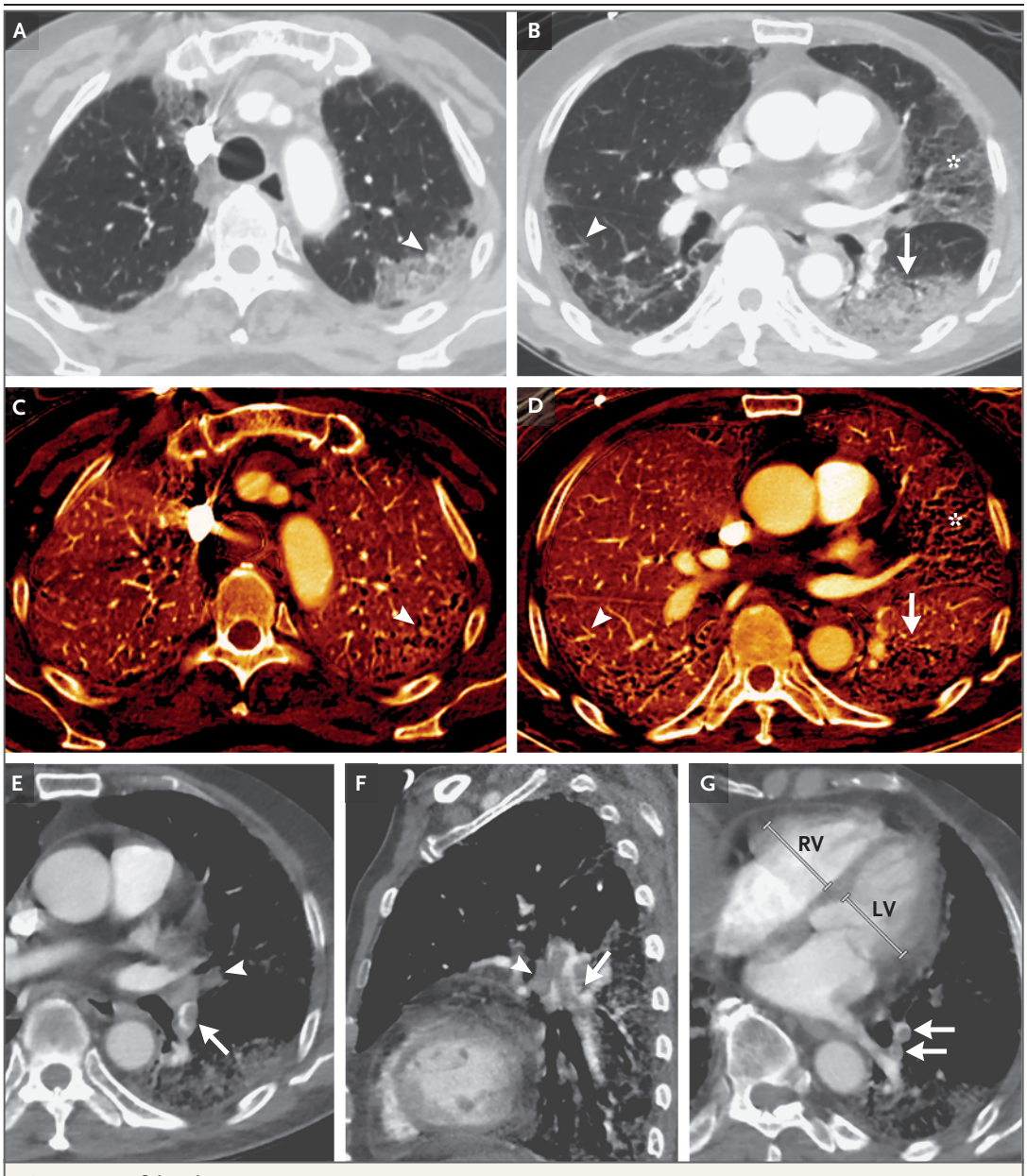

Figure 3. CT of the Chest.

Dual-energy CT was performed after the administration of intravenous contrast material according to a pulmonary embolism protocol. Axial CT images at different levels (Panels A and B) with their corresponding dual-energy iodine maps (Panels C and D) show peripheral ground-glass opacities (asterisks and arrowheads) with areas of consolidation (arrows). The ground-glass opacities that appear least opaque have the greatest perfusion defect (asterisks), disproportionate to that seen in other areas of abnormal lung. Axial and sagittal images (Panels E and F, respectively) show occlusive thrombosis (arrowheads) in the proximal lingular arteries and nonocclusive thrombosis (arrows) of the basal segmental arteries of the left lower lobe, findings that correspond to the perfusion defects seen on the iodine map images. A four-chamber view of the heart without cardiac gating (Panel G) shows that the ratio of the size of the right ventricle (RV) to the size of the left ventricle (LV) is approximately 1.1; additional nonocclusive thrombi are also noted (arrows).

D-dimer, fibrinogen, C-reactive protein, and ferritin. Interleukin-6 elevation is another feature of SARS-CoV-2 infection, although the level was not measured in this patient. The classic laboratory profile of Covid-19 is contrary to the usual profile of disseminated intravascular coagulation,

in which the fibrinogen level is low, the prothrombin time and activated partial-thromboplastin time are prolonged, and thrombocytopenia predominates. This patient had the profile more commonly associated with Covid-19, which is that of marked elevation of inflammatory markers, with a relatively preserved prothrombin time, activated partial-thromboplastin time, and platelet count.

A D-dimer elevation alone (even when markedly elevated) is not sufficient to confirm a diagnosis of venous thromboembolism, even in SARS-CoV-2–infected patients, since the D-dimer level can be elevated in many physiologic and pathophysiological states. In patients with Covid-19, an elevated D-dimer level has been associated with numerous poor outcomes, including ICU admission, the need for mechanical ventilation, thrombosis, bleeding, and death.[16-18] Circulating D-dimers are generated after clot formation and subsequent lysis. Initially, the production of fibrinogen is enhanced by interleukin-6, and fibrinogen is converted to a fibrin clot in the presence of thrombin. As plasmin breaks down the fibrin clots, D domains from adjacent fibrin monomers are released into the circulation and can be quantified with the use of the D-dimer assay. Thus, an elevated D-dimer level can occur in venous thromboembolism but also in small-vessel microthrombosis, endothelial inflammation, cancer, advanced age, pregnancy, and liver and renal failure. Because there is no threshold of D-dimer level that distinguishes thrombosis from endothelial damage alone in a SARS-CoV-2–infected patient, a high clinical suspicion of venous thromboembolism is indicated. For example, in a patient with worsening respiratory status or hypotension that is out of proportion to findings on chest radiography, appropriate diagnostic imaging is warranted, as was the case in this patient.

Once thrombosis in the pulmonary artery is identified, risk stratification is necessary to determine the appropriate treatment strategy — specifically, the need for mechanical intervention as opposed to anticoagulation alone.[19] This assessment is based primarily on the associated hemodynamic effect. Options for mechanical intervention can vary depending on local expertise and institutional experience and can include thrombolysis (systemic [at a full or reduced dose] or catheter-directed) or thrombectomy (catheter-based or surgical). The pulmonary embolism severity index is a tool for stratifying patients according to a high or low risk of death and includes blood pressure, heart rate, oxygen saturation, age, and a history of cancer, lung disease, or heart failure. Additional considerations in the scoring system include respiratory rate, sex, mental status, and body temperature. The Pulmonary Embolism Response Team Consortium defines a pulmonary embolism as massive when the systolic blood pressure is less than 90 mm Hg or there is a need for vasopressor support; a pulmonary embolism is defined as submassive when the pulmonary embolism severity index score indicates high risk or there is evidence of right ventricular dysfunction (as observed on imaging or suggested by an elevated troponin or N-terminal pro–B-type natriuretic peptide level). A massive or submassive pulmonary embolism is preferentially managed with mechanical intervention.[20] In this case, the patient's condition was hemodynamically stable; thus, he was assessed as having a lower-risk pulmonary embolism, for which anticoagulation alone was initiated.

In patients with pulmonary embolism, achieving therapeutic anticoagulation early is associated with decreased mortality[21] and therefore is critical to achieve expeditiously. However, the use of dose-adjusted unfractionated heparin often fails to achieve a therapeutic effect on the activated partial-thromboplastin time within 48 hours after initiation.[22] Low-molecular-weight heparin at a weight-based dose is more biologically predictable and is associated with a lower risk of additional thrombus formation and bleeding, as well as smaller thrombi, than dose-adjusted intravenous unfractionated heparin.[23] The use of up-front direct oral anticoagulant agents (factor II and X inhibitors) is also appropriate for patients with lower-risk pulmonary embolism. In this case, low-molecular-weight heparin was chosen to ensure rapid anticoagulation within the therapeutic range, to minimize staff exposure to twice-daily injections, and to avoid drug interactions.

Because this patient received a diagnosis of venous thromboembolism during his hospitalization, the venous thromboembolism is classified as provoked. In cases of provoked venous thromboembolism, a finite course of anticoagulation is usually advised, whereas longer-term anticoagulation is appropriate in cases of unprovoked thromboses.

FOLLOW-UP

Dr. Emmett: The patient was admitted to the ICU, where he remained for 3 days. His oxygenation was monitored closely, and the pulmonary embolism was initially treated with enoxaparin. During this time, he was able to maintain appropriate oxygenation while he was receiving supplemental oxygen through a nasal cannula at a rate of 6 liters per minute. After 3 days, he was transferred to the general medical floor. He began having clinically significant episodes of pleuritic chest pain and aspiration events that were associated with periods of hypoxemia. He also began to have substantial bleeding from the nose and mouth. At this point, with the assistance of the palliative care service, the patient and family decided to transition the goals of care to comfort measures only. He received dedicated care for intensive end-of-life care support. Ultimately, he died peacefully on the 16th hospital day.

FINAL DIAGNOSIS

Pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and acute pulmonary embolism.

This case was presented at the Medicine Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Black AD. Non-infectious mimics of community-acquired pneumonia. Pneumonia (Nathan) 2016;8:2.

2. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002;165:277-304.

3. De Giacomi F, Vassallo R, Yi ES, Ryu JH. Acute eosinophilic pneumonia: causes, diagnosis, and management. Am J Respir Crit Care Med 2018;197:728-36.

4. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med 2014; 371:1619-28.

5. Massachusetts Department of Public Health COVID-19 dashboard. April 28, 2020 (https://www.mass.gov/doc/covid-19-dashboard-april-28-2020/download).

6. Chivukula RR, Maley JH, Dudzinski DM, Hibbert K, Hardin CC. Evidence-based management of the critically ill adult with SARS-CoV-2 infection. J Intensive Care Med 2021;36:18-41.

7. The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.

8. Pandharipande PP, Shintani AK, Hagerman HE, et al. Derivation and validation of Spo2/Fio2 ratio to impute for Pao2/Fio2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. Crit Care Med 2009;37: 1317-21.

9. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562-72.

10. Greene R, Zapol WM, Snider MT, et al. Early bedside detection of pulmonary vascular occlusion during acute respiratory failure. Am Rev Respir Dis 1981;124:593-601.

11. Ryan D, Frohlich S, McLoughlin P. Pulmonary vascular dysfunction in ARDS. Ann Intensive Care 2014;4:28.

12. Wardrop D. Ockham's razor: sharpen or re-sheathe? J R Soc Med 2008;101:50-1.

13. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. J Pathol 2004;203:631-7.

14. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120-8.

15. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417-8.

16. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020;136: 489-500.

17. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med 2020;382: 2372-4.

18. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.

19. Rosovsky R, Chang Y, Rosenfield K, et al. Changes in treatment and outcomes after creation of a pulmonary embolism response team (PERT), a 10-year analysis. J Thromb Thrombolysis 2019;47:31-40.

20. Rivera-Lebron B, McDaniel M, Ahrar K, et al. Diagnosis, treatment and follow up of acute pulmonary embolism: consensus practice from the PERT Consortium. Clin Appl Thromb Hemost 2019;25: 1076029619853037.

21. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. Chest 2010;137:1382-90.

22. Prucnal CK, Jansson PS, Deadmon E, Rosovsky RP, Zheng H, Kabrhel C. Analysis of partial thromboplastin times in patients with pulmonary embolism during the first 48 hours of anticoagulation with unfractionated heparin. Acad Emerg Med 2020;27:117-27.

23. Robertson L, Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. Cochrane Database Syst Rev 2017;2:CD001100.