OBSERVATION: CASE REPORT

Cardiac Endotheliitis and Multisystem Inflammatory Syndrome After COVID-19

Background: Endotheliitis and microangiopathy have been identified as key features of the pathophysiology of severe coronavirus disease 2019 (COVID-19) (1, 2). In addition, a multisystem inflammatory syndrome (MIS) similar to Kawasaki disease has been increasingly reported in association with COVID-19 in children and young adults (3–5). Although vascular damage seems to be a component of both of these presentations, the pathologic features of MIS remain elusive.

Objective: To provide what we believe to be the first report on the pathologic findings of vasculitis of the small vessels of the heart, which likely represents MIS, leading to death in a young adult after presumed resolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Case Report: The patient was a 31-year-old African American woman with a body mass index of 36.1 kg/m^2, hypertension controlled with lisinopril, and diabetes with poor adherence to metformin and glipizide (hemoglobin A_{1c} level, 13.9%). She was admitted for fever, dry cough, and abdominal discomfort of 5 days. She was positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction testing of a nasopharyngeal swab specimen and was treated with a course of azithromycin and 2 days of hydroxychloroquine. At discharge, she was afebrile and her oxygen saturation was 95% on room air.

The patient returned 12 days later with sudden fever; throbbing, left-sided neck pain; nausea; and vomiting. She had a fever of 39.8 °C, with sinus tachycardia of approximately

Table. Laboratory Studies

Study	Patient Value	Reference Range
D-dimer level, *nmol/L**	2.48	<1.37
Total creatinine kinase level, *μkat/L*	0.43	<3.17
Creatinine kinase–MB level, *μg/L*	1.9	<5.2
Brain-type natriuretic peptide level, *ng/L*	46	<100
Lactate dehydrogenase level, *μkat/L*	2.74	<3.36
Hemoglobin A_{1c} level, %*	13.9 on admission for COVID-19	<5.7
Glucose level*		
mmol/L	16.09	3.61–5.49
mg/dL	290	65–99
Leukocyte count, × 10^9 *cells/L**	17.7	4.5–11.0
Hemoglobin level, *g/L**	93	120–160
Hematocrit*	0.287	0.350–0.460
Platelet count, × 10^9 *cells/L*	174	130–400
Neutrophil count, × 10^9 *cells/L**	12.92	1.80–8.00
Lymphocyte count, × 10^9 *cells/L*	2.12	1.10–5.00
Monocyte count, × 10^9 *cells/L*	0.35	0.2–1.10
Eosinophil count, × 10^9 *cells/L*	0.2	0.00–0.60
CD56 absolute count, × 10^9 *cells/L**	0.210	0.045–0.157
C-reactive protein level, *mg/L**	580 near death (26 during prior admission for COVID-19, and 165 at current admission)	<9
Ferritin level, *μg/L**	411.2	10.0–150.0
Lactic acid level, *mmol/L**	3.1	0.3–2.0
Blood urea nitrogen level		
mmol/L	6.07	2.50–8.92
mg/dL	17.0	7.0–25.0
Creatinine level*		
μmol/L	202.44	44.20–97.24
mg/dL	2.29	0.50–1.10
Estimated glomerular filtration rate (African American), *mL/min/1.73 m^2**	32	>89
Aspartate aminotransferase level, *U/L**	189 at death (18 at admission)	<45
Alanine aminotransferase level, *U/L**	52 at death (17 at admission)	<46
Alkaline phosphatase level, *μkat/L*	1.15	0.33–2.00
Sodium level, *mmol/L**	134	135–146
Potassium level, *mmol/L*	3.9	3.6–5.2
Chloride level, *mmol/L*	96	96–110
Carbon dioxide level, *mmol/L**	22	24–32
HIV, hepatitis B and C, influenza A and B, mumps polymerase chain reaction and IgM, mycobacterium tuberculosis enzyme-linked immunospot test, and blood cultures	Negative	–

COVID-19 = coronavirus disease 2019.
* Abnormal value.

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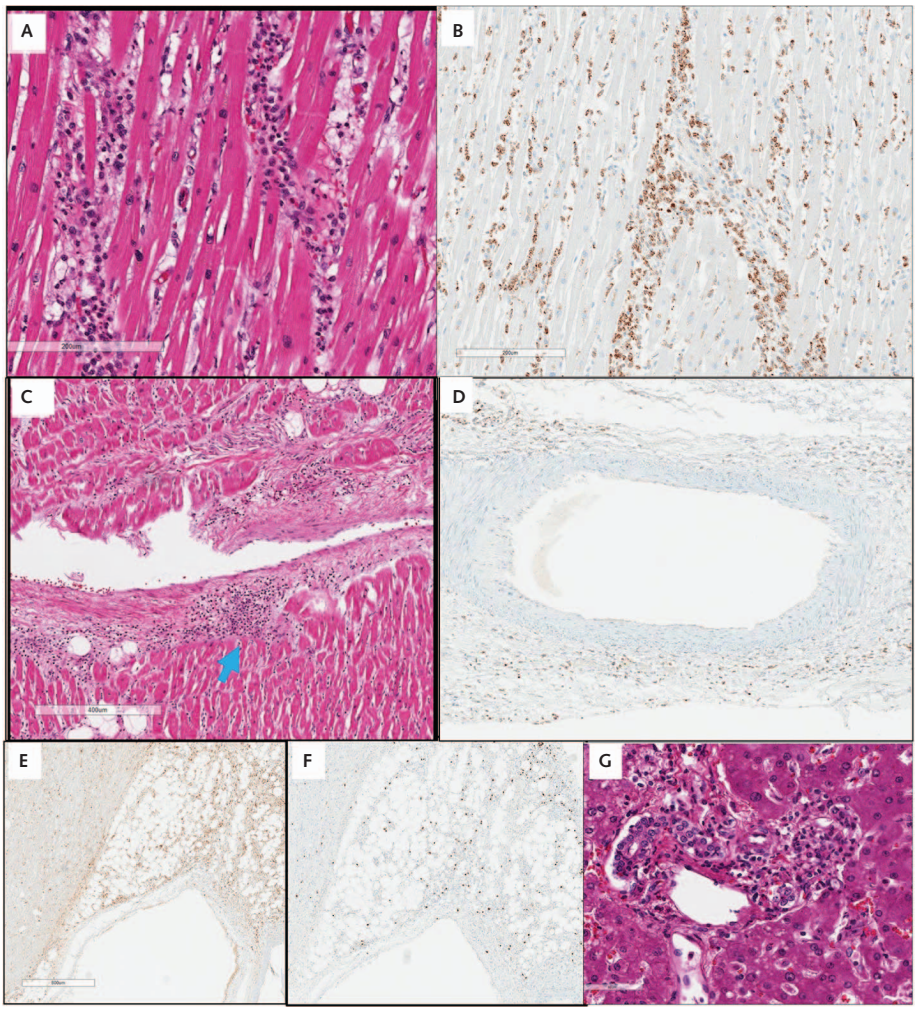
Figure. Pathologic characteristics of cardiac endotheliitis and multisystem vasculitis.



A. Intact cardiac myocytes with a pattern of endotheliitis and vasculitis involving intervening small blood vessels and interstitial spaces, seen throughout extensive sampling of the heart (hematoxylin–eosin stain). **B.** Low-power image of a cardiac blood vessel with inflammatory cuffing (*blue arrow*) and no evidence of direct myocardial involvement. **C.** Myeloperoxidase immunostain highlighting a prominent neutrophilic component to the inflammation in small vessels (compare with **D**). **D.** Myeloperoxidase stain showing no significant endothelial inflammation in a coronary artery. **E.** CD4 immunostain showing $CD4^+$ lymphocytes around small blood vessels in the epicardial fat, with large vessels relatively spared. **F.** CD8 immunostain showing reduced numbers of $CD8^+$ compared with $CD4^+$ lymphocytes. **G.** A similar neutrophilic vasculitis was seen in occasional portal triads of the liver, involving small arteries and veins with surrounding congestion and no direct inflammation of hepatocytes. Levels of aspartate aminotransferase and alanine aminotransferase became elevated just before death (**Table**).

120 beats/min on electrocardiography. Her physical examination was remarkable for parotitis. A computed tomography scan of her neck showed bilaterally enlarged parotid glands and swelling in the posterior nasopharynx to oropharynx, and a computed tomography scan of her chest showed interval improvement of bibasilar ground-glass opacities, with cervical and anterior mediastinal lymphadenopathy. Reverse transcriptase polymerase chain reaction of a new nasopharyngeal swab was negative for SARS-CoV-2. Laboratory results at the time showed an elevated leukocyte count of 17.7 $x10^9$ cells/L, a D-dimer level of 2.48 nmol/L, and C-reactive protein levels trending upward (**Table**). While she was being evaluated for hospital admission, she developed hemodynamic instability and ventricular fibrillation and could not be resuscitated. Permission for autopsy was granted by the next of kin, and this study was determined to be exempt by the institutional review board at Louisiana State University Health Sciences Center.

Gross abnormalities noted at autopsy (4 hours after death) were conjunctival injection, enlarged cervical and mediastinal lymph nodes, and vascular thrombi with focal surrounding hemorrhage in the left lower lung, which probably contributed to illness but were not likely the primary cause of death. Pulmonary microscopic examination showed focal acute hemorrhage and numerous megakaryocytes, consistent with our previously reported findings (2). Most of the lung showed predominantly reparative changes. Flow cytometry of an enlarged cervical lymph node revealed reactive changes, with a ratio of CD4 to CD8 T cells of 3:1.

The heart had a grossly normal appearance, without evidence of coronary artery aneurysm, atherosclerosis, or steno-

sis. Microscopically, however, endotheliitis and vasculitis were present, diffusely involving the small cardiac vessels and extending into the surrounding epicardial fat and interstitial spaces (**Figure**, *A* and *B*). There was no lymphocytic infiltrate of the myocardium (2, 3). The vasculitis was composed of numerous neutrophils (**Figure**, *C*), as well as $CD4^+ > CD8^+$ lymphocytes (**Figure**, *E* and *F*). Inflammation was not present in the coronary arteries or larger blood vessels (**Figure**, *D*). Similar inflammation was noted in occasional portal triad vessels within the liver (**Figure**, *G*).

Discussion: Multisystem inflammatory syndrome is currently defined as fever, systemic inflammation, end-organ dysfunction, or symptoms similar to Kawasaki disease or toxic shock syndrome (4, 5). The clinical picture in this adult patient of sudden lymphadenopathy and parotitis combined with small-vessel cardiac vasculitis after COVID-19 is strongly suggestive of a similar systemic inflammatory process. Of note, the coronary arteries were spared, and neutrophils were identified along with $CD4^+ > CD8^+$ lymphocytes. The appearance was not that of a lymphocytic or eosinophilic myocarditis, and cardiac myocytes did not seem to be the target of the inflammatory process.

The autopsy was also significant for the presence of new pulmonary thrombi in a background of otherwise reparative changes in the lungs. These thrombi indicate a potential for hypercoagulability affecting the pulmonary vasculature beyond the initial course of COVID-19, as well as the need for continued monitoring of laboratory markers and possible anticoagulation.

Our report highlights the potential for serious complications due to endothelial damage and describes potential pathologic characteristics of MIS after COVID-19, a possible mimicker of true myocarditis. Careful monitoring of laboratory markers of inflammation, as well as therapeutic intervention to target this inflammatory process, may improve patient outcomes.

Sharon E. Fox, MD, PhD
Louisiana State University Health Sciences Center and
Southeast Louisiana Veterans Health Care System
New Orleans, Louisiana

Fernanda S. Lameira, MD
Elizabeth B. Rinker, MD
Richard S. Vander Heide, MD, PhD
Louisiana State University Health Sciences Center
New Orleans, Louisiana

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Corresponding Author: Sharon E. Fox, MD, PhD (e-mail, sfox3@lsuhsc.edu), and Richard S. Vander Heide, MD, PhD (e-mail, rvand3@lsuhsc.edu), 1901 Perdido Street, Department of Pathology MEB 5th Floor, New Orleans, LA 70112.

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