COVID-19 in a Hispanic Woman

Autopsy Report With Clinical-Pathologic Correlation

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• Since making its debut on the global stage in December 2019, coronavirus disease 2019 (COVID-19) has afflicted nearly 4 million people and caused hundreds of thousands of deaths. Case reports and case series depicting the clinical effects of the causative virus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—have been published, yet few demonstrate the cytopathologic alterations of this disease. We present a clinical-pathologic correlation report of a previously healthy Hispanic woman with laboratory-confirmed COVID-19 who had typical features of acute respiratory distress syndrome (ARDS) and also showed cardiac abnormalities thought to represent fulminant viral myocarditis. Congruent with the ARDS clinical impression, autopsy findings were remarkable for extensive and markedly severe acute lung injury consistent with viral pneumonia, characterized by diffuse alveolar damage, pulmonary infarction, severe pulmonary edema, desquamation of pneumocytes with intra-alveolar aggregation, and pneumocyte morphologic alterations suggestive of viral cytopathic effect. However, there was incongruence between the clinical impression and the cardiovascular pathology findings in that viral myocarditis was not detected on histopathologic evaluation. This case highlights the importance of pathologic corroboration of the clinical impression and, in addition, illuminates the key role autopsy plays during a pandemic by providing valuable insight into viral pathology in tissues.

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The coronavirus family of RNA positive-strand viruses attained global recognition with the 2002–2003 outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) in the Chinese province of Guangdong, and, later, the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), first reported in 2012 in Saudi Arabia.[1] The newest player on the global stage is the closely related SARS-CoV-2 virus, the causative agent of novel coronavirus disease 2019 (COVID-19), which was first identified in Wuhan City, Hubei Province of China.[2,3] Like SARS-CoV and MERS-CoV, SARS-CoV-2 is a coronavirus that is predominantly transmitted via respiratory droplets, although a fecal-oral mechanism of spread is possible.[4–6] In addition, COVID-19 is clinically characterized by the presence of bilateral ground glass opacities on imaging[7,8] as well as lower respiratory symptoms, such as cough and dyspnea, that vary widely in severity, ranging from life-threatening respiratory compromise to asymptomatic carriage.[8–12]

Since its initial detection in December 2019, SARS-CoV-2 has spread to all continents except Antarctica. The first COVID-19 case in the Americas was confirmed in late January 2020 in a traveler who visited Wuhan and carried the virus to his home state of Washington in the United States. The first known death due to COVID-19 in the United States occurred in early February 2020 and involved a Hispanic woman whose autopsy report was publically released.[13]

Between December 2019 and April 2020, SARS-CoV-2 has infected nearly 4 million people in more than 200 countries and is responsible for more than 250 000 deaths worldwide and nearly 90 000 deaths in the Americas.[14] Despite the toll in lives lost on a global scale, there are few peer-reviewed publications that describe pathologic findings in tissues obtained from SARS-CoV-2–infected individuals, many of whom are of Chinese nationality and male sex.[15–21] To our knowledge, there are no peer-reviewed publications in the medical literature describing the tissue pathology findings with clinical correlation in Hispanic persons. We present the first COVID-19 clinical-pathologic correlation report that depicts the clinical course and autopsy pathology findings of a previously healthy Mexican American woman.

REPORT OF A CASE

Clinical Presentation

A 44-year-old obese Hispanic woman (body mass index: 45.1 kg/m^2) presented to our emergency department in San Antonio, Texas, 6 days antemortem with a 1-week history of fever, cough, and dyspnea. She reported no travel history. Her only sick contacts

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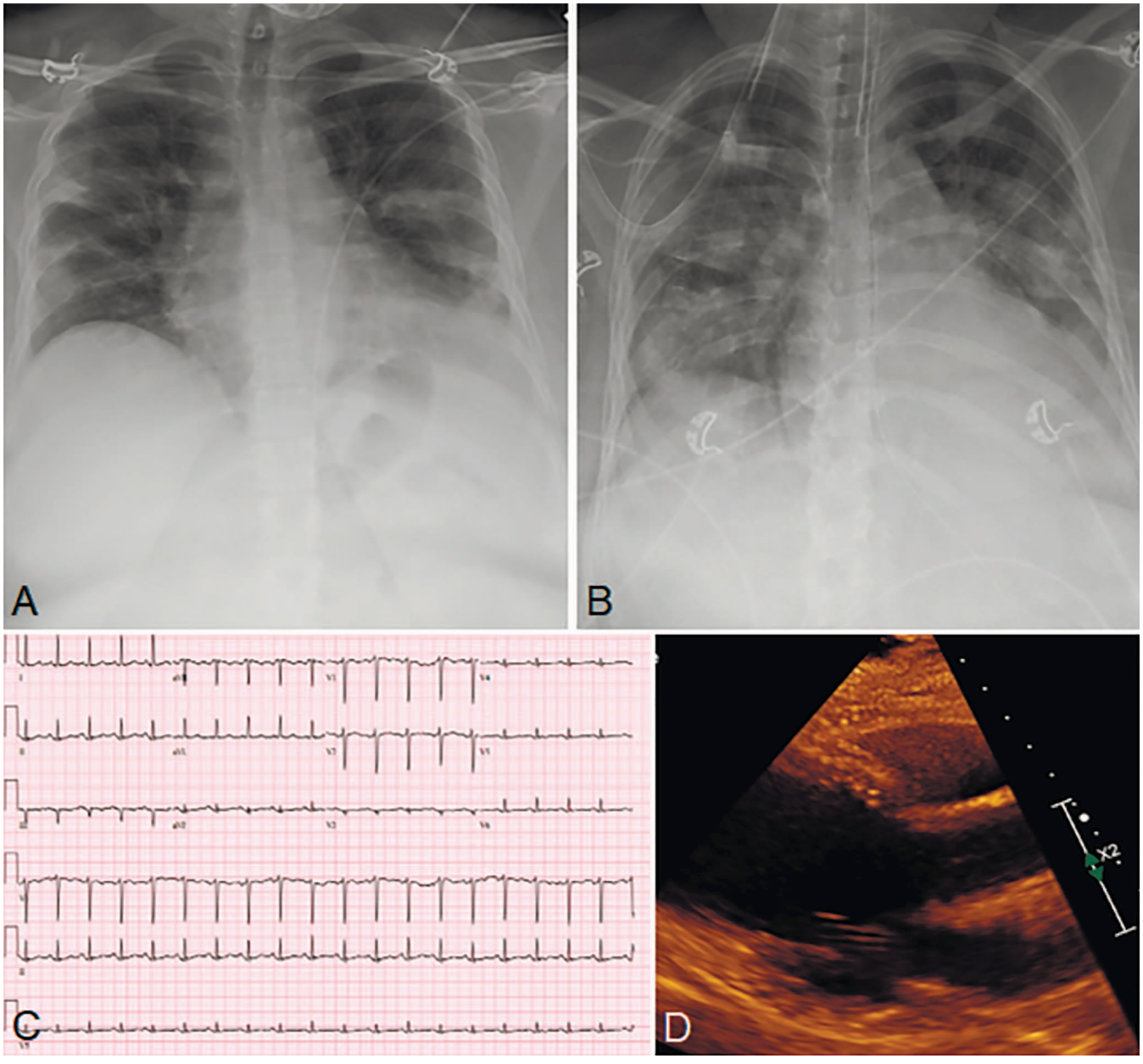

Figure 1. *A, Anteroposterior view of chest radiogram on the first day of admission showing bilateral patchy airspace opacities. B, Anteroposterior view of chest radiogram on day 5 of hospitalization with slightly more consolidated pattern of patchy opacities. C, Electrocardiography showing sinus tachycardia and slow R wave progression in lead V2 and V3, concerning for anterior wall ischemia. D, Parasternal long view on transthoracic echocardiography showing normal left ventricular size.*

were members of her household: her 25-year-old son who had a 2-day history of cough and her 44-year-old husband who was asymptomatic at that time, but later experienced mild respiratory symptoms; her son and husband later tested positive for COVID-19. Upon arrival, she was noted to have a temperature of 99.1°F (37.3°C), heart rate of 116 beats per minute, respiratory rate of 32 breaths per minute, and oxygen saturation of 94% while receiving 6 L/min of oxygen via a nasal cannula.

Initial laboratory investigations revealed a white blood cell count of 5870 cells/μL (reference range [ref]: 3400–10,400) with an absolute peripheral lymphocyte count of 850 cells/μL (ref: 900–3600). Serum C-reactive protein level was elevated at 114 mg/L (ref: <10), as was the erythrocyte sedimentation rate (56 mm/h; ref: 2–37), troponin I level (0.33 ng/mL; ref: <0.051), and D-dimer level (781 ng/mL; ref: <500). Brain natriuretic peptide (BNP) (3 pg/mL; ref: <101), serum creatinine (0.87 mg/dL; ref: <1.10), and procalcitonin (0.05 ng/mL; ref: <1.01) levels were normal. Interleukin-6 (IL-6) level was undetectable on admission. A nasopharyngeal swab was collected and real-time reverse transcription–polymerase chain reaction (RT-PCR) assay was performed, which resulted positive for SARS-CoV-2 at 24 hours after initial presentation. Initial chest radiography showed patchy bilateral airspace peripheral opacities (Figure 1, A) that progressively worsened during the course of her admission (Figure 1, B). Initial 12-lead electrocardiogram (ECG) showed sinus tachycardia along with slow R wave progression from V2 and V3; no ST-segment elevation was detected (Figure 1, C).

The patient was admitted to the medical intensive care unit for further care. Invasive mechanical ventilation with endotracheal intubation was immediately initiated owing to rapidly worsening hypoxemia. A conservative fluid management strategy was adapted and the patient soon required intravenous vasopressor support to

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?1 keep mean arterial blood pressure above 65 mm Hg. A transthoracic echocardiogram (Figure 1, D) revealed severe septal, mid-anterolateral, and mid-inferior hypokinesis; apical and inferolateral wall motion was preserved. Mildly to moderately depressed left ventricular systolic function with an estimated left ventricular ejection fraction of 40% to 45% was observed. The left ventricle size and wall thickness were normal. The patient was diagnosed with reverse Takotsubo cardiomyopathy with clinical suspicion of viral myocarditis.

The patient was given oral hydroxychloroquine 400 mg twice a day on the day of admission, followed by 200 mg twice a day and intravenous azithromycin 500 mg daily. She also received 1 dose of intravenous tocilizumab 400 mg on day 2 of hospitalization owing to rising IL-6 levels, which increased from below the limit of detection on admission to 397 pg/mL on day 6. She was approved for compassionate use of remdesivir, but she died before she could receive the first dose.

During the course of her hospitalization, her serum inflammatory markers, including procalcitonin, IL-6, and C-reactive protein, continued to increase. Additional history obtained endorsed a probable prior diagnosis of systemic lupus erythematous; therefore, an antinuclear antibody (ANA) test was obtained, which yielded a positive result at a very low titer of 1:40 with a coarsely speckled pattern. The serum troponin I levels increased, peaking at 2.390 ng/mL on day 2. Her serum BNP level also rapidly trended up to 225 pg/mL within the first 24 hours after presentation. Her renal function tolerated aggressive diuresis and creatinine peaked at 1.29 mg/dL. Left heart catheterization, cardiac magnetic resonance imaging, and endomyocardial biopsy could not be performed because of the patient's clinically unstable condition. Owing to progression to severe ARDS, on day 3 of hospitalization the patient underwent prone position ventilation, but her respiratory and hemodynamic status progressively worsened. Despite maximum efforts, she developed severe multiorgan failure and she was not a candidate for extracorporeal membrane oxygenation. She died on day 6 of hospitalization.

Autopsy Procedure

The autopsy was performed 18 hours postmortem in a negative pressure room with the use of personal protective equipment that included an N95-mask, face shield, and appropriate coverings for the head, trunk, and limbs. A minimalist approach was used owing to concern for infectious disease risk to autopsy personnel during a pandemic of a novel virus. The brain was not extracted in the effort to avoid aerosol generation. To minimize sharps exposure, most visceral organs were biopsied in situ without full dissection or weighing, with exception of the heart, which was procured owing to clinical concern for viral myocarditis. The heart was weighed and soaked in formalin fixative at 10% concentration for 5 days before evaluation.

Autopsy Findings

Lungs and Upper Airways.—Mucous secretions were present in the bronchi, trachea, and nares. The peribronchial lymph nodes were enlarged and the mucosal surfaces of the trachea and primary bronchi were edematous and erythematous. On external examination, both lungs were subjectively heavy and had evidence of pleuritis featuring dull, tan, and flat macule-like lesions with thin radial extensions on the pleural surfaces without fibrous adhesions. The pleura also had large areas of intense erythema overlying regions of consolidation that, when biopsied, emitted blood-tinged fluid consistent with pulmonary edema. Multiple samples for microscopic investigations were biopsied from both lungs, which were left in situ and not further dissected.

Examination of lung sections by light microscopy showed that the areas of dense consolidation noted grossly consisted of large regions of pulmonary edema as well as isolated areas of infarction. The pulmonary parenchyma showed evidence of an acute lung injury pattern with diffuse interstitial lymphocytic infiltrates and fibrinous exudates, consistent with viral pneumonia. Hyaline membranes, a characteristic feature of diffuse alveolar damage (DAD), were observed in patchy areas (Figure 2, A). There was extensive disassociation of pneumocytes from their basal attachments to the alveolar wall in a desquamation-like pattern. Within the alveolar spaces, the sloughed pneumocytes formed aggregates that resembled multinucleated giant cells (Figure 2, B). Some pneumocytes showed ample cytoplasm and enlarged nuclei with alterations that were suggestive of viral cytopathic effect (Figure 2, C), although the possibility that these might represent marked reactive pneumocyte hyperplasia could not be entirely excluded. The pulmonary blood vessels were remarkable for extensive and widespread perivascular lymphocytic cuffing with a few foci revealing lymphocytic infiltration within vessel walls without fibrinoid necrosis, consistent with nonnecrotizing lymphocytic vasculitis (Figure 2, D). Despite sampling tissue from all lobes of both lungs, no microthrombi were identified.

Transmission electron microscopy (EM) was performed on lung tissue that was deparaffinized, osmicated, and embedded in plastic. The analyzed pieces were obtained from areas of lung that contained enlarged pneumocytes with viral cytopathic effect-like changes. Electron microscopy showed the presence of structures resembling viral capsids suggestive of coronavirus, having an average diameter of approximately 50 to 75 nm and peripheral densities resembling a halo; these were located within cytoplasmic vesicles of reactive-appearing pneumocytes and also free within extracellular alveolar spaces. Although this patient had a known positive PCR result for SARS-CoV-2, the positive identification of these viral-like structures as SARS-CoV-2 could not be confirmed owing to the absence of a confirmatory immunogold labeling assay, which was not performed because of funding restrictions.

Notably, EM also revealed the presence of numerous ultrastructural fibrin aggregates within blood vessels, suggesting an increased propensity toward clot formation, as well as increased fibrinous exudates within alveolar spaces. Many reactive pneumocytes and vacuolated alveolar macrophages were also present ultrastructurally. Enlarged interstitial fibroblasts and activated lymphocytes with abundant rough endoplasmic reticulum were also noted. Collagen in the alveolar wall was slightly increased; this is suggestive of early-stage fibrosis but also falls within normal variation seen with aging.

Heart.—The heart weight (410 g) was on the upper end of the normal range. Gross examination was remarkable for streaking of the right atrial wall myocardial tissue, characterized by thin myocardial trabeculae alternating with areas of epicardium lacking underlying myocardial tissue; this impression was confirmed on microscopic examination. No grossly apparent coronary artery disease was appreciated. No focal lesions suggestive of acute or chronic hypoxic injury were identified in the left ventricle and, although the wall thickness appeared slightly increased at 1.3 cm, it was within normal range (ref: 1.5 cm). Despite the tricuspid valve circumference of 11.5 cm within normal range (ref: 11–12 cm), the right ventricular chamber appeared dilated, suggesting that there might have been increased antemortem right outflow pressure.

Microscopic examination of the heart revealed mild myxoid edema, mild myocyte hypertrophy, and focal nuclear pyknosis. Notably, rare foci with few scattered $CD45^{+}$ lymphocytes were identified in the left ventricular papillary muscle (Figure 2, E and F), although no definitive findings of acute or chronic myocyte necrosis were appreciated within any sections of heart tissue.

Kidney.—Grossly, the kidneys were unremarkable. Amidst a background of autolysis, light microscopic examination of renal sections showed evidence of focal acute tubular injury featuring tubules with flattened epithelium and lumens containing sloughed epithelial lining cells, granular casts, and Tamm-Horsfall protein. The intraluminal accumulation of cellular debris was noted in focal areas. There was no evidence of acute interstitial nephritis or acute glomerulitis. Although some congestion of peritubular capillaries was noted, there was no definitive evidence of thrombotic microangiopathy or disseminated intravascular coagulopathy identified by light microscopy of the kidneys.

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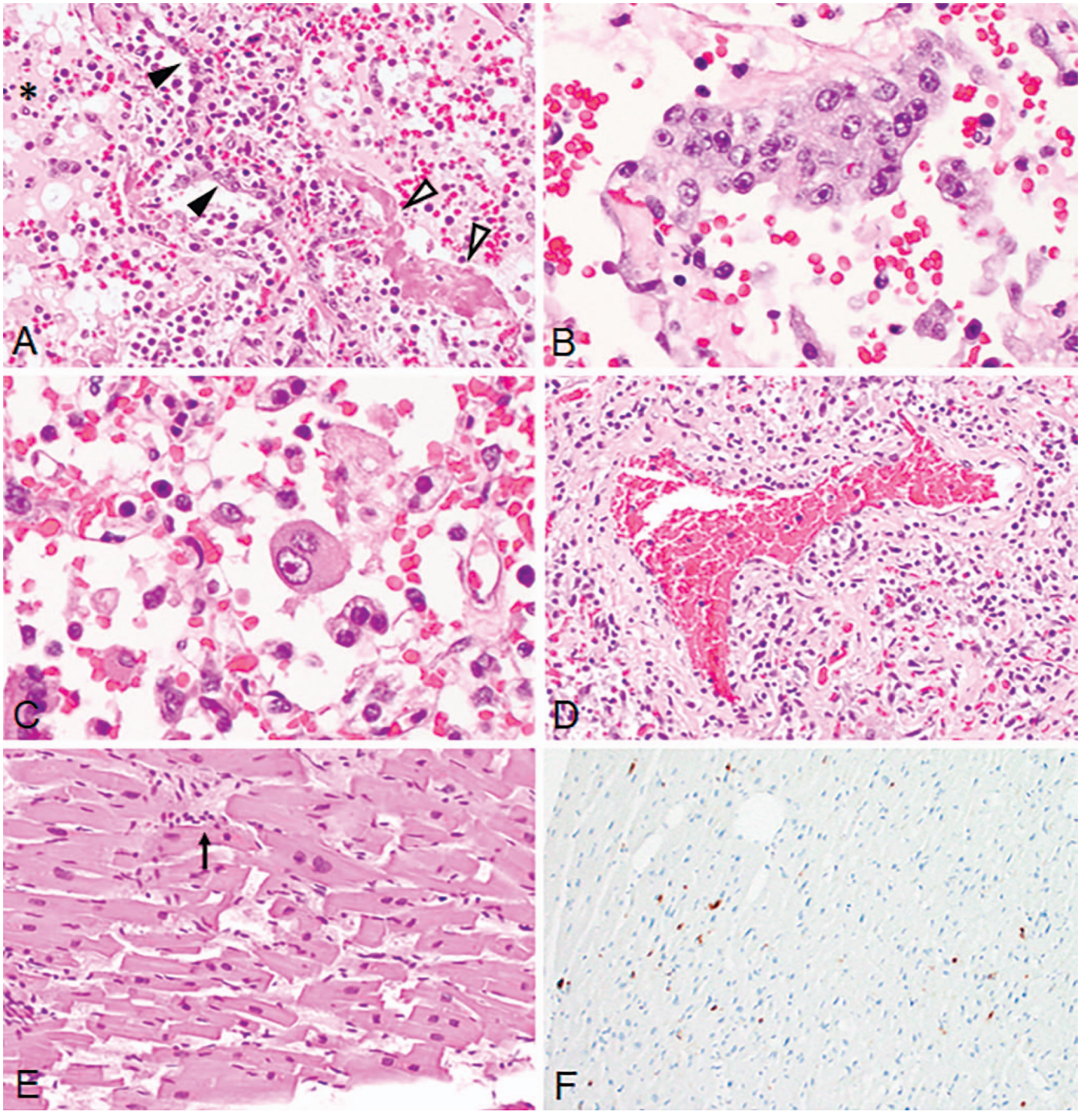

Figure 2. *A, Lung with diffuse alveolar damage featuring hyaline membranes (white arrowheads), intra-alveolar edema (*), and reactive pneumocyte hyperplasia (black arrowheads). B, Aggregates likely formed from desquamated pneumocytes and resembling multinucleated giant cells, some of which have alterations suggestive of viral cytopathic effect. C, Enlarged atypical cells with possible viral cytopathic effect. D, Pulmonary vessels with extensive perivascular lymphocytic cuffing and nonnecrotizing vasculitis focally. E, Myocardium with edema and few scattered lymphocytes (arrow). F, Immunohistochemical stain highlighting rare lymphocytes within myocardial tissue (hematoxylin-eosin, original magnifications ×200 [A, D, and E] and ×400 [B and C]; CD45, original magnification ×100 [F]).*

DISCUSSION

We present here the first report of the pathologic findings with clinical correlation in a Hispanic woman with COVID-19 infection. As of this writing, COVID-19–associated histopathologic features have been described in 16 patients in peer-reviewed publications.[15–21] An additional 44 patient cases have also been described in several unpublished preprints,[22–25] which include 1 large study of 33 male and 5 female Northern Italians ranging in age from 32 to 86 years,[22] as well as 1 preprint depicting the autopsy results of 4 African Americans aged 44 to 76 years,[23] 1 Swiss report relaying the renal biopsy findings of a 63-year-old black man,[24] and 1 report describing the findings of an explanted lung from a 66-year-old Asian man undergoing lung transplant for severe COVID-19.[25] In addition, the autopsy

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report of the first known death due to COVID-19 in the United States, that of a 57-year-old Hispanic woman who died on February 6, 2020, was made publically available.[13]

Of the 7 peer-reviewed publications that describe pathologic findings of COVID-19 patients, these relay results from persons ranging in age from 42 to 84 years who were predominantly of Chinese nationality and male sex; except for two,[20,21] all of the patients had preexisting chronic diseases. Pathologic specimens of the lungs were obtained at the time of autopsy for 13 patients and at the time of surgery for 2 patients who underwent lobectomy for lung adenocarcinoma.[18] All tissue specimens were acquired from patients who were manifesting symptoms of ARDS and in the late stages of COVID-19, except for 2 patients who were asymptomatic for COVID-19 at the time of tissue harvesting[18] and 1 SARS-CoV-2–positive patient with aspiration pneumonia.[15]

The current autopsy report outlines the histopathologic findings of SARS-CoV-2 infection with clinical correlation of a patient with COVID-19; to our knowledge, this report is the first of its kind concerning a Hispanic person and, at the time of this writing, this is the second peer-reviewed publication to describe the clinical-pathologic findings in an American patient.

Pulmonary Clinicopathologic Correlation

The patient had symptoms typical of COVID-19,[3,7,9,26] including cough and dyspnea, and developed ARDS with worsening hypoxemia and bilateral pulmonary infiltrates. Congruent with the clinical impression, the pulmonary findings noted on autopsy were consistent with viral pneumonia with severe acute lung injury, pulmonary infarction, and severe pulmonary edema that was likely responsible for the antemortem hypoxemia due to impaired gas exchange. Pathologic alterations in this patient consisted of pulmonary edema, DAD, and intra-alveolar proteinaceous and fibrinous exudates; these findings were also reported in 10 COVID-19 patients as described in peer-reviewed publications.[15,16,19–21] A preprint Italian manuscript describing the lung findings of 38 patients with COVID-19 noted that all had DAD, although 5 cases (13%) had no detectable hyaline membranes.[22] The absence of DAD was reported in 2 asymptomatic oncology patients who underwent lobectomy for the treatment of lung adenocarcinoma,[18] 1 SARS-CoV-2–positive patient with aspiration pneumonia,[15] and 1 woman with left ventricular rupture.[13]

The pneumocytes in this case showed extensive disassociation from their septal basilar attachments and, though this finding can occur as postmortem artifact, it has been reported by other authors who had obtained lung biopsies from COVID-19 patients within 1 hour of death.[16,21] The pneumocytes in this case collected in the alveolar spaces and some formed aggregates that resembled multinucleated giant cells. Multinucleated giant cells, which are classically associated with foreign body reaction or granulomatous inflammation, have been reported in other pathologic reports of SARS-CoV-2 infection.[18,20–22,25] The aggregated, possibly syncytial cells in our patient were labeled with thyroid transcription factor 1 (TTF-1) immunostain, thereby confirming their pneumocyte identity. Also noted in this patient was the presence of severe pneumocyte hypertrophy. A few enlarged pneumocytes exhibited altered morphology suggestive of viral cytopathic effect, although marked pneumocyte hypertrophy was also considered as an etiology for this change. Ultrastructural evaluation showed structures morphologically consistent with viral capsids located within pneumocytes and also free within the alveolar spaces, similar to other reports of viral particles in COVID-19 patients.[17,20,22,23,25]

A prominent monocytic infiltrate with extensive perivascular lymphocytic cuffing and nonnecrotizing lymphocytic vasculitis was observed in our patient. Of note, this patient also had a positive ANA test result though with a very low titer of 1:40; therefore, the extent to which these findings may have been influenced by a previously undiagnosed autoimmune disorder, such as systemic lupus erythematous, is unknown. One publication by Varga et al[17] reported the presence of lymphocytic endotheliitis in 3 COVID-19 patients of unknown race, including the heart and lungs of 2 autopsied patients and the small intestine of 1 patient with mesenteric ischemia.[17] Of note, pulmonary vasculitis was not reported in any of the 38 Italian patients as described in a preprint manuscript.[22]

As our case is the first of its kind to report vasculitis in a known Hispanic patient, this finding raises the possibility that COVID-19 may have slightly different mechanisms of pathogenesis in different racial and ethnic groups. Recent data have suggested that Latino and African Americans with COVID-19 have disproportionately worse outcomes, which has been attributed to the prevalence of underlying comorbidities in these populations as well as socioeconomic factors and access to health care. However, the autopsy findings in this Mexican American patient indicates that more pathology-based studies are needed for further clarification of how the virus might differentially affect members of different racial and ethnic groups.

Increased thrombotic propensity in SARS-CoV-2–infected patients has been suggested from clinical reports of vaso-occlusive events and laboratory findings noting increased fibrin/fibrinogen degradation products, elevated D-dimer levels, and decreased prothrombin time activity.[27,28] These reports, along with the fact that microthrombi have been reported in SARS patients,[29] have led some practitioners to advocate for the utilization of fibrinolytic agents for COVID-19 patients. Indeed, the presence of microthrombi within lung tissue of COVID-19 patients has been reported in 2 published articles[15,21] and 3 preprint manuscripts,[22,23,25] including 1 Italian preprint indicating that 33 of 38 decedents had microthrombi and all 26 persons who had undergone D-dimer testing had elevated values.[22] In our patient, who had an elevated D-dimer level and pathologically confirmed pulmonary infarction, microthrombi were not detected by light microscopy despite obtaining multiple sections from all lobes of both lungs. However, EM did reveal increased fibrin aggregations within blood vessels, thereby suggesting that the light microscopic evaluation may have missed microthrombi owing to sampling error.

One of the major limitations of this autopsy report is that it conveys the pathology findings of a single patient; however, the ultrastructural findings in this case support mounting evidence that SARS-CoV-2 may promote a prothrombotic coagulopathy by a yet undiscovered mechanism.

Cardiac Clinicopathologic Correlation

This 44-year-old obese patient, who had no known history of cardiovascular disease, developed multiple cardiac functional abnormalities, including severe septal, mid-anterolateral, and mid-inferior hypokinesis. She was ultimately diagnosed with reverse Takotsubo cardiomyopathy,

and viral myocarditis was strongly suspected. Viral myocarditis is characterized by inflammation of the myocardium that, in fulminant cases, can result in myocyte necrosis and edema leading to cardiogenic shock, fatal ventricular tachyarrhythmias, or bradyarrhythmia.[30] The autopsy findings of this case were discongruent with the clinical impression in that no myocarditis was detected and the microscopic findings showed only rare foci of myocardium containing few scattered $CD45^+$ interstitial lymphocytes with no associated myocyte injury.

Several clinical reports of viral myocarditis in COVID-19 patients have been published[31,32] but, notably, most have lacked pathology confirmation. A minor component of myocarditis was found in association with transmural myocardial infarction and rupture in a publicized autopsy report of a 57-year-old woman.[13] However, of the 10 SARS-CoV-2–infected patients with postmortem heart tissue findings that have been reported in peer-reviewed publications thus far, all showed no definitive evidence of viral myocarditis.[15–17,20,21]

Nevertheless, some COVID-19 patients manifest evidence of cardiac injury that is mediated by a yet undiscovered mechanism. Detection of viral genome in heart tissue of patients with SARS has led some investigators to suspect that the novel coronavirus may cause direct damage to cardiac myocytes.[33] The autopsy report of a 57-year-old woman with COVID-19 who died of ventricular wall rupture claimed that RNA for the SARS-CoV-2 virus was detected in heart tissue[13]; however, no viral RNA was detected in 3 COVID-19 cases described by Yao et al[21] via PCR, EM, or immunohistochemistry modalities. Others have postulated that the cardiac injury may be secondary to the effect of systemic inflammation induced by viral infection.[34,35] Indeed, coronavirus infection is typically associated with a high inflammatory burden, which may generate an environment conducive to cardiac arrhythmias, vascular inflammation, or myocarditis.[33–35]

Myocardial injury with ST-segment elevation has been reported in COVID-19 patients; a case series from 6 New York hospitals described 18 COVID-19 patients with ST-segment elevation,[36] all of whom had increased D-dimer levels. About half of the patients underwent coronary angiography and, of these, about two-thirds had obstructive coronary artery disease. The lack of baseline coronary artery disease in one-third of the patients raises the possibility that the myocardial injury seen in COVID-19 patients may be due to myocardial ischemia secondary to obstructive or nonobstructive alterations in the coronary arteries. The patient in our case had an elevated D-dimer level, but she did not have a history of ST-segment elevation on ECG during her hospitalization; in addition, her coronary arteries were widely patent and free of significant atherosclerotic disease on autopsy, which was also the case for a 57-year-old Hispanic woman with SARS-CoV-2 who died following left ventricular rupture.[13] Some authors have proposed that, especially in patients with no significant arteriosclerosis or cardiovascular disease, virus-mediated cardiac injury may be induced by ischemia related to vasospasm of the coronary arteries by a yet unknown mechanism.

It is also possible that, in our patient, the infection may have exacerbated a previously unknown congenital cardiac abnormality. This woman had a remarkably thin right atrial wall suspected to be of congenital origin and, in addition, the right ventricle appeared slightly dilated, which may have been the result of increased pulmonary pressure related to severe acute lung injury. This combination of factors may have impaired the normal electrical conduction and mechanical propulsion of atrial myocardial tissues, resulting in arrhythmia or hypokinesis. In addition, just before her death the patient had received hydroxychloroquine, which is known to have cardiac-related toxicity, though usually in patients who have received the drug for a longer period.

The discordance between the clinical impression of viral myocarditis and the lack thereof on microscopic examination may potentially be explained by the diagnosis of reverse Takotsubo cardiomyopathy, a variant of Takotsubo cardiomyopathy and reversible left ventricular dysfunction that often mimics acute coronary syndrome and ischemic heart disease.[37] The pathogenesis of Takotsubo cardiomyopathy or reverse Takotsubo cardiomyopathy is not well understood, although catecholamine-induced cardiotoxicity triggered by emotional and/or physical stress is currently the most accepted hypothesis.[37] The criteria for diagnosis of reverse Takotsubo cardiomyopathy include basal hypokinesis/akinesis in the left ventricle, and new ECG abnormalities or elevated cardiac troponin levels in the absence of obstructive coronary disease, pheochromocytoma, or myocarditis.[37] Clinically this patient met the criteria for a diagnosis of reverse Takotsubo cardiomyopathy and, although this cannot be proved on autopsy examination owing to a lack of specific associated histopathologic changes in this disease, it is possible that the cardiovascular pathology findings identified in this patient were induced by reverse Takotsubo cardiomyopathy. In addition, we cannot rule out the possibility that COVID-19 may have been the trigger for development of reverse Takotsubo cardiomyopathy.

Although the specific mechanism of SARS-CoV-2–induced cardiac injury is not fully elucidated, acute myocardial injury is the most commonly reported extrapulmonary finding in COVID-19 patients. Whether this is due to specific viral mechanisms, systemic inflammatory burden, coronary artery vasospasm, or exacerbation of underlying cardiovascular disease has yet to be determined and additional studies are needed.

Renal Clinicopathologic Correlation

The patient was admitted with normal blood urea nitrogen and serum creatinine levels, but during the course of her admission, these markers progressively rose and her urine output concurrently declined despite aggressive diuresis. The clinical impression of acute kidney injury was confirmed on microscopic evaluation, which showed evidence of focal acute tubular injury and an absence of infarction, thrombotic microangiopathy, or coagulopathy. Of note, the patient did not have a known history of diabetes and no evidence of diabetic nephropathy was identified.

Clinical observations of COVID-19–induced renal injury have been reported, but those that include histopathologic findings are scarce. Lymphocytic endotheliitis was identified on postmortem examination of a 58-year-old woman of unknown race.[17] Postmortem renal biopsies of 3 Chinese patients reportedly showed glomerular endothelial cell swelling, a small amount of transudate in the Bowman capsule, thrombi in the glomerular capillaries, and renal tubular epithelial changes, including edema, vacuolar degeneration and disassociation, as well as protein casts and pigment casts in the lumen[21]; notably, the SARS-CoV-2 virus was not detected in the renal tissues by immunohis-

tochemistry or EM.[21] However, viral inclusion bodies detected by ultrastructural evaluation were reported in a Swiss preprint manuscript depicting the renal biopsy findings of a 63-year-old, hypertensive, COVID-19–positive black man, which showed severe collapsing focal segmental glomerulosclerosis without nephritis.[24] A publicized autopsy report of a 57-year-old Hispanic woman revealed rare glomerulosclerosis.[13]

The conspicuous absence of nephritis in all of these reports suggests that renal injury induced by SARS-CoV-2 is not mediated by a diffuse inflammatory process, but by some other unknown modalities.

CONCLUSION

Worldwide, the number of COVID-19–related deaths continues to increase, but much is still unknown regarding SARS-CoV-2 pathogenesis. Current data available to health care providers and researchers are primarily based on case reports, small case series, and anecdotal evidence. With the absence of microscopic confirmation of clinically suspected viral myocarditis, this case illuminates a major limitation that underlies the currently burgeoning mass of COVID-19–related clinical reports that lack pathologic confirmation of findings. Reports based only on clinical findings, although useful, do not provide much needed depth into the pathogenic mechanisms of this novel and highly contagious virus.

Peer-reviewed publications of pathologic findings in COVID-19 patients are especially scarce. The COVID-19 pandemic highlights the importance of autopsy studies, which provide invaluable insight into the viral pathogenic mechanisms and epidemiologic differences in disease progression and also inform treatment and prevention strategies. Here, we present the first report of autopsy findings with clinical correlation of a Hispanic patient in the United States who died of COVID-19 viral infection.

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