A 49-Year-Old Woman with Mild Symptoms of COVID-19 and Vasospasm-Induced Acute Limb Ischemia

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Abstract

Background: The novel SARS-CoV-2 virus was thought to affect the respiratory system primarily. During the Coronavirus Disease 2019 (COVID-19) pandemic, it became apparent that it affected many organ systems, resulting in numerous extra-respiratory manifestations. Though much has been learned about the disease during the pandemic, various clinical features still have unclear pathophysiology. Here we outline the case of a 49-year-old with mildly symptomatic COVID-19 infection and bilateral acute limb ischemia (ALI).

Case report: This is the case of a 49-year-old female with a past medical history of essential hypertension and Prinzmetal angina, and fully vaccinated for COVID-19, who had a positive home rapid antigen test for COVID-19 after developing mild respiratory symptoms. One week after her initial symptoms, she reported the onset of sharp pain in both lower extremities, radiating from her toes to her knees proximally. On presentation, she was noted to have mottled, cool lower extremities with absent palpable and audible pulses. Non-invasive and invasive angiography showed no acute thromboses or significant atherosclerotic disease but instead showed bilateral diffuse vasospasm of the lower extremity vessels. Laboratory workup was not suggestive of hypercoagulability or antineutrophil cytoplasmic-associated vasculitides. Given the timing of the onset of vascular symptoms in relation to COVID-19 infection and the many reported cases of COVID-19-related vascular disease, this is likely a vascular manifestation of COVID-19.

Conclusion: This case highlights a novel manifestation of COVID-19. It demonstrates that there is still more to be learned about the underlying pathophysiologic mechanisms that lead to the varied clinical presentations of the SARS-CoV-2 virus.

MeSH Keywords

COVID-19, SARS-CoV-2, Ischemia, Thrombosis

Background

Since it was first identified in Wuhan, China, in December 2019, the Coronavirus Disease 2019 (COVID-19) caused by the novel SARS-CoV-2 virus has spread rapidly across with world, affecting more than 200 territories. Due to the rising number of cases of COVID-19 and its associated morbidity and mortality, and its ensuing threat to healthcare and economic systems worldwide, the World Health Organization declared it a pandemic in March 2020 [1].

At the outset of the pandemic, life-threatening respiratory complications of the novel SARS-CoV-2 virus caught the attention of many clinicians. However, as COVID-19 cases increased worldwide, many extra-respiratory manifestations of the disease became apparent, including vascular and dermatologic manifestations [2]. The vascular manifestations associated with COVID-19 presented in many ways, including thromboses in the venous system, such as both lower limb and upper limb deep vein thromboses and portal vein thrombosis; arterial thrombosis, including acute myocardial infarctions, ischemic strokes, and acute limb ischemia [3]. In rare cases, COVID-19 has been associated with severe vasospasm affecting the
coronary vessels, which have predisposed to cardiac ischemia and cardiac arrest in at least one case [4,5].

Acute limb ischemic (ALI), a limb-threatening condition characterized by a sudden reduction in the arterial blood flow to a limb, is an infrequently reported manifestation of COVID-19. The incidence of ALI in COVID-19 from 3-5%. When ALI occurs in patients with COVID-19, it is most commonly observed in patients with severe COVID-19 requiring critical care admission and usually on a background of underlying vascular disease and pre-existent risk factors for atherosclerosis [6]. In most cases, COVID-19-associated ALI is attributed to acute arterial thrombosis [7]. Here we present a patient with recent recovery from mildly symptomatic COVID-19, presenting with ALI without significant atherosclerotic peripheral vascular disease and traditional risk factors for ALI. In our case, severe vasospasm of the lower extremity arteries, triggered by mild COVID-19 infection, is considered the primary mechanism for this presentation.

Case Presentation

We present the case of a 49-year-old female with a history of Prinzmetal angina and essential hypertension who presented with a two-day history of worsening bilateral lower extremity pain and numbness. One week before her presentation, she had experienced a sore throat, nasal congestion, and generalized malaise, and she took home a rapid antigen test for COVID-19, which she reported was positive. She commenced treatment with Nirmatrelvir/ritonavir. Two days before completing the five-day course of Nirmatrelvir/ritonavir, she reported the onset of sharp pain in both lower extremities, radiating from her toes to her knees proximally. The pain progressively worsened and was extremely severe on the day before the presentation, preventing her from ambulating. She also reported a “blue discoloration” to the great toes of both feet, which spread proximally to the mid-tarsal region during this period. She denied any preceding trauma, symptoms of intermittent claudication, rest pain, paresthesia, or numbness in the lower extremities. She also denied a history of thrombotic events, prolonged exposure to cold temperatures, or any history of blue discoloration of the digits on exposure to the cold or with physical or emotional stress. She had no history of tobacco or illicit drug use and denied any recent use of over-the-counter cough medication or antihistamines. Her initial symptoms of COVID-19 had resolved by the time she presented.

The patient reported a prior hospitalization for chest pain four years prior, in which she underwent extensive cardiac workup inclusive of a left heart cardiac catheterization. Reports of her left heart catheterization were reviewed at the time of presentation and reported no significant coronary artery disease; however, it was significant for coronary vasospasm.

On presentation to the emergency room, she had a blood pressure of 154/61 mmHg, a heart rate of 58 beats per minute, a respiratory rate of 18 breaths/minute, temperature of 98 °F, and was saturating at 97% on room air. The physical exam was significant for mottled discoloration of both feet with clear demarcation to the midtarsal region. Both feet were noted to be cold to touch with nonpalpable bilateral dorsal pedis and posterior tibialis pulses and decreased sensation to the toes bilaterally (Figure 1). Careful evaluation of the digits did not reveal any splinter hemorrhages, Janeway lesions, or Osler nodes. Nailfold capillaroscopy evaluation was normal at the fingers and toes. Bedside Doppler of the lower extremities revealed inaudible bilateral dorsalis pedis and posterior tibialis pulses. Upper extremity pulses were palpable bilaterally, and a cardiovascular exam revealed a regular pulse rhythm, with normal heart sounds without any additional heart sounds or murmurs. The remainder of the physical examination was within normal limits. Given the concerns for acute limb ischemia, she immediately commenced on an intravenous heparin infusion.

Complete blood count, kidney function tests, and hepatic function tests were normal on initial lab investigations. Her lipid panel was significant for elevated low-density lipoprotein cholesterol; hemoglobin A1c was 4.6% (Table 1). Rapid antigen testing for COVID-19 and COVID-19 polymerase chain reaction (PCR) testing at the time of her presentation to the hospital were both negative. The electrocardiogram showed normal sinus rhythm. Venous duplex doppler of bilateral lower extremities was negative for deep or superficial vein thromboses. Computerized-tomography (CT) angiogram of bilateral lower extremities (Figure 2) revealed normal aorta but overall diminutive bilateral femoropopliteal
and tibial-peroneal vasculature without significant atherosclerotic disease and with grossly patent vasculature. However, the tibia-peroneal vessels in the left lower extremity were not well visualized beyond the level of the calf, most likely related to their small caliber. An echocardiogram showed normal right and left ventricular function, no wall motion abnormalities, and a normal left ventricular ejection fraction of 60%. She underwent intra-operative angiogram by vascular surgery, which showed no significant atherosclerotic disease of the aorta or lower extremity vessels, smooth and patent superficial femoral and popliteal arteries bilaterally with severely diminished caliber, and severely restricted flow to the proximal calf and occluded mid-calf with no runoff to the feet bilaterally.

C-reactive protein and erythrocyte sedimentation rate were within normal limits, and further lab investigations revealed negative antinuclear antibody tests by immunofluorescence. C3 and C4 complement levels were within normal limits. Anti-beta-2-glycoprotein I antibodies, anti-cardiolipin antibodies, and lupus anticoagulants were negative. Anti-myeloperoxidase (anti-MPO) antineutrophil cytoplasmic antibodies (ANCA) and anti-proteinase 3 (anti-PR3) antineutrophil cytoplasmic antibodies (ANCA) were both negative. Human immunodeficiency virus was negative, and Hepatitis B and C serology were also negative. Serum cryoglobulins were undetected.

Given the absence of arrhythmia, atherosclerotic disease on vascular studies and no prior personal or family history of hypercoagulable states, negative work-up for hypercoagulable disease and the temporal relation of the symptoms to COVID-19 infection and literature documenting varied vascular manifestations as common complications of COVID-19, we postulated this presentation was likely a vascular complication of COVID-19. She commenced anticoagulation with intravenous heparin infusion, antiplatelet therapy with aspirin, vasodilator therapy with a calcium channel blocker nifedipine, intravenous glucocorticoids, and cilostazol. Within the subsequent days, she noted some improvement in pain and numbness in her extremities. There was slow but progressive improvement in

### Table 1: Laboratory investigations on hospital admission.

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.9</td>
<td>14-18</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>88.3</td>
<td>80.0-100.0</td>
</tr>
<tr>
<td>Platelets (K/UL)</td>
<td>203</td>
<td>130-400</td>
</tr>
<tr>
<td>White blood cells (K/UL)</td>
<td>8.2</td>
<td>4.5-11.0</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>11.5</td>
<td>12-15.1</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>0.97</td>
<td>0.85-1.14</td>
</tr>
<tr>
<td>Partial thromboplastin time (sec)</td>
<td>36.3</td>
<td>25.4-36.7</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140</td>
<td>136-145</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.8</td>
<td>3.5-5.1</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>104</td>
<td>98-107</td>
</tr>
<tr>
<td>Serum bicarbonate (mmol/L)</td>
<td>28</td>
<td>20-31</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>9</td>
<td>9-23</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.78</td>
<td>0.70-1.30</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.5</td>
<td>8.7-10.4</td>
</tr>
<tr>
<td>Aspartate aminotransferase (Units/L)</td>
<td>19</td>
<td>8-34</td>
</tr>
<tr>
<td>Alanine aminotransferase (Units/L)</td>
<td>13</td>
<td>10-49</td>
</tr>
<tr>
<td>Alkaline phosphatase (Units/L)</td>
<td>100</td>
<td>46-116</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>154</td>
<td>10-150</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>178</td>
<td>25-200</td>
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<tr>
<td>Low-density lipoprotein cholesterol (mg/dl)</td>
<td>138.1</td>
<td>5-100</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dl)</td>
<td>38</td>
<td>40-60</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>4.6</td>
<td>3-5.7%</td>
</tr>
</tbody>
</table>
perfusion to the lower extremities with the return of palpable lower extremity pulses and near complete resolution of the mottling of the left foot and partial resolution of the mottling to the right foot on day 5 of admission. On day five of her admission, she was transitioned to oral anticoagulation with apixaban to complete a 30-day course and a tapering dose of oral glucocorticoids. She was discharged on day 10 of admission.

Discussion

We describe here a case of a unique case of a mildly symptomatic COVID-19-positive patient with an intriguing past medical history of presumed coronary vasospasm, who presented with macrovascular arterial involvement, in the absence of thrombosis and pre-existing traditional risk factors for endothelial injury, with negative antiphospholipid antibodies and negative laboratory work-up for known immune-mediated vascular disease.

ALI is defined by a sudden decrease in arterial perfusion within 14 days. It is a potentially limb-threatening condition. It is characterized by sudden severe pain, numbness and parathesias of the lower extremity, which is found to be pale, cold, and pulseless on physical exam [8]. In most cases of ALI, the etiology can be attributed to embolism, usually from a cardiac source, or in situ thrombosis due to acute atherosclerotic plaque rupture in the lower extremity blood vessels. Atrial fibrillation is a significant risk factor for embolic causes of ALI. Other potential causes of embolic ALI include recent valvular or cardiac surgery, myocardial infarction with a left ventricular aneurysm, and thrombus formation. Thrombotic ALI occurs when an atherosclerotic plaque ruptures within the blood vessel, resulting in sudden occlusion of the vessel lumen. Thrombotic ALI may result from spontaneous thrombus formation within the blood vessel in a patient with an underlying hypercoagulable state, such as antiphospholipid syndrome, or a chronic process, as in thromboangiitis obliterans [8]. In most cases, patients presenting with ALI have cardiovascular risk factors, such as diabetes, hyperlipidemia, and hypertension, the lead to pre-existing vascular endothelial damage. In rare cases, ALI may be the presentation of immune-mediated thrombosis due to vascular inflammation in medium and large vessels, such as in patients with a history of polyarteritis nodosa, giant cell arteritis, Takayasu arteritis, and Behcet syndrome [9].

COVID-19 infection has been frequently associated with both macrovascular and microvascular manifestations. Macrovascular complications of COVID-19 include but are not limited to, venous thromboembolism, pulmonary embolism, cerebrovascular events, and mesenteric ischemia [7]. ALI is a macrovascular event that has been infrequently reported as a complication of COVID-19, most commonly in patients who are critically ill with pre-existing risk factors such as a history of peripheral arterial disease, atrial fibrillation, and hypercoagulable states [10].

The pathogenesis of arterial thrombosis associated with COVID-19 is thought to differ from that of traditional cases of arterial thrombosis and can occur in vessels without pre-existing atherosclerosis. In these cases, ALI is thought to result from an immune-mediated hypercoagulable state with elevated levels of coagulation factors, antiphospholipid antibodies, fibrinogen, and D-dimers, is associated with reduced levels of Protein C and S [10].

Microvascular manifestations of COVID-19 have been increasingly reported in the literature throughout the pandemic. One commonly recognized manifestation is the occurrence of pernio-like acral lesions, also known as pseudo-chilblains and commonly referred to as “COVID toes” [11]. “COVID toes” describes the appearance of painful, erythematous to violaceous purpuric macular lesions, which commonly occur in the extremities and are similar in clinical appearance to those lesions seen in cases of classic chilblains, which occur secondary to cold exposure. Unlike classic chilblains, “COVID toes” or pseudo-chilblains occur in the absence of cold exposure and, similar to the macrovascular complications of COVID-19, are thought to be caused by an immune-mediated thrombosis of the microvasculature [12].

Vasculopathy associated with COVID-19 infection is thought to be due to immune-mediated endothelial injury, which involves activation of the direct activation of the angiotensin-converting-enzyme-II (ACE2) receptors by the SARS-CoV-2 virus [13]. ACE2 receptors are the primary receptor facilitating the entry of the SARS-CoV-2 virus into the pulmonary cells [10]. These ACE2 receptors are also expressed in other tissues, including...
the endothelium of the vasculature. It is hypothesized that on binding to ACE2 receptors, the SARS-CoV-2 virus leads to activation of the renin-angiotensin system resulting in vasoconstriction and the induction of inflammatory and thrombotic processes within the vasculature, which results in a hypercoagulable state [14].

Another pathophysiologic mechanism used to explain immunothrombosis in COVID-19, such as the occurrence of pernio-like acral lesions, involves the robust release of interferon-1 in response to SARS-CoV-2 infection. Interferon-1 plays an essential role in the immune response to viral infections. It is hypothesized that there is massive production of interferon-1 in a vigorous immune response to the SARS-CoV-2 infection, which leads to the control of the virus early in the course of the infection and, therefore, mild or no symptoms of COVID-19 infection [14]. Interferon-1 released in this host immune response inhibits nitric oxide synthesis. Nitric oxide is a potent vasodilator, and reduced nitric oxide levels due to the significant interferon release may lead to vasoconstriction and decreased tissue perfusion [15].

We hypothesize that the ALI, in our case, is likely multifactorial. As described above, the primary underlying mechanism is likely severe vasospasm related to decreased nitric oxide levels due to significant interferon release in COVID-19. Additionally, given her history of coronary vasospasm, she likely had an underlying predisposition to vasospasm. Our primary treatment focused on vasodilatation with a systemic calcium channel blocker - nifedipine - to treat this underlying vasospasm. Cilostazol was used in our case primarily due to its vasodilator and antiplatelet properties. Additionally, we postulated that the pleiotropic effects of cilostazol, including its anti-inflammatory and antioxidant properties, would also be beneficial in treating this inflammatory response to COVID-19. Because of these properties, cilostazol has been suggested in the literature to be a possible adjunctive therapy in the management of COVID-19 as well as vascular and thrombotic complications of COVID-19 [16]. Systemic glucocorticoids were initiated for the management of underlying inflammation due to COVID-19, postulated to be the primary trigger for our patient’s presentation.

Arterial thrombi often arise because of injury to a pre-existing atherosclerotic plaque. These atherosclerotic plaques may rupture, exposing tissue factor, which increases the risk of thrombus formation. Platelets often adhere to tissue factors at the site of vascular injury and subsequently aggregate to form a platelet plug. This platelet plug can then activate clotting factors leading to clot formation. In the setting of a hypercoagulable state, which may predispose thrombus formation, this process may be accelerated [17].

The underlying pathophysiology of venous thrombus is outlined by Virchow’s triad of - (1) Vascular injury in the setting of hypertension, hyperlipidemia, and smoking, among others; (2) Venous stasis, often due to prolonged immobilization and (3) Hypercoagulable state [17]. With these 3 factors, venous thrombosis can occur in a similar manner to that of arterial thrombosis with platelet adherence to the site of injury, platelet aggregation, and clot propagation with clotting factors [18,19].

COVID-19 has been commonly identified as a hypercoagulable state, as many cases documented in the literature associate COVID-19 with an increased risk for both venous and arterial thrombosis [20,21]. This increased risk of thrombosis can remain for more than 6 weeks after COVID-19 is diagnosed [3].

With our patient’s history of hypertension and elevated low-density lipoprotein level, she was likely at risk for vascular injury, with some degree of underlying atherosclerotic disease though not significant enough to be seen on angiography or contribute to the cause of her ALI. In this setting, with a history of recent COVID-19 infection (an acquired hypercoagulable state), and presenting with significant vascular involvement with ALI, she was at high risk for both arterial and venous thrombus formation. Therefore, we commenced therapy with antiplatelet drugs (aspirin) and anticoagulation (initially with intravenous heparin followed by oral anticoagulation). Noting that the risk of thrombus formation associated with COVID-19 can be prolonged, as outlined above, we continued anticoagulation with low-dose apixaban to complete a duration of 6-weeks, the period which we thought she would be at the highest risk for thrombus formation, especially due to her lack of usual mobility on discharge.

Conclusion

Our case describes ALI, a rarely reported manifestation of COVID-19. In addition, it describes an interesting presentation of ALI in a patient with mild symptomatic COVID-19, without significant pre-existing risk factors for peripheral atherosclerotic disease or hypercoagulability, with a negative hypercoagulable workup and negative work-up for ANCA vasculitides. These clinical characteristics suggest the pathophysiology is likely immune-mediated secondary to COVID-19, like other COVID-19-induced immunothrombotic manifestations such as “COVID toes.” This case demonstrates that we have only begun to scratch the surface of understanding the immune pathophysiology of COVID-19 and that significant complications of COVID-19 can occur in even patients with mild respiratory symptoms. Although the respiratory manifestations of COVID-19 are the most commonly recognized and potentially life-threatening, given the ubiquitous distribution of vasculature in the body, vascular events due to COVID-19 can potentially cause significant morbidity. Furthermore, our case
demonstrates that vascular disease in COVID-19 may not necessarily be due to thrombosis or immunothrombosis but that vasospasm may also play a role, similarly to the few reported cases of coronary vasospasm in COVID-19. As more cases are reported in the literature and more studies regarding COVID-19 are carried out, the underlying mechanisms leading to multi-organ involvement in COVID-19 may become more apparent.

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Conflict of Interest
The authors have no conflicts of interest to declare.

References