Circulation

CARDIOVASCULAR CASE SERIES

Microthrombi and ST-Segment–Elevation Myocardial Infarction in COVID-19

Information about a real patient is presented in stages (boldface type) to expert clinicians (Drs Guagliumi, Virmani, and Finn), who respond to the information, sharing their reasoning with the reader (regular type). A discussion by the authors follows.

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Patient presentation: A 43-year-old woman complained of abrupt onset of chest pain, which started while she was assisting her husband who had just been hospitalized for coronavirus disease 2019 (COVID-19) interstitial pneumonia. A 12-lead ECG performed 2 hours after symptom onset documented an ST-segment elevation in the inferior and lateral leads (Figure 1A). She was transferred to our hub center for urgent coronary angiography and primary percutaneous coronary intervention.

On admission, she was awake, complaining of persistent chest pain. She reported neither fever nor dyspnea in previous days but a transient episode of angina the day before. She was hypotensive and tachycardic (systolic blood pressure, 70 mm Hg; heart rate, 130 bpm). Coffee ground emesis was present. While she was breathing room air, her So_2 was 100%, Pao_2/Fio_2 ratio was normal, and lactate was moderately increased to 4.39 mmol/L. Focused echocardiography examination revealed severe left ventricular dysfunction (ejection fraction, 25%) with global hypokinesia and inferior and lateral akinesia (Figure 1C and Movie I in the Data Supplement). A moderate pericardial effusion (13 mm) without signs of cardiac tamponade was observed. Blood test documented normal white and red cell counts, mild acute kidney and liver injury, and slightly increased high-sensitivity C-reactive protein (1.4 mg/dL). The international normalized ratio and partial thromboplastin time were in normal range. High-sensitivity troponin I was 11795 ng/L (Figure 2).

Dr Guagliumi: Clinical suspicion for COVID-19 was very high given the clinical history of exposure. Very little is known about the nature of how COVID-19 infection causes injury to the heart, but the differential diagnosis at this point with ST-segment elevations and chest pain included epicardial coronary thrombosis in the inferior (likely right coronary artery) territory, myocarditis-induced electrocardiographic changes, coronary spasm, and acute pericarditis. Given the clinical history of chest pain in a relatively young woman with no coronary risk factors and marked increase of troponin, suspicion was high for myocarditis, but an acute coronary syndrome was important to rule out.

Patient presentation (continued): Emergency coronary angiography showed normal epicardial coronary vessels with TIMI (Thrombolysis in Myocardial Infarction) grade 2 flow in the left anterior descending artery and intense, persistent myocardial blush in the distal right coronary artery
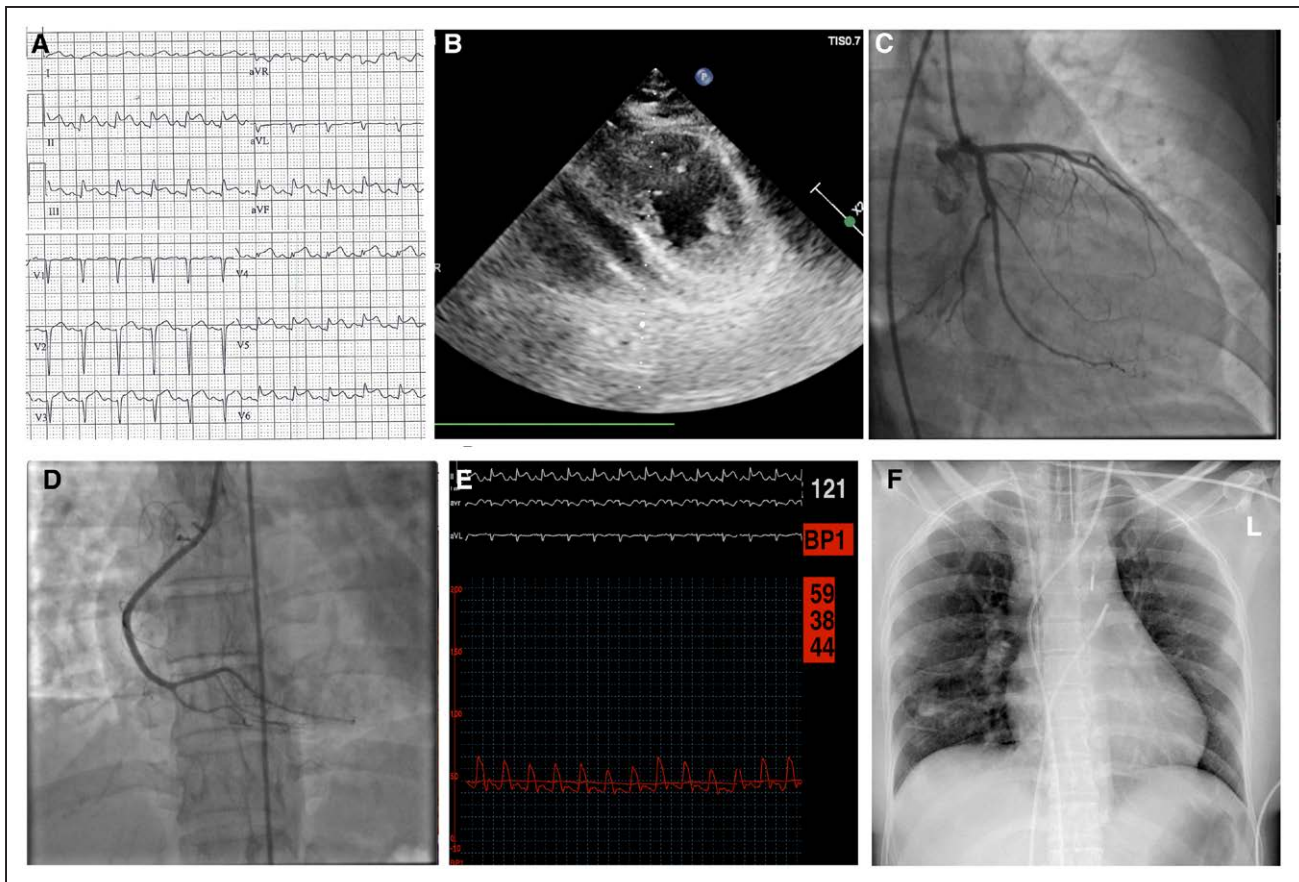
Figure 1. Cardiac clinical evaluation.

A, Presenting 12-lead ECG showing inferior and lateral ST-segment elevation. **B**, Transthoracic echocardiogram, left ventricular short-axis view, shows anteroapical hypokinesis with akinesis of the inferior and later walls with significant right ventricular dysfunction. **C** and **D**, Left (**C**) and right (**D**) coronary angiography showing no significant obstructive coronary artery disease. **E**, Aortic hemodynamic tracing during initial catheterization showing ST-segment elevation on the ECG with a heart rate of 121 bpm (**top**) and blood pressure of 59/38 mm Hg. **F**, Chest radiograph demonstrating no obvious interstitial infiltrate pattern.

(Figure 1C and 1D and Movies II and III in the Data Supplement). Because of progressive cardiogenic shock (invasive blood pressure, 60/40 mm Hg), vasopressors and intra-aortic balloon pump were initiated for hemodynamic support (Figure 1E). The patient was transferred to the intensive care unit. Chest radiography showed pulmonary congestion without signs of interstitial pneumonia (Figure 1F).

A nasopharyngeal swab was positive for severe acute respiratory syndrome coronavirus 2 infection by reverse-transcriptase polymerase chain reaction assays, and antiretroviral therapy (darunavir/cobicistat) was started in the intensive care unit. Blood tests for concomitant bacterial or viral infections were negative. Despite hemodynamic support, she remained hypotensive (72/34 mm Hg) with a cardiac index of 1.1 L·min−1·m−2 and oliguria (20 mL/h). Blood lactate increased, requiring escalating doses of inotropes, intubation, and mechanical ventilation. A repeat ECG showed diffuse ST-segment elevation, whereas an echocardiogram confirmed severe left ventricular

dysfunction with progressive impairment of the right ventricle. Pericardial effusion was stable.

Dr Guagliumi: On the basis of the clinical presentation, the absence of epicardial coronary artery disease, and the ominous hemodynamic course in the first hours, COVID-19–related myocarditis was assumed. Because of the unstable nature of her clinical condition, it was hoped that immunosuppressive therapy might help. She was started on a high dose of methylprednisolone (1 g/d, ie, 17.2 mg/kg) and immunoglobulin infusion (60 g/d, ie, 1 g/kg). Heparin intravenous infusion was continued during intensive care unit stay as per standard practice.

Patient presentation (continued): **Nevertheless, her clinical and hemodynamic conditions continued to deteriorate. Irreversible multiorgan failure developed (Figure 2). Blood cell count demonstrated platelet depletion, whereas hemoglobin was stable at 13.3 mg/dL. The partial thromboplastin time ratio rose to 6.69, and the international normalized ratio was 3.5, hinting**
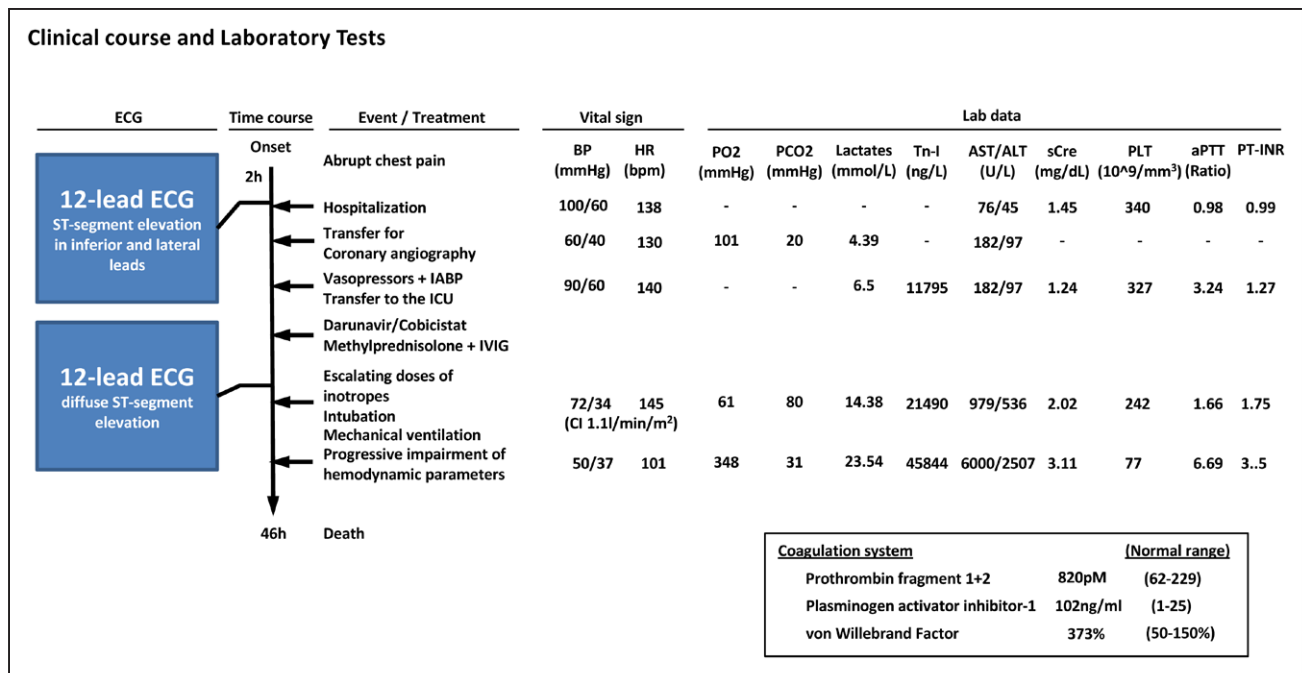
Clinical course and Laboratory Tests

ECG	Time course	Event / Treatment	Vital sign		Lab data								
			BP (mmHg)	HR (bpm)	PO2 (mmHg)	PCO2 (mmHg)	Lactates (mmol/L)	Tn-I (ng/L)	AST/ALT (U/L)	sCre (mg/dL)	PLT (10^9/mm³)	aPTT (Ratio)	PT-INR
Onset		Abrupt chest pain											
12-lead ECG ST-segment elevation in inferior and lateral leads	2h	Hospitalization	100/60	138	-	-	-	-	76/45	1.45	340	0.98	0.99
		Transfer for Coronary angiography	60/40	130	101	20	4.39	-	182/97	-	-	-	-
		Vasopressors + IABP Transfer to the ICU	90/60	140	-	-	6.5	11795	182/97	1.24	327	3.24	1.27
		Darunavir/Cobicistat Methylprednisolone + IVIG											
12-lead ECG diffuse ST-segment elevation		Escalating doses of inotropes Intubation Mechanical ventilation	72/34 (CI 1.1l/min/m²)	145	61	80	14.38	21490	979/536	2.02	242	1.66	1.75
		Progressive impairment of hemodynamic parameters	50/37	101	348	31	23.54	45844	6000/2507	3.11	77	6.69	3..5
	46h	Death											

Coagulation system		(Normal range)
Prothrombin fragment 1+2	820pM	(62-229)
Plasminogen activator inhibitor-1	102ng/ml	(1-25)
von Willebrand Factor	373%	(50-150%)

Figure 2. Hospital course and laboratory tests.
A timeline of the patient's clinical course including vital signs and relevant laboratory tests is shown. aPTT indicates activated partial thromboplastin time; AST/ALT, aspartate transaminase/alanine aminotransferase; BP, blood pressure; HR, heart rate; IABP, intra-aortic balloon pump; ICU, intensive care unit; IVIG, intravenous immunoglobulin; PLT, platelet; PT-INR, prothrombin time–international normalized ratio; sCre, serum creatinine; and TnI, troponin I.

at an underlying acute coagulopathy. There was a marked increase in plasminogen activator inhibitor, prothrombin activation fragments (F1 and F2), and plasma level of von Willebrand factor (Figure 2). Despite intensive management and hemodynamic support, the patient died on the 46th hour after admission.

Dr Guagliumi: Although we were in the midst of the worst of the COVID-19 pandemic in Italy, because of the remaining diagnostic uncertainties and the tragic outcome, we asked Drs Gianatti and Sonzogni to perform a complete autopsy. Given the expertise of CVPath for cardiac pathology, the heart and some selected organs (ie, lung, spleen, kidney) were sent for analysis.

Pathological examination: The heart weight was 285 g. There was right coronary dominance with mild atherosclerosis (<40% cross-sectional area narrowing of all major coronary arteries, ie, <25% diameter reduction), consistent with the patient's angiogram. The ventricles were sliced parallel to the atrioventricular sulcus at 1- to 1.5-cm intervals, and a focal regional infarction involving the lateral and inferior wall of the left ventricle was visible as rounded focal areas measuring 2 to 3 mm in diameter that extended from the endocardium to the epicardium (Figure 3A). Similar areas were also observed in the inferior wall of the right ventricle. There was mottling of the subendocardial region of the septum and anterior wall. All 4 valves were normal. Histological examination confirmed the presence of circumferential, patchy areas of myocardial necrosis with contraction band necrosis and focal, interstitial acute inflammatory infiltrate with foci of mild hemorrhage (Figure 3B through 3D). In addition, small vessels showing platelet/fibrin thrombi were prominent in the areas of myocardial necrosis with inflammation, which stained positive for fibrin and CD61, and with a positive immunofluorescence for VE-cadherin (endothelial marker) and CD61/CD42b (platelet marker; Figure 3E through 3I). All sections showed changes in terminal ischemia with hypereosinophilic fibers and contraction band formation in the right and left ventricular walls, consistent with shock. Lung sections showed focal areas of pulmonary edema and few microthrombi in small alveolar capillaries (Figure 3J). Rare microthrombi were also observed in the kidney with greater frequency and in the spleen (Figure 3K and 3L).

Dr Virmani: The pathological examination suggested microvascular thrombi in the inferior wall of the left and right ventricles as the initial cause of the ST-segment–elevation myocardial infarction. Acute inflammatory infiltrates in these territories, together with contraction band necrosis, suggested an infarct of ≈1 to 2 days, consistent with the onset of her chest pain
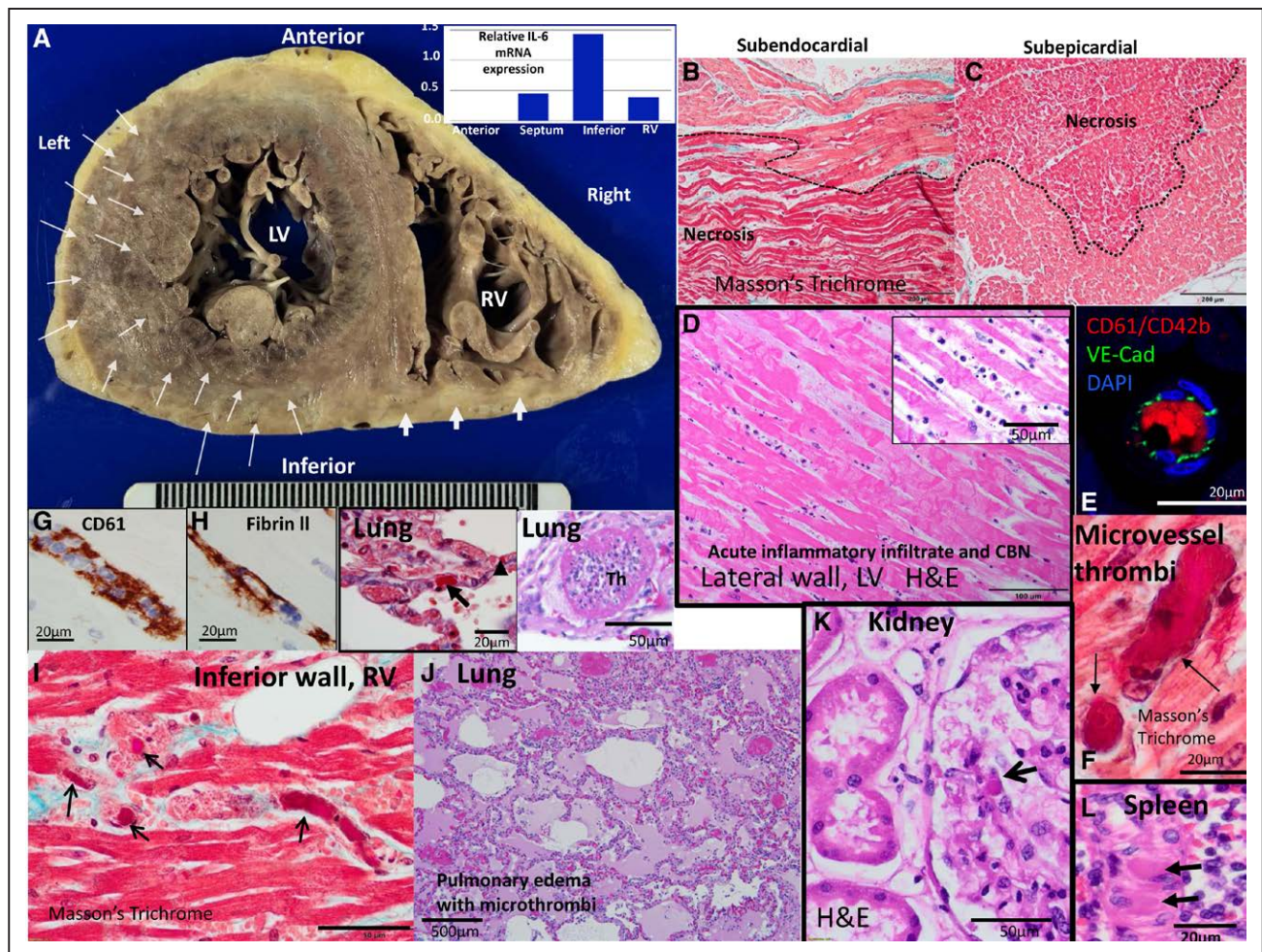
Figure 3. Pathological findings.
A slice of the left and right ventricular myocardium is shown in the center of figure (**A**) with arrows pointing to focal pale areas of myocardial necrosis that collectively resulted in a transmural infarction in the lateral and inferior wall of left ventricle (LV) and inferior wall of right ventricle. Inset graph shows IL-6 RNA transcript levels from areas of the heart as detected by quantitative PCR. On the top right (**B** and **C**) are shown Masson's trichrome stained heart sections of the inferior wall of the left ventricle, showing patchy areas of myocyte necrosis that extended from the endocardium to the epicardium. **D**, Photomicrograph of the lateral wall of the left ventricle illustrating myocyte coagulation and contraction band necrosis with diffuse, acute inflammatory cell infiltrate undergoing karyorrhexis (insert). **E**, Immunofluorescence stain showing an intramyocardial small vessel with intravascular platelet thrombus (red), and endothelial cells staining by VE-cadherin (green), and nuclei stained with DAPI (blue). **F**, Intramyocardial capillaries cut longitudinally and in cross-section with intramyocardial thrombi (Masson's trichrome stain). **G** and **H**, Immunoperoxidase stained sections stained with antibody to Fibrin II and CD42b/CD61 (platelets) from areas of myocardium. **I**, Section of right ventricle showing multiple thrombi (arrows) in an area of myocardial necrosis (Masson's trichrome stain). **J**, A section of lung showing pulmonary edema but no evidence of interstitial pneumonia, inserts (**above**) show thrombi (arrows) within capillaries of the alveolar wall (**left**) and arteriole (**right**). **K** and **L**, Section of kidney and spleen showing rare microvascular thrombi (**arrows**). CBN indicates contraction band necrosis; IL-6, interleukin-6; LV, left ventricle; RV, right ventricle; and Th, thrombus.

(ie, 46 hours before presentation). The pathological cause of death was cardiogenic shock resulting from myocardial necrosis that was extensive through the left ventricle and part of the right ventricle and likely caused by poor perfusion of the heart.

Molecular analysis: **Molecular analysis of RNA extracted from the lungs and various areas of the heart revealed the presence of virus in the lungs, but it was undetectable in all areas of the heart. Through polymerase chain reaction, interleukin (IL)-6, a major cytokine associated with thrombosis and disease progression in patients with** COVID-19, was found in the inferior wall, septum, and right ventricle (Figure 3L).

Dr Finn: Polymerase chain reaction examination showed that severe acute respiratory syndrome coronavirus 2 was present in the lungs of this subject, although there was no evidence of diffuse alveolar damage, a pattern typical of COVID-19 infection. Even with the presence of microvascular thrombi, there was no evidence of viral infection in any part of the heart.

DISCUSSION

COVID-19 infection continues to be a major cause of mortality throughout the world. Cardiac injury as

indicated by elevated levels of cardiac troponins increases risk of death, but the pathogenesis of cardiac injury remains uncertain. A better mechanistic understanding is needed to guide potential candidate therapies to improve outcomes.

In a case series from New York involving 18 patients with confirmed diagnosis of COVID-19 and ST-segment elevation, 44% received a diagnosis of acute coronary thrombosis causing myocardial infarction, and 56% had evidence of noncoronary myocardial injury (defined as either nonobstructive disease on coronary angiography or normal wall motion). Of those with noncoronary myocardial injury, 90% died in this series, suggesting a desperate need to better understand its pathogenesis and how best to treat it.

Although many studies have focused on pulmonary findings of COVID-19, few pathology studies have been conducted specifically examining the

effects of COVID-19 on the heart, and most of these did not involve subjects with ST-segment–elevation myocardial infarction or even cardiac injury. The largest published pathology series that included analysis of the heart are listed in the Table.[1–5] Of the collective 67 hearts examined, in 5 cases, investigators found some evidence of lymphocytic myocarditis of unclear extent and nature.

Given the low overall expression of angiotensin-converting enzyme 2 receptor in myocardial cells, tropism of severe acute respiratory syndrome coronavirus 2 for the heart may not be likely. Indeed, quantification of viral load in 22 patients dying of COVID-19 in Germany showed extremely low to no viral load in the heart in all cases. In the case report presented here, similar results were found, with no detectable virus in several sections of myocardial tissue despite multiple microemboli in the heart with virus readily detectable in the lung.

Although clinical COVID-19 cases with myocardial injury and normal coronary arteries have been reported and thought to be caused by myocarditis, here we show for the first time that ST-segment–elevation myocardial infarction may be caused by extensive microvascular thrombosis in the absence of epicardial coronary obstruction. A larger series of autopsy cases from patients with COVID-19 with evidence of myocardial injury is needed to determine how frequently cardiac microthrombi contribute to myocardial damage in the absence of coronary epicardial thrombosis. Until then, physicians should keep this possibility in mind when treating these patients.

Although direct infection of the lungs with resulting multifocal pneumonia is thought to be the major cause of death in patients with COVID-19, inflammatory cytokine syndrome may also be an important cause of morbidity and mortality. Levels of IL-8, IL-6, tumor necrosis factor-α, monocyte chemoattractant protein-1, and regulated upon activation, normal T cell expressed and presumably secreted (RANTES) are significantly elevated in severe COVID-19 cases and IL-6 and IL-8 have been associated with disease progression. It is thought that severely ill patients with COVID-19 are at an increased risk for thromboembolic events, including pulmonary microthrombi and venous thrombosis perhaps resulting from cytokine storm. Here, we present a case with extensive cardiac microthrombi that were a direct cause of myocardial ischemia in the absence of epicardial coronary occlusion. This type of injury would not be detectable clinically because no laboratory test can specifically detect microthrombi. In this case, infarction of the inferior and lateral walls of the left ventricle with right ventricular involvement was the likely cause of cardiogenic shock and death.

Physicians should be aware of this possible complication and of the potential of anticoagulant and

Table.   Published Autopsy Series of COVID-19 That Included Heart Analysis

Location of Case Series	No. of Hearts Examined	Description	Findings	Reference
New Orleans, Louisiana, USA	9	Blacks from New Orleans	Nonspecific myocyte necrosis with rare lymphocytes, 2 with evidence of significant myocardial injury (ie, troponin I >50 ng/mL)	1
Augsburg, Germany	10	Cases from Augsburg; ages 64–90 y	Mild lymphocytic myocarditis in 4 cases; cardiac injury not reported	2
Mount Sinai, New York, USA	25	Cases from Mount Sinai Health System; ages 34–94 y	Two cases of patchy mild interstitial chronic inflammation; 3 cases with small vessel thrombi; cardiac injury not reported	3
Styria, Austria	11	Cases from Hospital Graz II; ages 66–91 y	One case with intramyocardial mural thrombi; 1 case with focus of fragmented cardiomyocytes with lymphocytic/granulocytic reaction; 2 cases with elevated troponin levels	4
Hamburg, Germany	12	Mandated autopsies from the State of Hamburg; ages 52–87 y	One case of lymphocytic myocarditis in right ventricle; cardiac injury not reported	5

COVID-19 indicates coronavirus disease 2019.

anticytokine therapies as conceivable therapeutic options, which need to be further explored in clinical trials. In such cases when there is evidence of cardiac injury as indicated by elevated troponins and wall motion abnormalities but no evidence of epicardial coronary occlusion, the possibility of myocardial microthrombi should be entertained and appropriate treatment initiated.

CONCLUSIONS

The case presented here challenged the traditional differential diagnosis of ST-segment–elevation myocardial infarction in the setting of COVID-19 and revealed the potential for microvascular thrombi in the absence of epicardial coronary artery disease to be a cause of acute myocardial infarction. The curiosity of the treating physicians led to further analysis of autopsy, which revealed a novel mechanism by which COVID-19 could cause cardiac injury.

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Supplemental Materials

Data Supplement Movies I–III

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