Spontaneous Multiple Arterial Dissection in a COVID-19–Positive Decedent

Christine James, DO and Diane C. Peterson, MD

Abstract: Spontaneous multiple arterial dissection (SMAD) is a rarely reported phenomenon and has been previously linked to connective tissue diseases and specifically the genetic mutations in *SMAD3* and *COL3A1*. Herein we describe a case of SMAD with scattered thrombi in a COVID-19–positive patient with a history of unspecified mitochondrial myopathy. Vasculopathy involved the splenic artery, inferior mesenteric artery, internal mammary arteries, omental arteries, mesenteric arteries, and small renal arteries. Dissections were confirmed by histology in the splenic artery, inferior mesenteric artery, and bilateral renal medullary arteries. Genetic studies were done to rule out *SMAD3* and *COL3A1* mutations. Because the Smad3 protein has been previously implicated in COVID-19–associated tissue fibrosis, it may play a role in endothelial dysfunction as well.

Key Words: forensic pathology, COVID-19, arterial dissection, endothelial dysfunction, SMAD

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COVID-19, otherwise known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the etiological agent of the ongoing global pandemic. Although the majority of infections are asymptomatic to mild, acute respiratory distress syndrome has widely been reported, especially in patients with multiple comorbidities. Vascular abnormalities have also been reported in the literature and include endotheliitis, thromboemboli, and atypical endovascular cell morphology.[1,2]

Isolated arterial dissection occurring without aortic dissection is uncommon but has been reported in the carotid arteries and renal arteries. The splanchnic circulation comprises the gastric, pancreatic, hepatic, splenic, and intestinal circulations. Dissection of any of these vessels is rare but is most common in the superior mesenteric artery, followed by the celiac artery and hepatic artery.[3] Risk factors include atherosclerosis, hypertension, fibromuscular dysplasia, cystic medial necrosis, trauma, and connective tissue disorders.[4] When dissection does occur, acute abdominal pain is the most common presenting symptom.[3]

A review of the literature produced only a few results regarding spontaneous multiple arterial dissections (SMADs). Aubart et al[5] published an article in 2014 regarding this finding in carriers of *SMAD3* gene mutations. They described 95% (18 of 19) of known *SMAD3* gene carriers possessed either aortic or extra-aortic vascular disease. Forty-four percent of carriers (8 of 19) had involvement of the medium-sized vessels to include the subclavicular, renal, splenic, and iliac arteries. One patient had multiple simultaneous dissections of the subclavian, carotid, vertebral, renal, and mesenteric arteries. They also describe neurological symptoms to include motor and sensory neuropathy, reminiscent of Charcot-Marie-Tooth syndrome without the associated *CMT2* gene mutation.[5] Amitai Komem et al[6] reported a case of 7 simultaneous arterial dissections in 2019. Dissected arteries included the right internal carotid artery, celiac trunk, splenic artery, right renal artery, inferior mesenteric artery, and bilateral external iliac arteries. The right kidney had an associated partial infarction. An underlying connective tissue disorder was sought and a *COL3A1* mutation was discovered.

Although the *SMAD3* gene has been implicated in SMADs, the Smad3 protein also has been shown to play an important role in COVID-19 infections via the viral N protein. It has been proposed that the SARS-CoV N protein may potentiate the Smad3-mediated transcriptional responses of transforming growth factor β leading to tissue fibrosis. The N protein is also thought to interfere with transforming growth factor β–induced and SMAD4-mediated proapoptotic gene expression.[7]

CASE REPORT

We present a case of a 40-year-old White man with a history of an unspecified mitochondrial myopathy who presented to the hospital with complaints of fatigue, weakness, shortness of breath, and fever. He was positive for COVID-19 on admission by COVID-19 RNA testing. He was treated with plasmapheresis and dexamethasone. After 2 consecutive negative COVID-19 RNA test results, he was released to a rehabilitation facility approximately 10 days after admission. However, on the following day, he complained of abdominal pain and shortness of breath. He was diaphoretic and became unresponsive. Cardiopulmonary resuscitation efforts were unsuccessful, and he was pronounced at the scene.

At autopsy, a measured 1600 mL of clotted and liquid blood was present in the peritoneal cavity. The splenic artery had a ruptured dissection along the body of the pancreas. The inferior mesenteric artery was occluded by thrombus at its origin from the aorta. The internal mammary vessels, omental vessels, and mesenteric

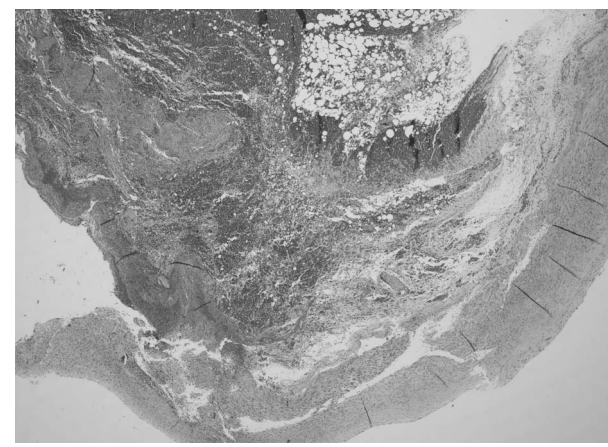

FIGURE 1. Hematoxylin and eosin stain (×2): splenic artery dissection with hemorrhage into the adjacent fibroadipose tissue.

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Reprints: Christine James, DO, Johnson County Medical Examiner's Office, 11894 S. Sunset Drive, Olathe, KS 66061.
E-mail: Christine.James@jocogov.org.

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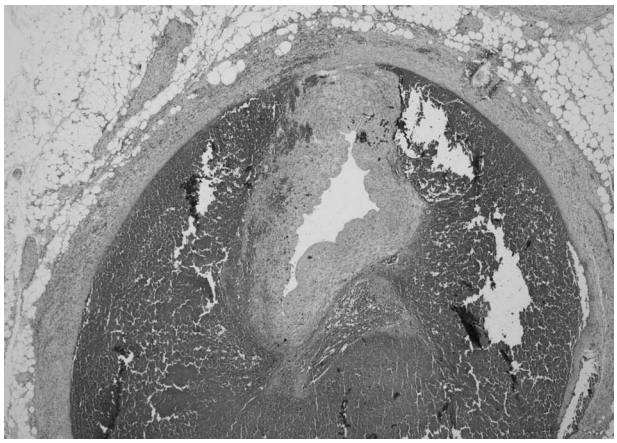

FIGURE 2. Hematoxylin and eosin stain (×2): inferior mesenteric artery dissection and overlying thrombus.

vessels had numerous thrombi. Thrombi were also present in small vessels within the calyces and hila of the kidneys, bilaterally. The right kidney had an area of cortical infarction. No emboli or thrombi were identified within the vasculature of the lungs or heart.

Histological evaluation of the splenic artery confirmed transmural dissection with hemorrhage into the adjacent fibroadipose tissue (Fig. 1). Microscopic evaluation of the inferior mesenteric artery revealed transmural dissection and resultant overlying thrombosis (Fig. 2). Atypical cells and focal necrosis were noted within the vessel wall (Fig. 3). The right renal infarct was confirmed by histology (Fig. 4). A renal medullary artery of the right kidney exhibited transmural dissection with adjacent acute and chronic inflammation, including numerous eosinophils (Fig. 5). A section of the left kidney also showed dissection of a hilar artery with thrombosis and mild chronic inflammation (Fig. 6). Paraffin blocks were submitted to the Centers for Disease Control and Prevention for immunohistochemical stains. Sections of the heart, inferior mesenteric artery, splenic artery, lungs, and right kidney were surprisingly negative for SARS-COV-2 COVID-19 nucleocapsid HL448. Muscle histology was not performed as part of the postmortem investigation.

A postmortem nasopharyngeal test for SARS-CoV-2 RNA yielded a positive result. Postmortem toxicology was noncontributory. Postmortem vitreous electrolytes were within expected parameters. Genetic studies performed on postmortem blood for

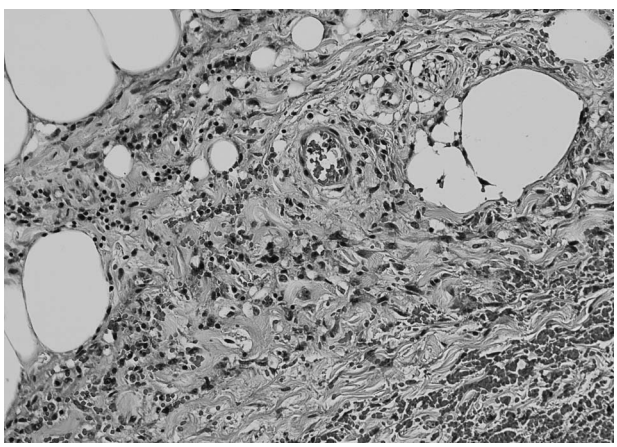

FIGURE 3. Hematoxylin and eosin stain (×20): atypical cells within the adventitia of the inferior mesenteric artery.

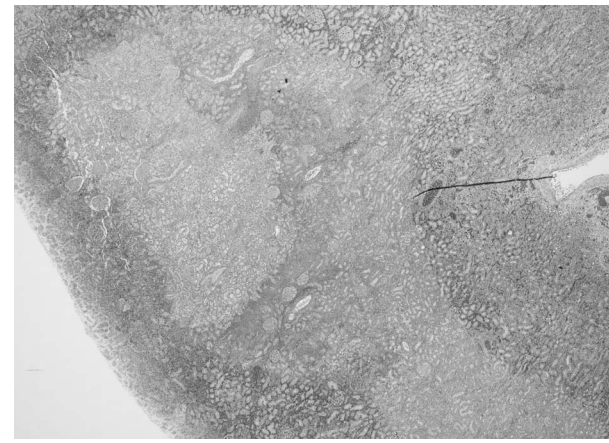

FIGURE 4. Hematoxylin and eosin stain (×2): right renal infarct.

aortopathy gene variants showed negative results, including variants in *COL3A1*, *SMAD3*, and *SMAD4*. A comprehensive neuromuscular disorder gene panel revealed 2 variants of uncertain significance involving the *MTM1* [c.734C > T (p.Pro245Leu)] and *PLEC* genes [c.13192G > A (p.Ala4398Thr)]. *CMT2* was unfortunately not part of the comprehensive gene panels. Medical records regarding the decedent's initial diagnosis of mitochondrial myopathy could not be located because of temporal remoteness.

DISCUSSION

COVID-19–associated SMAD has not previously been reported in the literature. The rare phenomenon of SMAD has only been reported in connective tissue disorders to date, based on a review of the literature. Previously reported patients with SMAD have been found to be carriers of mutations in either the *SMAD3* or *COL3A1* genes. To our knowledge, this case represents the first case of viral etiology. Although the decedent had a diagnosis of an unspecified mitochondrial myopathy, only 2 variants of unknown significance were detected on a comprehensive neuromuscular genetics panel. No mutations were detected on a comprehensive aortopathy genetics panel. The decedent was positive for COVID-19 by postmortem nasopharyngeal swab; however, immunohistochemical

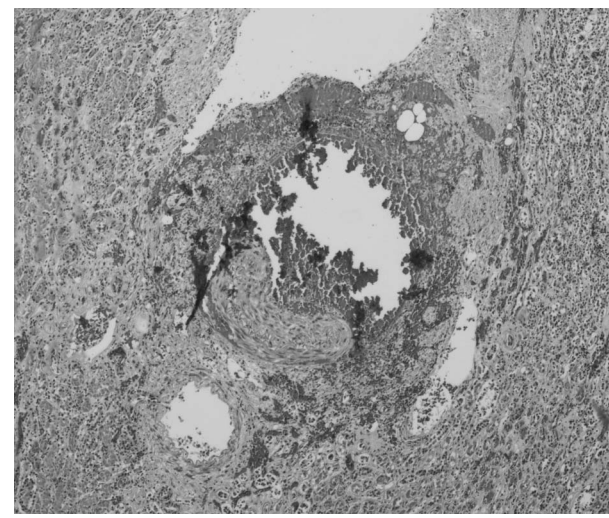

FIGURE 5. Hematoxylin and eosin stain (×4): right medullary artery dissection.

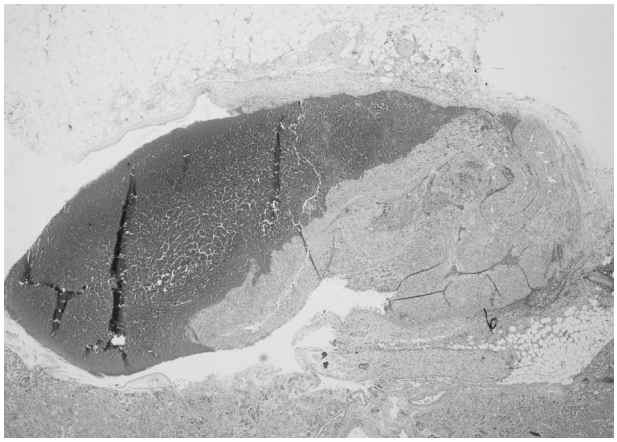

FIGURE 6. Hematoxylin and eosin stain (×2): left renal hilar artery with dissection and thrombus.

stains were interestingly negative for COVID-19 nucleocapsid HL448 in the submitted tissues.

Because the Smad3 protein has been previously implicated in COVID-19-associated tissue fibrosis, that is, acute respiratory distress syndrome, it may stand to reason that it also plays some role in the vasculopathies reported in COVID-19 infections because the *SMAD3* gene mutation has been shown to be the cause of its namesake SMADs.

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