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Endotheliitis in Coronavirus Disease 2019–Positive Patients After Extremity Amputation for Acute Thrombotic Events

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Background: Both arterial and venous thrombotic events of the extremities occur in coronavirus disease 2019 (COVID-19) infection, but the etiology of these events remains unclear. This study sought to evaluate pathology specimens of COVID-19-positive patients postamputation, who were found to have Rutherford 3 acute limb ischemia requiring amputation.

Methods: A retrospective review was performed of all vascular surgery emergency room and inpatient consultations in patients who presented to the Mount Sinai Health System from March 26, 2020, to May 10, 2020. Pathology specimens were examined using hematoxylin and eosin stain. The specimens were assessed for the following: inflammatory cells associated with endothelium/apoptotic bodies, mononuclear cells, small vessel congestion, and lymphocytic endotheliitis. Of the specimens evaluated, 2 patients with a known history of peripheral vascular disease were excluded.

Results: Inflammatory cells associated with endothelium/apoptotic bodies were seen in all 4 patients and in 4 of 5 specimens. Mononuclear cells were found in 2 of 4 patients. Small vessel congestion was seen in all patients. Lymphocytic endotheliitis was seen in 1 of 4 patients.

Conclusions: This study shows endotheliitis in amputation specimens of four patients with COVID-19 disease and Rutherford Class 3 acute limb ischemia. The findings in these patients is more likely an infectious angiitis because of COVID-19.

INTRODUCTION

Patients with coronavirus disease 2019 (COVID-19) disease are hypercoagulable.[1,2] The etiology of hypercoagulability is not completely understood but may be due to underlying endotheliitis.[3,4] Previous studies have shown evidence of endotheliitis in postmortem examination of COVID-19 patients.[5] These studies have shown diffuse alveolar damage in the respiratory tract, lymphocyte infiltration in the alveolar space[5] with evidence of pulmonary embolism in some studies.[6] There is evidence of significant limb ischemia in COVID-19 patients,[7,8] but recent tissue studies have not focused on the extremities. Both arterial[9] and venous thrombotic events[10] of the extremities occur in COVID-19 infection, but the etiology of these events remains unclear. This study sought to evaluate pathology specimens of COVID-19-positive patients postamputation, who were found to have Rutherford 3 acute limb ischemia requiring amputation.

METHODS

A retrospective review was performed of all vascular surgery emergency room and inpatient consultations in patients who presented to the Mount Sinai Health System from March 26, 2020, to May 10,

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Table I. Summary of findings

Case number	Inflammatory cells associated with endothelium/apoptotic bodies	Mononuclear cells	Small vessel congestion	Lymphocytic endotheliitis	Comments
1	Positive	Negative	Positive	Negative	Two amputations; the above-knee amputation site was negative for findings
2	Positive	Positive	Positive	Negative	Inflammation not only involve the endothelium but the rest of the vessel wall
3	Positive	Positive	Positive	Positive	Plasma cells are present in vessel wall
4	Positive	Negative	Positive	Negative	Small vessels with acute endotheliitis and apoptosis

2020. There were more than 45 COVID-19 patient consultations, of which 30 consults were for acute thrombotic events. Six patients underwent primary amputation; there was one below-knee amputation, and there were six above-knee amputations. One of the patients had above-knee amputations on bilateral lower extremities. Pathology specimens were examined using hematoxylin and eosin (H&E) stain. The stains were reviewed by 2 pathologists at Mount Sinai Morningside-West. The specimens were assessed for inflammatory cells associated with endothelium/apoptotic bodies, mononuclear cells, small vessel congestion, and lymphocytic endotheliitis. Of the specimens evaluated, 2 patients with a known history of peripheral vascular disease were excluded. All patients consented to this study. Hypercoagulable workup was not performed for any of these patients. Institutional review board approval was obtained.

RESULTS

Inflammatory cells associated with endothelium/apoptotic bodies were seen in all 4 patients and in 4 of 5 specimens. In Case 1, there were 2 amputations. The left above-knee amputation site of Case 1 was free of findings. However, the subsequent hip disarticulation site for this patient was positive for findings. Mononuclear cells were found in 2 of 4 patients. Small vessel congestion was seen in all patients. Lymphocytic endotheliitis was seen in 1 of 4 patients (Table I).

Cases

Case 1. A 62-year-old man presented with acute limb ischemia of the bilateral lower extremities. The patient reported left lower extremity numbness and weakness of 2 days duration. He was COVID-19 positive but denied respiratory complaints. His past medical history included hypertension, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease (CKD) on hemodialysis, and he was an active smoker. On examination, the right femoral pulse was palpable, and the left femoral pulse was nonpalpable. There were no signals in the left dorsalis pedis (DP) or posterior tibial (PT) artery. There were DP and PT signals on the right lower extremity. The right lower extremity was warm, with motor and sensory function intact. The left foot was cool, and there were sensorimotor deficits. His d-dimer on presentation was >20 mcg/mL. Transthoracic echo (TTE) showed no evidence of patent foramen ovale (PFO) or left ventricular (LV) thrombus. Computed tomography showed extensive thrombus within the distal abdominal aorta, with approximately 75% luminal narrowing extending to the bifurcation. There was complete occlusion of the left common iliac artery and distal branches through the foot. There was some reconstitution of flow within the distal left internal iliac artery. In addition, there was thrombus with approximately 50% luminal narrowing of proximal right common iliac artery and an occlusive thrombus of distal right popliteal artery with flow in the runoff vessels of the right lower extremity. There were bilateral pulmonary emboli. The patient was taken to the operating room (OR) for left above-knee amputation and thromboembolectomy of the left aortoiliofemoral arteries. He also underwent right femoropopliteal thromboembolectomy. There was devitalized muscle and significant clot removed. The patient subsequently was extubated and managed with a heparin drip. Postoperatively, there were DP and PT signals in bilateral lower extremities. However, within 24 hours, he no longer had right DP or PT signals. Therefore, he was taken emergently to the OR for Fogarty

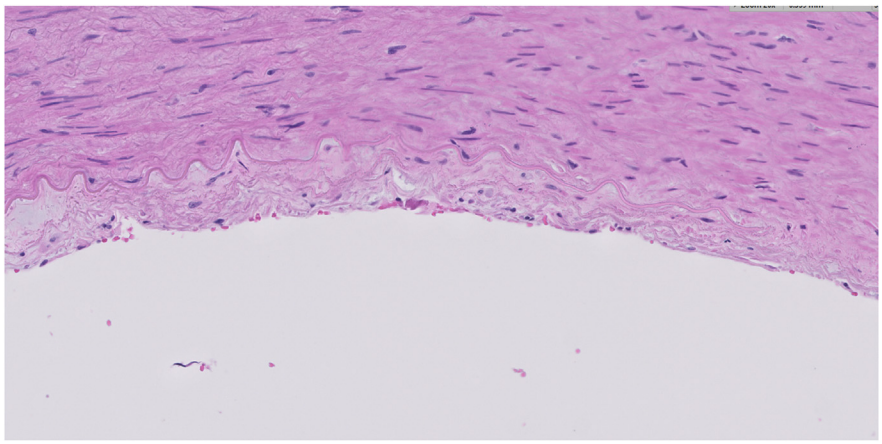

Fig. 1. The popliteal artery of the left above-knee amputation specimen with no evidence of inflammation.

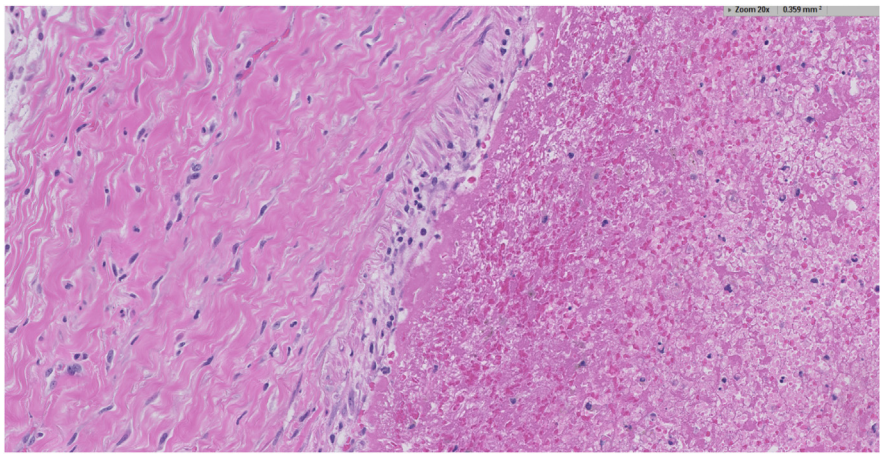

Fig. 2. Femoral artery of the hip disarticulation specimen.

thromboembolectomy of the right iliac down to the popliteal and tibial arteries. Given the preoperative deep vein thrombosis (DVT), an inferior vena cava filter was placed. His postoperative course was complicated by a nonhealing left above-knee amputation wound, and he was taken to the OR for left hip disarticulation with orthopedic surgery and plastic surgery. He ultimately expired on postoperative day 46. Figure 1 shows the popliteal artery of the left above-knee amputation specimen with no evidence of inflammation. Figures 2 and 3 show the femoral artery of the hip disarticulation specimen. There are inflammatory cells associated with endothelium and apoptotic bodies.

Case 2. A 79-year-old man presented to the hospital with the complaint of right lower extremity pain. The patient had a history of hypertension and gastroesophageal reflux. He reported upper respiratory symptoms, specifically a productive cough 2 weeks prior to presentation but this was managed in the outpatient setting. He reported left lower extremity swelling and was started on Eliquis for concern of DVT. On presentation, he denied respiratory complaints. He was COVID positive. On examination, he had frank gangrene of the right foot with blistering. The right foot was cool. There was diminished motor and sensation. There were no pedal signals in the right foot. There was a palpable left lower extremity DP pulse. TTE was negative for PFO or LV thrombus. Electrocardiogram (EKG) was sinus rhythm. Duplex of the lower extremities was negative for DVT. He was taken to the OR for attempted revascularization but ultimately required a right below-knee amputation. Figures 4 and 5 show

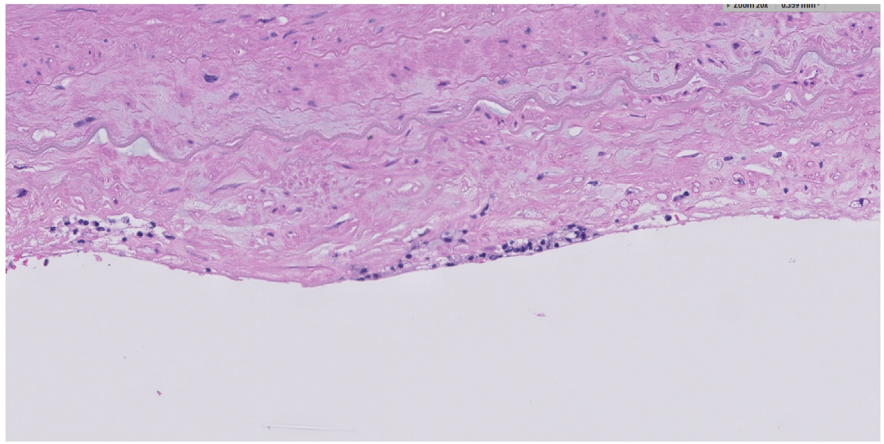

Fig. 3. Femoral artery of the hip disarticulation specimen.

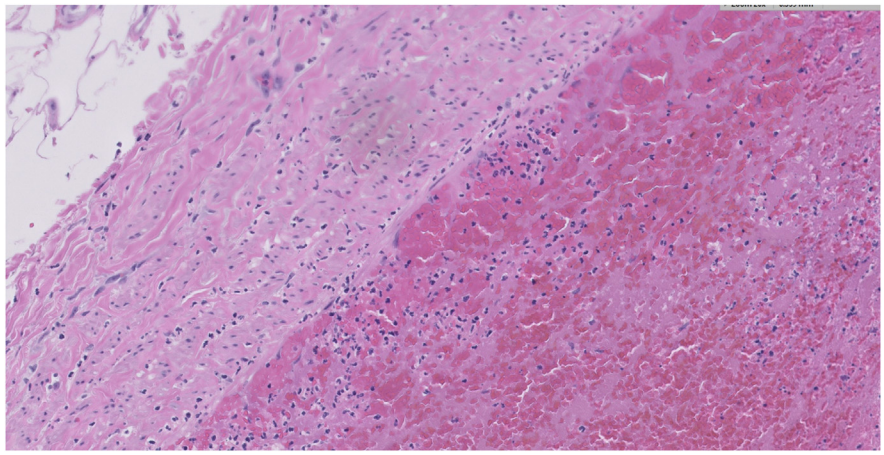

Fig. 4. Evidence of inflammation not only involving the endothelium but the rest of the vessel wall.

evidence of inflammation not only involving the endothelium but the rest of the vessel wall.

Case 3. A 69-year-old woman with a past medical history of multiple falls, diabetes, hypertension, and hyperlipidemia was presented with worsening left lower extremity pain for 2 days. The patient was found down at her home and brought to the hospital by ambulance. On examination, the left leg was cool to touch below the knee with mottling extending to the knee. There were no pedal signals nor popliteal signals. She had significant sensorimotor deficits. She had evidence of irreversible ischemia at the below knee level. Neither TTE nor venous duplex was performed. EKG was sinus rhythm. She was taken to the OR for arteriogram, which showed extensive thrombus of the superficial femoral artery origin and the profunda femoral artery; she ultimately underwent left above-knee amputation for Rutherford 3 ischemia. Figures 6 and 7 show plasma cells are present in vessel wall. Overall the degree of inflammation in this patient's tissues was the most severe of the 4 cases.

Case 4. A 89-year-old woman was admitted to the hospital for septic shock because of an obstructing ureteral stone and COVID-positive pneumonia. She had a past medical history of atrial fibrillation on warfarin, bioprosthetic mitral valve replacement, and CKD. The patient had a radial arterial line placed in the left arm during nephrostomy procedure. She was on vasopressors. Vascular surgery was consulted postoperatively when the patient was found to have a cold left wrist and hand. On

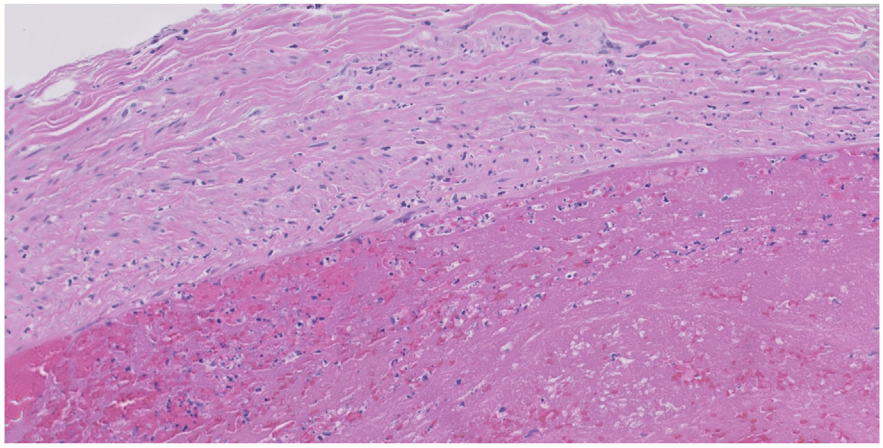

Fig. 5. Evidence of inflammation not only involving the endothelium but the rest of the vessel wall.

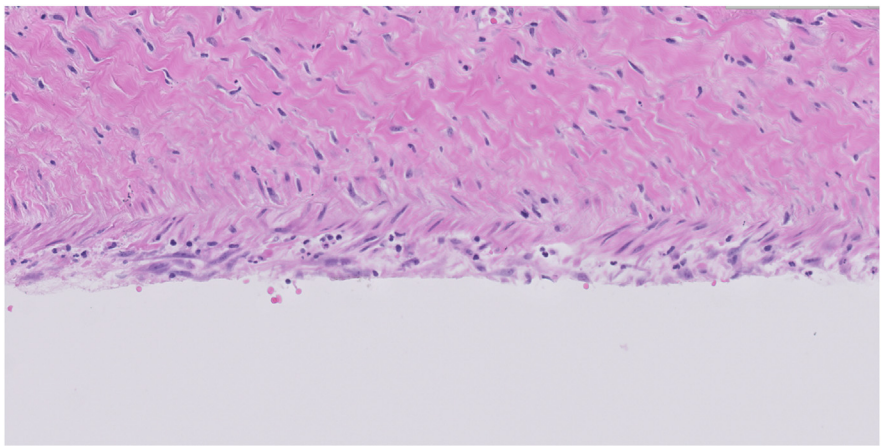

Fig. 6. Plasma cells are present in vessel wall.

examination, the left hand was mottled. There were no signals in the radial or ulnar arteries. There were significant motor and sensory deficits. TTE was negative for PFO. Duplex was negative for DVT. EKG showed atrial fibrillation. The patient underwent a left forearm amputation once she had stabilized medically. Figures 8 and 9 show small vessels with acute endotheliitis and apoptosis.

DISCUSSION

The pathophysiology of COVID-19 thrombosis is multifactorial. Viral invasion occurs via angiotensin-converting enzyme 2 (ACE-2) receptors on endothelial cells, and COVID-19 infection subsequently induces endothelial cell damage.[11] Infection-mediated endothelial injury and endotheliitis may result in activation of the coagulation cascade and result in thrombosis.[12] In addition, a cytokine storm evidenced by elevated levels of interleukin-2, tumor necrosis factor alpha, and other inflammatory cytokines likely contributes to coagulopathy.[13]

Most recently, studies have assessed COVID-19 induced vasculitis in dermatologic biopsy specimens as well as in children with diagnoses of Kawasaki and Kawasaki-like disease.[12] Several studies have evaluated autopsy reports in patients with COVID-19,[1,5] and then many studies have reviewed acute limb ischemia in patients with COVID-19.[8,14] However, the authors are unaware of any study that has evaluated surgical pathology, particularly of

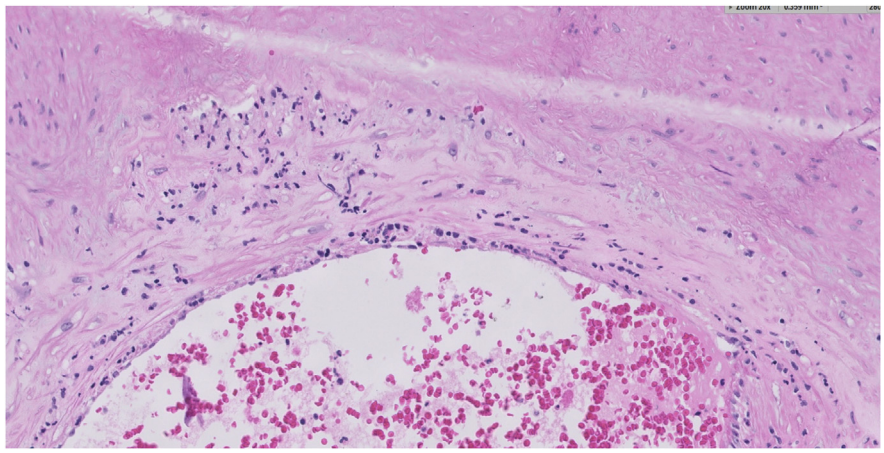

Fig. 7. Plasma cells are present in vessel wall.

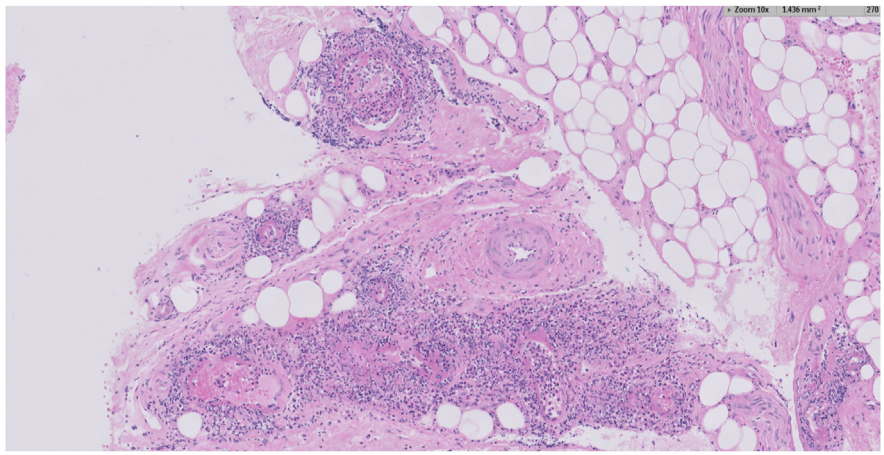

Fig. 8. Small vessels with acute endotheliitis and apoptosis.

amputation specimens in these patients. This study shows endotheliitis in amputation specimens of four patients with COVID-19 disease and Rutherford Class 3 acute limb ischemia. This was primarily characterized as inflammatory cells associated with endothelium/apoptotic bodies (Cases 1–4), mononuclear cells (Cases 2 and 3), and lymphocytic endotheliitis (Case 3). There is limited data on histopathologic findings in amputation specimens of patients with Rutherford 3 acute limb ischemia. Amputation specimens for Rutherford 3 acute limb ischemia demonstrate acute thrombus with fibroatheroma within large vessels such as the popliteal artery.[15] In their study, Narula et al. do not mention inflammatory findings in these specimens. This is understandable because acute limb ischemia is not typically associated with endotheliitis. Rather, endotheliitis evident by intimal thickening with inflammatory cell infiltration has been observed in vessel walls in lower extremity amputation specimens of patients with Buerger's disease and Rickettsia infection.[16] Given the currently available literature, the findings in this case series of patients is more likely an infectious angiitis due to COVID-19.

This series is limited by the small sample size and retrospective nature. It is also limited by what can be gleaned from H&E stain. Many studies have used electron microscopy to identify COVID-19 viral particles in tissue specimens; however, there has been

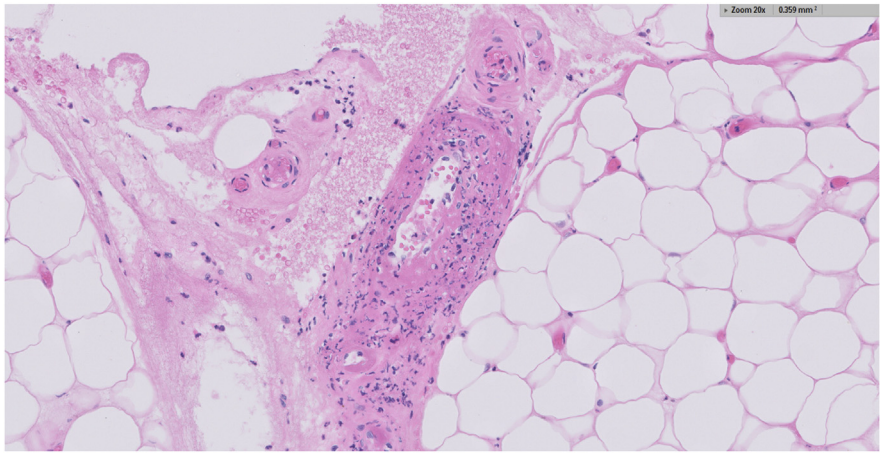

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Fig. 9. Small vessels with acute endotheliitis and apoptosis.

controversy about the validity of this approach. Some authors, such as Goldsmith et al., argue that viral particles were not seen in these specimens[4,17,18] but rather cross-sections of the rough endoplasmic reticulum.[19] More studies will be needed to better understand the mechanism of thrombosis in COVID-19.

Disclosures: None.

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