CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 18-2020: A 73-Year-Old Man with Hypoxemic Respiratory Failure and Cardiac Dysfunction

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PRESENTATION OF CASE

Dr. Lila M. Martin: A 73-year-old man was transferred to the intensive care unit (ICU) of an academic health center in Boston for acute hypoxemic respiratory failure in March 2020, 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 6 days before this transfer, when a dry cough, fever, and worsening fatigue developed. Two days later, his symptoms had not resolved, and he presented to the emergency department at a local hospital. The temperature was 38.8°C, the blood pressure 94/62 mm Hg, the heart rate 91 beats per minute, the respiratory rate 12 breaths per minute, and the oxygen saturation 97% while he was breathing ambient air. On examination, he appeared well, and the lung sounds were clear. The white-cell count was 5600 per microliter (reference range, 4800 to 10,500); 56% of the cells were neutrophils and 33% were lymphocytes. A nasopharyngeal swab was submitted to the Massachusetts State Laboratory for nucleic acid testing for SARS-CoV-2 RNA. Tests for influenza A and B viruses and respiratory syncytial virus were not performed owing to a statewide shortage of nasopharyngeal swabs.

Dr. Diana Litmanovich: Computed tomography (CT) of the chest, performed without the administration of intravenous contrast material, revealed small (1 to 1.5 cm in diameter), rounded central and peripheral ground-glass opacities in both lungs (Fig. 1A).

Dr. Martin: Oseltamivir was prescribed for the empirical treatment of influenza, and the patient was discharged from the emergency department and instructed to self-quarantine at home. During the next 4 days, his symptoms persisted; when dyspnea developed, he contacted his primary care physician and was referred back to the emergency department at the local hospital. The temperature was 38.6°C, the blood pressure 158/91 mm Hg, the heart rate 108 beats per minute, the re-

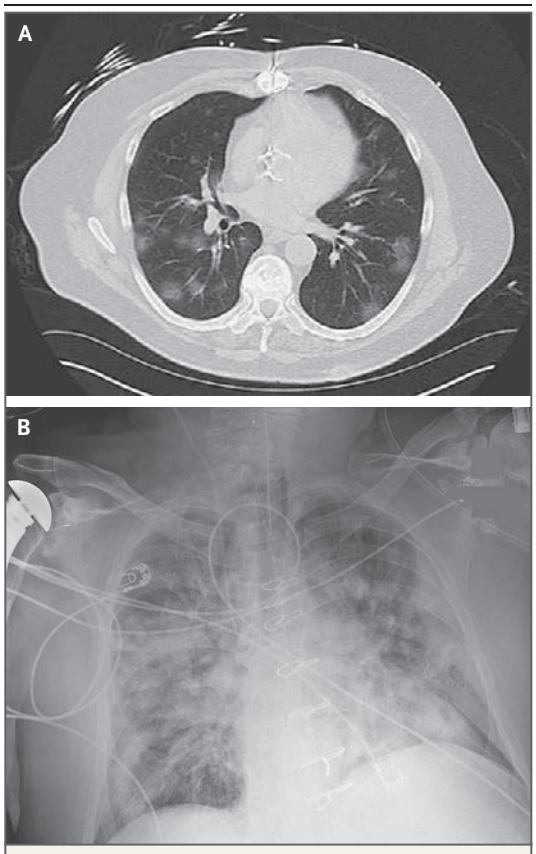

Figure 1. Imaging Studies of the Chest.

An axial CT image (Panel A), obtained without intravenous contrast enhancement during the initial emergency department presentation, shows scattered, confluent central and peripheral ground-glass opacities in both lungs. A radiograph (Panel B) obtained on admission to the intensive care unit shows extensive confluent parenchymal opacities in both lungs. The endotracheal tube is 7 cm above the carina, prompting subsequent adjustment; the central venous catheter in the right internal jugular vein is in an appropriate position, terminating in the superior vena cava, and there is no evidence of pneumothorax. Sternal wires and right shoulder arthroplasty from the patient's previous surgeries are visible.

spiratory rate 28 breaths per minute, and the oxygen saturation 90% while he was breathing ambient air. He appeared fatigued, tachypneic, and distressed; auscultation of the lungs revealed decreased breath sounds bilaterally. The trachea was intubated, and mechanical ventilation was initiated. Intravenous propofol, cisatracurium, cefepime, and norepinephrine were administered, and the patient was transferred by helicopter to an academic health center in Boston for further evaluation and management of symptoms.

On the patient's arrival at the academic health center, his family was available to provide information regarding medical history, surgical history, and a recent review of systems by telephone. The review of systems was negative for conjunctivitis, nasal congestion, sinusitis, anosmia, abdominal pain, bloating, diarrhea, light-headedness, dizziness, chest pain, and edema. The patient's status with respect to influenza and pneumococcal vaccination was unknown. His medical history was notable for hypertension, diabetes mellitus, atrial fibrillation, and obstructive sleep apnea, for which nightly continuous positive airway pressure had been prescribed. He had undergone surgical aortic-valve replacement for severe symptomatic aortic stenosis 1 year earlier; there had been no evidence of obstructive coronary artery disease on preoperative angiography. Radiofrequency ablation for recurrent atrial flutter had been performed 2 years earlier, and he had undergone right shoulder arthroplasty. Medications included metformin, insulin lispro, atenolol, losartan, and apixaban. Multiple statin medications had previously caused myalgia with elevated creatine kinase levels.

The patient was a health care worker but had no known sick contacts. No family members were ill. He had not traveled recently or had other environmental exposures. He did not use tobacco, drink alcohol, or use illicit substances. His family history was notable for coronary artery disease in multiple relatives; there was no history of pulmonary disease.

The patient was admitted to a dedicated Covid-19 ICU at the academic health center. The temperature was 38.9°C, the blood pressure 100/60 mm Hg while he was receiving intravenous norepinephrine, the heart rate 112 beats per minute, the respiratory rate 25 breaths per minute, and the oxygen saturation 95% while he was receiving oxygen through a mechanical ventilator (positive end-expiratory pressure, 5 cm of water; tidal volume, 410 ml; fraction of inspired oxygen, 1.0). The patient was sedated. There was no jugular venous distention. Auscultation of the chest revealed a tachycardic rhythm with no murmur and coarse breath sounds with rhonchi in both lungs. His arms and legs were cool and clammy. The remainder of the examination was normal.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission, Intensive Care Unit
Hemoglobin (g/dl)	13.5–17.5	15.7
Hematocrit (%)	40–51	44.5
White-cell count (per μl)	4000–10,000	18,400
Differential count (%)		
Neutrophils	34–71	82.2
Lymphocytes	19–53	11.4
Monocytes	5–13	5.3
Eosinophils	1–7	0.0
Platelet count (per μl)	150,000–400,000	222,000
Sodium (mmol/liter)	135–147	138
Potassium (mmol/liter)	3.4–5.4	4.9
Chloride (mmol/liter)	96–108	100
Carbon dioxide (mmol/liter)	22–32	16
Urea nitrogen (mg/dl)	6–25	17
Creatinine (mg/dl)	0.5–1.2	1.8
Calcium (mg/dl)	8.4–10.3	8.0
Alanine aminotransferase (U/liter)	0–40	19
Aspartate aminotransferase (U/liter)	0–40	88
Creatine kinase (U/liter)	47–322	395
Lactate (mmol/liter)	0.5–2.0	3.5
Troponin T (ng/ml)	<0.01	4.19
Central venous oxygen saturation (%)	70–80	78
N-terminal pro–B-type natriuretic peptide (pg/ml)	0–229	1298
Lactate dehydrogenase (U/liter)	94–250	572
D-dimer (ng/ml)	0–500	3838
C-reactive protein (mg/liter)	0–5.0	118.2
Ferritin (ng/ml)	30–400	2695
Prothrombin time (sec)	9.4–12.5	15.6
International normalized ratio	0.9–1.1	1.4
Arterial blood gases		
Fraction of inspired oxygen		1.0
pH	7.35–7.45	7.29
Partial pressure of carbon dioxide (mm Hg)	35–45	42
Partial pressure of oxygen (mm Hg)	80–105	118

* 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 calcium to millimoles per liter, multiply by 0.250. To convert the values for lactate to milligrams per deciliter, divide by 0.1110.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Beth Israel Deaconess Medical Center 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.

Catheters were placed in the right internal jugular vein and the left radial artery. The central venous pressure was 4 mm Hg. The partial-thromboplastin time and blood levels of phosphorus and magnesium were normal; other laboratory test results are shown in Table 1. A blood sample was obtained for culture, and a nasopharyngeal swab was obtained for nucleic acid testing for the detection of community-acquired respiratory pathogens and SARS-CoV-2 RNA.

Dr. Litmanovich: An anteroposterior radiograph of the chest (Fig. 1B) showed extensive confluent central and peripheral parenchymal opacities in both lungs. The central venous catheter in the right internal jugular vein was in an appropriate position.

Dr. Martin: An electrocardiogram (Fig. 2A) showed normal sinus rhythm with left atrial abnormality, a borderline prolonged PR interval, ST-segment depressions of 1 mm in the inferior leads, ST-segment elevations of 1 mm in leads I and aVL, PR-segment deviations (a depression in lead II and an elevation in lead aVR), and a corrected QT (QTc) interval of 425 msec. A transthoracic echocardiogram showed severe global left ventricular hypokinesis, as well as dysfunction of the right ventricular free wall and the apex (see Videos 1 and 2, available with the full text of this article at NEJM.org). These findings were new relative to an echocardiogram that had been obtained 2 months earlier as part of routine surveillance after aortic-valve replacement, that had shown normal biventricular function. The size of the left ventricular chamber was normal. There was mild symmetric thickening of the left ventricular wall (12 mm; normal thickness, ≤11), a finding that was unchanged from the previous echocardiogram. No evidence of pericardial effusion was observed, and the bioprosthetic aortic valve was well seated and appeared to be functioning normally.

The patient received intravenous propofol, fentanyl, midazolam, and cisatracurium, as well as empirical intravenous vancomycin, cefepime, and doxycycline. Treatment with apixaban was discontinued, and intravenous heparin was initiated. Hydroxychloroquine was administered enterally.

Additional management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Dhruv S. Kazi: This 73-year-old man with a history of coronary, valvular, and arrhythmic heart disease presented with hypoxemic respiratory failure and bilateral pulmonary infiltrates during the Covid-19 pandemic. His presentation is also notable for hypotension, ST-segment abnormalities, and biventricular dysfunction.

HYPOXEMIC RESPIRATORY FAILURE WITH PULMONARY INFILTRATES

The differential diagnosis of this patient's pulmonary findings includes cardiogenic pulmonary edema, multifocal pneumonia, and acute respiratory distress syndrome (ARDS). Prosthetic-valve dysfunction and endocarditis can cause pulmonary edema, but there were no examination findings suggestive of prosthetic aortic stenosis or aortic regurgitation. Furthermore, the limited echocardiographic views that were available suggested that the prosthesis was functioning normally. Despite the presence of ventricular dysfunction and an elevated N-terminal pro–B-type natriuretic peptide level, cardiogenic pulmonary edema is an unlikely diagnosis in this patient, given the low central venous pressure and the absence of physical examination findings to support congestion.

Videos showing transthoracic echocardiography are available at NEJM.org

ACUTE RESPIRATORY DISTRESS SYNDROME

Although this patient has a history of clinically significant cardiac disease, multifocal pneumonia and ARDS are the likely causes of his hypoxemic respiratory failure. The diagnosis of ARDS is made if a patient has sudden onset (or progression) of symptoms within 1 week after a known clinical insult, bilateral pulmonary opacities on chest imaging, respiratory failure that is not fully explained by cardiac failure or fluid overload, and moderate-to-severe impairment of oxygenation[1]; this patient met all four criteria. ARDS can be precipitated by various triggers, including infection, aspiration, trauma, transfusion-related lung injury, the use of illicit drugs, or acute pancreatitis.[2] This patient had reported cough and fever in the week preceding the onset of respiratory failure, raising concern for viral or bacterial pneumonia. Although he presented

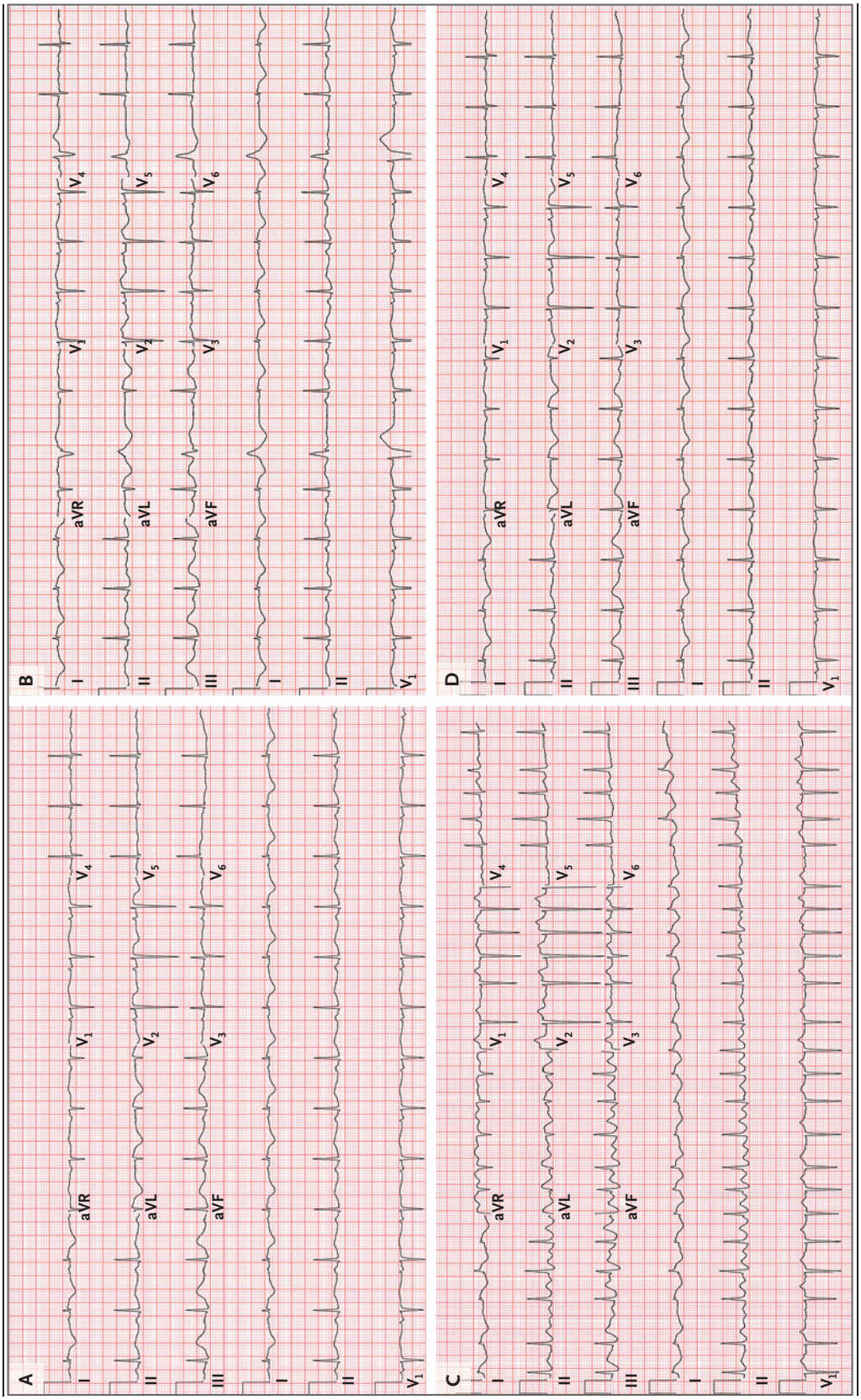

Figure 2 (facing page). Electrocardiograms.
An electrocardiogram obtained on presentation to the academic health center (Panel A) shows normal sinus rhythm with left atrial abnormality, a borderline prolonged PR interval, ST-segment depressions of 1 mm in the inferior leads, ST-segment elevations of 1 mm in leads I and aVL, and PR-segment depression in lead II and PR-segment elevation in lead aVR. Territorial ST-segment elevation raises the possibility of a coronary occlusion, but PR-segment deflections may indicate pericardial irritation, possibly consistent with myopericarditis. The corrected QT (QTc) interval is 425 msec. A repeat electrocardiogram obtained 4 hours after presentation (Panel B) shows normal sinus rhythm with persistent ST-segment elevations in leads I and aVL, with broad inverted T waves in those leads as well, and occasional ventricular ectopic beats that probably originate from the right ventricle. The QTc interval is 462 msec. An electrocardiogram obtained on the third hospital day (Panel C) shows atrial fibrillation with a ventricular rate of 135 beats per minute, as well as persistent ST-segment elevations of 1 mm in leads I and aVL; the QTc interval is approximately 475 msec. An electrocardiogram obtained on the seventh hospital day (Panel D) shows normal sinus rhythm, with reduced ST-segment elevations in the lateral leads; however, regional T-wave inversion and a reduction in R-wave voltage in lead aVL are present, findings that could be consistent with transmural necrosis.

while there was still substantial influenza activity in the area, his syndrome progressed rapidly while he was receiving oseltamivir. Because of the patient's presentation during the initial increase in SARS-CoV-2 infections in Massachusetts and the possibility of his occupational exposure to asymptomatic but infected patients, Covid-19 is the leading diagnosis in this case.[3] The patient's age, male sex, and history of cardiovascular disease, diabetes, and hypertension all increase his risk of having a severe form of SARS-CoV-2 infection.[4]

CARDIAC ABNORMALITIES

This patient had an elevated troponin T level suggestive of myocardial injury, which is common among critically ill patients with SARS-CoV-2 infection. In a retrospective single-center cohort study involving 416 hospitalized patients with Covid-19 in Wuhan, China,[5] cardiac injury, defined by a troponin T level above the 99th percentile (upper limit of the reference range), was present in 19.7% of the patients. This patient's ST-segment elevations in leads I and aVL arouse concern about an ST-segment elevation myocardial infarction (STEMI) in the lateral wall. However, the presence of subtle PR-segment deflections on the electrocardiogram, the finding of biventricular systolic dysfunction, and the high levels of inflammatory markers may suggest myopericarditis. The fact that the left ventricle was not dilated suggests that the cardiomyopathic process is most likely acute.

Other possible causes of this patient's findings on electrocardiography include ischemia (due to either sudden rupture of an atherosclerotic plaque in an epicardial coronary vessel or a supply–demand mismatch resulting from hypoxemia and sepsis), cytokine-mediated myocardial injury in the context of a hyperinflammatory state, or stress-induced cardiomyopathy (whereby an emotional or physical stressor produces transient ventricular systolic dysfunction).[6,7] It is important to rule out all other causes of myocardial dysfunction before making a diagnosis of stress-induced cardiomyopathy. Of note, this patient's normal central venous oxygen saturation and low central venous pressure suggest that the development of hypotension is probably due to the use of sedative and paralytic medications and to distributive shock in the context of infection, rather than a cardiogenic cause. To determine the next steps in the evaluation of this patient, urgent decision making about the need for coronary angiography is warranted, with attention given to the possible infectious risks associated with performing this procedure in a patient who most likely has SARS-CoV-2 infection.

CORONARY ANGIOGRAPHY

Dr. Duane S. Pinto: Coronary angiography can be used to determine whether revascularization is indicated, but there are additional considerations in a critically ill patient with confirmed or suspected Covid-19. First, it is important for clinicians to maintain a high index of suspicion for diseases such as myopericarditis or stress-induced cardiomyopathy that can produce ST-segment elevation. Second, even when STEMI is suspected, physicians must weigh the potential benefit of emergency revascularization against the risks of invasive procedures in a patient with a competing critical illness such as Covid-19.

In patients with Covid-19 who have suspected STEMI, the reperfusion strategy should be tailored to the individual patient. During the Covid-19 outbreak in Hong Kong, the median time from

the onset of symptoms to presentation increased from approximately 80 minutes to 320 minutes among patients with STEMI, a finding that implied that patients were avoiding the hospital, which possibly resulted in a reduced amount of myocardium that could be salvaged.[8] Medical management, with avoidance of procedural and bleeding risks, may be acceptable in patients with severe SARS-CoV-2 infection, particularly if the patient's condition is stable and the infarction is small.

Primary percutaneous coronary intervention is preferred over fibrinolysis if a substantial amount of myocardium can be salvaged and resources can be mobilized rapidly. If prolonged delays are anticipated because resources have been exhausted and the catheterization laboratory is unavailable, fibrinolytic therapy may become necessary.[9,10]

It is important to consider that the prevalence of myopericarditis is probably higher among patients with SARS-CoV-2 infection than in the general population. Given the increased prevalence of STEMI mimics, any risk of intracranial hemorrhage with fibrinolysis is unnecessary, even a risk as small as approximately 1%. Routine fibrinolysis is also unlikely to reduce resource utilization, staff exposure, or the length of stay and often necessitates the use of scarce ICU resources. Coronary angiography in combination with strategies to avoid nosocomial infection is the preferred option for ambiguous cases and may also be warranted in situations in which attempted fibrinolysis has failed.

Echocardiography can be useful in identifying wall motion abnormalities that differentiate myopericarditis from coronary occlusion. In this patient, given that the echocardiogram showed global biventricular systolic dysfunction, suspicion of an acute occlusion of an epicardial coronary artery is low relative to possible myopericarditis, and it is appropriate to defer emergency coronary angiography.

MYOPERICARDITIS

Dr. Kazi: Several reported cases of possible myopericarditis among patients with SARS-CoV-2 infection have been published.[11-14] Some of these patients presented with localized ST-segment elevations on electrocardiography but were subsequently noted to have no evidence of obstructive coronary disease on coronary angiography. One patient, a previously healthy 53-year-old woman who presented with a 1-week history of dyspnea and subjective fever, was noted to have diffuse ST-segment elevations, severe left ventricular dysfunction, and a small pericardial effusion, as well as cardiac magnetic resonance imaging (MRI) findings that were reportedly diagnostic of acute myopericarditis.[11] In another patient, cardiac tamponade developed from a pericardial effusion that was attributed to SARS-CoV-2 infection.[15] Although patients in whom myocardial injury develops also typically have moderate-to-severe lung involvement, cases with isolated cardiac involvement have also been reported.[11,15] Most case reports have suggested that if a patient survives the initial infection, there is recovery of myocardial function in the subsequent weeks, although acute and severe cardiac deterioration after pulmonary recovery have been reported. Although we are still learning about the findings of myopericarditis associated with SARS-CoV-2 infection that can be observed on electrocardiography, other causes of myopericarditis and cardiac irritation are known to produce a range of changes on electrocardiography, including ST-segment elevations that can mimic a STEMI.[16,17]

Given the constellation of clinical, laboratory, and imaging findings, the most likely diagnosis in this patient is myopericarditis due to infection with SARS-CoV-2.

DR. DHRUV S. KAZI'S DIAGNOSIS

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in acute respiratory distress syndrome and suspected myopericarditis.

DIAGNOSTIC TESTING

Dr. Martin: A repeat electrocardiogram obtained 4 hours after presentation to the academic health center (Fig. 2B) showed normal sinus rhythm with ventricular ectopic beats. There were persistent ST-segment elevations in leads I and aVL, with broad inverted T waves. The QTc interval was 462 msec.

The next day, the test of the nasopharyngeal swab obtained during the patient's evaluation at the first hospital returned positive for SARS-CoV-2 RNA. A repeat measurement of the C-reactive protein level was higher than the upper limit

detectable by the assay (300 mg per liter). The interleukin-6 level was 412 pg per milliliter (reference range, <5.0). Cardiac MRI was deferred.

DISCUSSION OF MANAGEMENT

Dr. Kevin J. Clerkin: Management of suspected myopericarditis with ventricular dysfunction in a critically ill patient with Covid-19 consists of primarily supportive care. However, there are a number of promising — albeit unproven — therapies, which can be categorized into two groups: those targeting SARS-CoV-2 and those targeting inflammation.

Remdesivir, a broad-spectrum antiviral agent that interrupts viral replication by acting as a nucleotide analogue, was suggested to have possible clinical benefit in a recent uncontrolled trial[18] and on the basis of preliminary results of a phase 3 clinical trial[19]; it is currently also being evaluated in other phase 3 clinical trials (ClinicalTrials.gov numbers, NCT04292899 and NCT04292730). Hydroxychloroquine has received considerable attention, given that it blocks entry of SARS-CoV-2 into cells in vitro; small, preliminary studies suggest clinical efficacy when the drug is used in combination with azithromycin.[20] At my institution, we initially administered this empirical combination frequently and then switched to hydroxychloroquine alone to treat patients with Covid-19 who did not have QTc prolongation (i.e., a QTc interval of <500 msec for patients with a QRS duration of ≤120 msec and a QTc interval of <550 msec for others). As a result of our observations,[21] we have stopped routinely using hydroxychloroquine. The combination protease inhibitor lopinavir–ritonavir also shows efficacy in vitro, but a randomized trial did not show a significant benefit among hospitalized patients with Covid-19.[22] Investigational antiviral strategies include recombinant human angiotensin-converting enzyme 2, convalescent serum (on the basis of an initial small report suggesting efficacy in patients with SARS-CoV-2 infection),[23,24] and intravenous immune globulin.

Therapies targeting inflammation and cytokine release include anti–interleukin-6 therapy. Tocilizumab, a humanized murine interleukin-6 receptor antagonist that has been recommended in Chinese guidelines,[25] and sarilumab, a human interleukin-6 receptor antagonist, are being studied in clinical trials. Glucocorticoids[13] have been used in critically ill patients with Covid-19 but are not routinely recommended because of the possibility of worsening lung disease in patients who also have ARDS[26] and because they have been associated with delayed clearance of SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) RNA.[27] The effectiveness and most appropriate timing of these therapies is uncertain. Similarly, the role of angiotensin-receptor blockers remains unknown but is being actively investigated in two trials of losartan (ClinicalTrials.gov numbers, NCT04311177 and NCT04312009) and other trials.[23]

FOLLOW-UP

Dr. Kazi: In line with the clinical practice at our institution at that time, we initiated empirical treatment with hydroxychloroquine and intravenous immune globulin. Azithromycin was not administered because of concern about the patient's prolonged QTc interval. Statin therapy was deferred, owing to the patient's previous adverse drug reaction. He received supportive therapy with a restrictive fluid strategy, and the electrolyte balance was monitored closely, given his ongoing treatment with hydroxychloroquine.[28]

Dr. Martin: Serial electrocardiograms were obtained to monitor the QTc interval while the patient was receiving hydroxychloroquine therapy. Paroxysmal atrial fibrillation with a rapid ventricular response was noted on the third day, with ST-segment elevations of 1 mm in leads I and aVL. The QTc interval was approximately 475 msec (Fig. 2C). Amiodarone was administered intravenously. The troponin T level was 5.97 ng per milliliter.

Dr. Peter J. Zimetbaum: Electrocardiograms obtained during the first 3 days of this patient's hospitalization at the academic health center showed serial prolongation of the QT interval. Broad and inverted T waves with QT prolongation in this context can be due to an underlying myopericarditis or the use of medications that can lead to QT prolongation. Other causes of QT prolongation to be considered in critically ill patients include ischemia and electrolyte abnormalities, but the levels of sodium, potassium, and magnesium were normal.

Since both hydroxychloroquine and azithromycin can prolong the QT interval and increase the risk of torsades de pointes, it is important

that patients receiving these agents undergo monitoring of the QTc interval every 6 to 8 hours if the interval is 500 msec or longer, or once daily otherwise. Although 12-lead electrocardiography is the standard of care for assessment of the QTc interval,[29] we try to minimize repeated use in patients with Covid-19 to prevent exposure of health care providers to SARS-CoV-2. We typically obtain a baseline electrocardiogram before initiation of agents known to cause QT prolongation and then rely on standard telemetry to monitor the patients. In the event that the rapidly increasing admissions for suspected or confirmed Covid-19 outstrip institutional capacity for telemetric monitoring, our contingency plan is to use ambulatory monitoring devices with continuous real-time telemetry.[30,31]

PAROXYSMAL ATRIAL FIBRILLATION

In this patient, who previously had had a radiofrequency ablation for atrial flutter, the occurrence of paroxysmal atrial fibrillation was probably a result of stress from critical illness, hypoxemia, and infection. Other forms of myopericarditis increase the risk of atrial tachyarrhythmias, ventricular tachyarrhythmias, and conduction abnormalities. Such arrhythmias have been described in patients with Covid-19, but clinical trials are urgently needed to examine the nature, incidence, and prognosis of arrhythmias associated with Covid-19.

The choice of intravenous amiodarone for the treatment of paroxysmal atrial fibrillation was reasonable, given the relative safety of this drug in the context of acute illness. The occurrence of pulmonary toxic effects associated with amiodarone would be a devastating complication in any patient with hypoxemic respiratory failure, but it is an extremely rare complication of treatment and seldom occurs during the first few weeks of therapy. Preexisting lung disease does not increase the likelihood of pulmonary toxic effects resulting from the use of amiodarone.[32] Of note, treatment with amiodarone produces QT prolongation; however, torsades de pointes arrhythmias resulting from the use of amiodarone are rare.[32]

Dr. Kazi: We monitored the QTc interval every 8 hours while the patient was receiving both hydroxychloroquine and amiodarone. Since evidence supporting the use of hydroxychloroquine in the management of Covid-19 was very limited, the patient's prolonged QTc interval prompted us to discontinue treatment with hydroxychloroquine in favor of amiodarone, which we continued in an effort to maintain sinus rhythm.

Dr. Martin: An electrocardiogram obtained on hospital day 7 (Fig. 2D) showed normal sinus rhythm with a rate of 82 beats per minute. The ST-segment elevations in the lateral leads were no longer as prominent, but there was a regional T-wave inversion and a reduction in R-wave voltage in lead aVL, findings that could be consistent with transmural necrosis. The troponin T level declined to 2.72 ng per milliliter. Chest radiography revealed a radiographically substantial decrease in bilateral opacities.

The patient's clinical course was complicated by progressive renal failure, for which he underwent intermittent hemodialysis, as well as metabolic encephalopathy. Subsequently, a high-grade fever and leukocytosis (predominantly neutrophilic) developed, and there was concern about a secondary bacterial infection. He was receiving escalating pressor support and had rising lactate levels, despite broad-spectrum antibiotic coverage for ventilator-assisted pneumonia. The troponin T level further decreased to 0.71 ng per milliliter; a repeat transthoracic echocardiogram showed a left ventricular ejection fraction of 70%, with unchanged mild symmetric left ventricular hypertrophy. After discussion with the patient's family, he was transitioned to comfort measures only. He died on hospital day 18. No postmortem examination was performed.

Dr. Kazi: During the course of the Covid-19 pandemic, providers have often been compelled to make clinical decisions on the basis of imperfect information. The changing practice patterns regarding the empirical use of hydroxychloroquine illustrate the need to update clinical practice in response to emerging evidence, as in this case.

Dr. David M. Dudzinski: Available reports from China, Italy, New York, and the state of Washington document heterogeneous cardiac manifestations associated with Covid-19. These include biomarker evidence of myocardial necrosis, ventricular dysfunction, pericardial effusion, dysrhythmia, and cardiogenic shock.[14,15,33,34] These conditions appear to occur in patients with severe respiratory dysfunction, although there are early reports of isolated cardiac manifestations from

SARS-CoV-2 infection. Cardiac manifestations may be related to indirect effects of SARS-CoV-2 on the heart, mediated through catecholaminergic tone, dysregulated coagulation with a prothrombotic state and possible microvascular obstruction, hypoxemia and tissue hypoxia, and a proinflammatory cytokine milieu.[33] Direct cytotoxic effects of the virus on myocardium may be another potential mechanism.

Knowledge, and proof, of myopericarditis — an inflammatory cellular infiltrate in the myocardium that may be accompanied by necrosis[16] — due to coronaviruses remains limited. Autopsy data from 20 patients who died during the SARS outbreak in 2003 identified viral RNA in the hearts of 7 of the patients.[35] A previous report described a patient in whom acute myopericarditis had developed due to infection with MERS-CoV; the diagnosis was based on cardiac MRI evidence of myocardial edema and regional late gadolinium enhancement in the left ventricle.[36] Two reports of patients with Covid-19 who presented with ST-segment elevations, an elevated troponin T level, and hypotension described increased ventricular wall thickness, with subsequent reductions in ventricular wall thickness temporally concurrent with overall recovery,[11,14] ostensibly reflecting a reduction in myocardial edema and inflammation. Normalization of cardiac dilatation, which suggests reversal of an acute cardiac process, has been reported.[13] Access to contemporary tools used for the assessment and diagnosis of myopericarditis — endomyocardial biopsy in certain clinical scenarios and cardiac MRI to assess for imaging evidence of myocardial inflammation[16] — has been a logistic challenge during the Covid-19 pandemic (although MRI was performed in one of the two patients with Covid-19 described above).[11] Cardiologists, intensivists, hospitalists, emergency physicians, and other health care providers should contemplate a broad differential diagnosis for acute cardiac dysfunction, including entities such as cardiac ischemia, stress-induced cardiomyopathy, and sepsis-induced cardiomyopathy. Guideline-based treatment for cardiomyopathy and supportive intensive care interventions should also be provided while attempting to enroll patients in clinical trials of investigational treatments.[33]

FINAL DIAGNOSIS

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with acute respiratory distress syndrome and suspected myopericarditis.

This case was presented at the Beth Israel Deaconess Medical Center Cardiology Clinical Case Conference, as part of a Boston-wide roundtable on cardiomyopathy associated with Covid-19.

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

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