COVID-19 Associated Peripheral Gangrene: A Case Series

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Abstract

Patients with COVID-19 may develop venous and arterial thrombosis due to severe inflammation, cytokine storm, and diffuse intravascular coagulation, increasing mortality and morbidity. The aim was to report the clinical profile and outcome of patients diagnosed with peripheral gangrene associated with COVID-19. In this case series, we discussed the clinical presentation, laboratory parameters, and outcome in a series of three patients with peripheral gangrene associated with COVID-19 and also compared those findings. Three patients (two males and one female, age range: 50–72 years, and mean: 61.6 years) were admitted with the diagnosis of COVID-19-associated peripheral gangrene. Three patients had clinical and laboratory evidence of disseminated intravascular coagulation. Marked thrombocytopenia was noted in two patients. Despite vigorous therapy, two patients succumbed to their illness within 9–21 days of intensive care admission. D-dimer level and procalcitonin increased in all cases, while those who succumbed to death showed a marked variation in the D-dimer level from day 1 to the day of death. Prothrombin time (PT) was markedly increased in all three cases, while activated partial thromboplastin time showed little change. Amputation was done in two patients, out of which one succumbed to death. Peripheral gangrene cases in the background of COVID-19 portend a fatal outcome and need strict monitoring of the D-dimer, procalcitonin, and PT level, and a marked variation in these values could be alarming and used as a marker for predicting survival in cases of COVID-19 with peripheral gangrene and also highlighted the limited role of amputation in reducing mortality.

Keywords: Amputation, COVID-19, gangrene

Introduction

The coronavirus pandemic demonstrated that COVID-19 could affect organs other than the lungs, such as the heart and brain, increasing the risk of various health problems. Autopsy studies revealed a predominance of lung microvascular thrombosis, which coincided with inflammation markers, a hallmark of prolonged infection and sepsis.[1] Patients with COVID-19 may develop venous and arterial thrombosis due to severe inflammation and hypoxia, prolonged immobilization, and diffuse intravascular coagulation.[2] The cause of this patient's pedal gangrene was most likely multifactorial, including venovenous extracorporeal membrane oxygenation and vasopressors, prone positioning without proper offloading, and the hypercoagulable nature of COVID-19.[3]

COVID-19 has perplexed the world with its diverse manifestations since its inception. COVID-19 has wreaked *havoc* with its notorious thrombo-inflammatory complications, common in critically ill patients, and associated with poor prognoses.[4] In patients with more severe occlusive vascular disease, livedoid and necrotic eruptions were more common. In the absence of large vaso-occlusion or vasculitis, symmetrical peripheral gangrene (SPG) is a dreaded complication that leads to symmetrical distal gangrene. It is a cutaneous indicator of critical illness, characterized by a triad of shock, disseminated intravascular coagulation (DIC), and natural anticoagulant depletion.[5,6]

Different deep-vein thrombosis (DVT) processes can occur depending on the vascular territories, vessel diameter, and sensitivity to the highly inflammatory milieu. Despite well-conducted anticoagulation in these patients, autopsies conducted by the German prospective series (12 cases), Swiss study (21 cases), and French series (five cases)

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revealed diffuse alveolar damage with the presence of microthrombi in the small-caliber pulmonary vessels with the accumulation of intra-alveolar fibrin deposits. DVT and thrombotic microangiopathy of the pulmonary capillaries are more frequent than pulmonary embolism in SARS-CoV-2 infection.[7]

COVID-19 is a coagulopathy that causes intravascular coagulation and is thought to be a major cause of mortality. Although the precise mechanism of COVID-19-associated coagulopathy has yet to be determined, endothelial dysfunction is considered to be important. Patients with severe COVID-19 develop Endotheliopathy (endotheliitis), which is characterized by the increase of inflammatory cells and viral inclusions in endothelial cells. The finding of viral inclusions in endothelial cells from autopsied COVID-19 patients supports this process. Vascular endothelial cells exhibit the angiotensin-converting enzyme-2 (ACE2) receptor, and ACE2 is expressed on the surface of the SARS-CoV-2 virus. Lymphopenia, thrombocytopenia, and increased levels of von Willebrand factor (VWF) and factor VIII (FVIII) may be laboratory characteristics linked with endothelial activation, cell recruitment, and activation. A significant increase in the VWF and FVIII levels was seen in a small series of severe COVID-19 patients, whereas ADAMTS13 activity (a disintegrin and metalloprotease known to modulate the size of VWF) was normal. In all patients, the levels of VWF antigen and soluble thrombomodulin were also strongly associated with mortality.[7]

Methods

The clinicodemographic profiles and outcomes of three consecutive patients diagnosed with COVID-19-associated SPG are described in this case series. Written informed consent and adequate ethical clearance were obtained. Positive reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 from oropharyngeal and nasopharyngeal swabs confirmed the presence of COVID-19.

Case 1

A 63-year-old male farmer complained of high temperature, difficulty breathing, and dry cough for 8 days. He was hypertensive and Type 2 diabetic for 18 and 11 years, respectively. He was RT-PCR positive. Before starting supportive medications, oxygen saturation was 98%. However, after 72 h, the patient suffered acute hypoxemia. His oxygen levels plummeted, requiring intubation and transfer to the intensive care unit (ICU). A high-resolution computed tomography (CT) scan showed ground-glass opacities and consolidation on both sides of his chest. His CT scan score was 17. Methylprednisolone and broad-spectrum antibiotics were added to his treatment. Since hospitalization, he has received subcutaneous enoxaparin prophylactic dosages (6000 IU). In addition, D-dimer, fibrinogen, and activated partial thromboplastin time (APTT) were increased and slightly low platelets. Acute ischemia in his left thumb and right-hand fingers worsened his condition. Dry gangrene developed in the days after revascularization failed. The radial and ulnar arteries were pulseless. CT angiography showed 80% occlusion of the ulnar artery 10 cm proximal to the wrist and practically complete radial artery thrombosis from the elbow level, requiring bilateral forearm amputation at the wrist. Amputation delayed wound healing without ischemic tissue. Medications and bandages were changed frequently [Figure 1]. The patient faced DIC complications but improved through them and survived. The D-dimer and procalcitonin levels did not show much variation from the day of admission to day 25 [Table 1].

Case 2

A 50-year-old diabetic female tested positive for COVID-19 while having intermittent fevers, coughing, and breathing problems for 12 days. The patient received 500 mg azithromycin daily and 1 g ceftriaxone 12 hourly. The lower lobes had a bilateral ground-glass appearance on a chest CT scan. After becoming hypoxic to 78% while using a nasal cannula, the patient was intubated and transported to the COVID ICU for treatment with hydroxychloroquine 400 mg loading dose and 200 mg 12 hourly. One hundred percent FiO2 and positive end-expiratory pressure kept the patient's saturation over 90%. She was on continuous heparin infusion for DVT prevention, with a goal-APTT of 50–70 s. The patient little improved; however, her left lower limb hurt and was numb. Clinical examination showed that the left lower leg was colder and darker than the right, and the anterior and posterior tibial arteries were pulseless. A left lower limb color Doppler (arterial) scan showed a blockage below the left popliteal artery. Gangrenous zones gradually lost toe mobility and sensation. No anticoagulant treatment improved forefoot vascularity. The D-dimer and procalcitonin levels varied dramatically from day 1 to day 15. The stump was loosely sutured after above-ankle amputation. Analgesics, antibiotics, and anticoagulants were given postoperatively [Figure 2]. However, the patient landed in DIC and succumbed to death after 12 days of admission [Table 1].

Figure 1: Dry gangrene of the, (a) Left thumb. (b) Dorsal aspect of the left hand. (c) Right-hand fingers. (d) Dorsal aspects of the right hand

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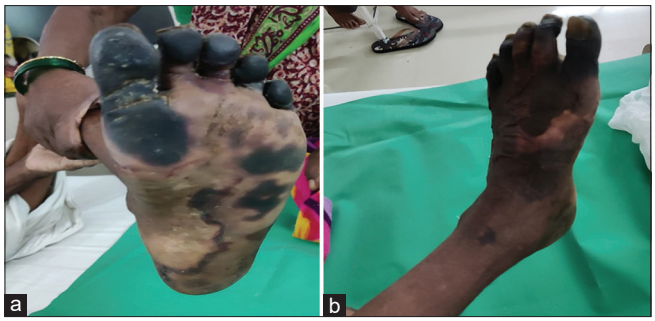

Figure 2: (a) Dry gangrene of left foot toes. (b) Gangrenous patches on the dorsum on the left foot

Case 3

A 72-year-old male presented with cough, expectoration, fever, and generalized weakness for 15 days. He had a history of Type 2 diabetes and cirrhosis. A CT chest revealed bilateral pneumonia with RT-PCR positive. Due to COVID-19-related pneumonitis, the patient was given an injection of ceftriaxone and a tablet of azithromycin 500 mg on admission. Injection of methylprednisolone reduced pulmonary inflammation. As his oxygen saturation decreased, he needed intubation and inotropic support and was transported to the ICU. The bedridden patient exhibited bilateral knee-joint pitting edema. The right foot was cyanotic and slightly ischemic. No such changes were found on the left foot. His arterial duplex ultrasonography (USG) showed triphasic waveforms in both lower legs, indicating no blockage or stenosis. A nonocclusive right mid-femoral venous duplex USG of the lower extremities showed DVT with right anterior, peroneal, and posterior tibial vein thrombosis. Gradually, cyanotic changes developed in the right foot that turned gangrenous in the ICU. Serial CT scan features worsened, showing diffuse bilateral airspace involvement and respiratory failure. The clinical examination, history, and test results did not suggest hematologic/thrombophilic diseases or malignancy. COVID infection caused right foot discomfort and blackish discoloration without any other DVT cause. The provisional diagnosis was the right lower limb DVT with acute kidney injury and acute-on-chronic hypoxic respiratory failure due to COVID-19 pneumonia. During the ICU stay, the right lower limb showed gangrenous changes in the right foot 10 cm above the ankle joint. He received outstanding ICU and nursing care. Unfortunately, the patient died [Figure 3]. The D-dimer, procalcitonin, and prothrombin time (PT) levels dramatically altered from the day of admission to the day of death [Table 1].

Figure 3: Gangrene involving the right foot and lower third leg

Discussion

It is well-known that severe COVID-19 associated with cytokine storm is a precursor to dysregulated coagulation homeostasis, which leads to thrombo-inflammation and consumption coagulopathy, increasing mortality and morbidity. Although the precise mechanism of COVID-19-induced thrombosis is unknown, increased thrombocyte activation with coagulation cascade and decreased fibrinolysis should be mentioned. SARS-CoV-2-mediated endothelial damage with subsequent collagen exposure may result in platelet adhesion and aggregation, followed by coagulation cascade activation and abnormal fibrinolysis.[6,8]

SPG has been linked to various infectious and noninfectious etiologies, although the pathogenesis is unknown. DIC with microcirculatory occlusion is frequently a contributing factor. The likely pathomechanisms involved in SPG are the shwartzman reaction, endotoxin, platelet plugging in peripheral vasculature due to hypercoagulable vasospasm, and DIC.[8] In most cases of SPG, DIC contributes to the final common pathway. Aside from noninfectious causes such as myocardial infarction, hypovolemic/septic shock, lymphoreticular malignancies, pulmonary embolism, and vasopressors, common offenders include bacterial, viral, and protozoal agents.[6] The typical presentation is pain in the extremities, followed by fever with or without constitutional symptoms in the presence of cold, pale, cyanotic acral parts of the body, which can progress to frank, dry gangrene if not reversed. Gangrene is typically symmetric, can spread proximally from the distal sites, is frequently associated with mummification, and can result in auto-amputation. SPG is not associated with distal pulse compromise; shock features may sometimes predominate.[6,9]

Tang *et al*.[10] revealed that patients with COVID-19 pneumonia with significantly higher D-dimers, fibrinogen degradation products, and longer PTs were more likely to die than those who did not have these abnormal parameters at the time of admission [Table 2]. Even though all three patients in the current study had elevated D-dimer levels, the first D-dimer after admission was only 0.60 mg/mL, whereas patient B's, who survived, was 0.92 mg/mL. The current study hypothesized that coagulopathies, particularly those of the hand, are a marker of severe illness and warrant close monitoring and early hand service consultation for appropriate intervention based on the clinical course of these two COVID-19 patients. To avoid permanent damage and limb loss, monitoring for thromboembolic events in the extremities of critically ill patients is critical. According to existing research, SPG is associated with a high amputation rate among survivors. SPG has a significantly higher mortality rate, with thrombocytopenia

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Table 1: Summary of cases

Parameters	Case 1	Case 2	Case 3
Age	63	50	72
Sex	Male	Female	Male
Medical history	Hypertension and Type 2 DM	Type 2 DM	Cirrhosis and Type 2 DM
Presenting symptom	Fever, breathing difficulty, and dry cough	Fever, cough, and breathlessness	Cough with expectoration, fever, and generalized weakness
CT value	26	24	16
CT score	17	7	22
Laboratory investigation			
Hb	10.9	13.8	9.3
WBCs	12,100	16,250	25,000
Platelets	120,000	34,000	47,000
ESR	90	24	63
C-reactive protein	166	62	106
Procalcitonin (ng/mL)	1.6	5.6	14
PT (s)	16.5	30.2	56.6
APTT (s)	34.5	36.4	39.3
D-dimer (mg/L)	4.1	9.1	18.1
Serum creatinine	0.83	1.1	4.2
Color Doppler	Radial artery thrombosis	Left lower limb popliteal artery obstruction	Thrombus at the anterior and posterior tibial vein
Reason for admission to ICU	Hypoxia	Hypoxia	Respiratory failure
Vasopressor use	No	No	Yes
Thrombotic manifestation	Dry gangrene of the left thumb and four fingers of the right hand	Gangrene of the left foot toes and gangrenous patches on the dorsal and plantar aspect	Gangrene involving the right foot and lower third of the leg
Anticoagulant	Yes	Yes	Yes
Days from ICU admission to a thrombotic event	5	8	11
Outcome	Survived	Death after 7 days of a thrombotic event	Death after 10 days of a thrombotic event

Hb: Hemoglobin, WBCs: White blood cells, CT: Computed tomography, DM: Diabetes mellitus, APTT: Activated partial thromboplastin time, PT: Prothrombin time, ICU: Intensive care unit, ESR: Erythrocyte sedimentation rate

Table 2: Summary of various studies conducted

Author	Study type	Sample size	Study duration	Follow-up duration	Outcomes
Klok *et al*.[2]	Prospective	184 ICU patients	March 7th and April 5th, 2020	7 days	VTE in 27%
Siegel *et al*.[3]	Retrospective	1 (case report)	55 days hospital stay	Lost to follow-up	Left plantar forefoot gangrene
Sil *et al*.[6]	Retrospective	2 cases	10–12 days	-	Peripheral gangrene involving both hands and feet. Both patients died
Tang *et al*.[10]	Prospective	183 patients with NCP	January 1–February 3, 2020	43 days	The nonsurvivors revealed significantly higher D-dimer and FDP levels and longer PT than survivors on admission

VTE: Venous thromboembolism, NCP: Novel coronavirus pneumonia, PT: Prothrombin time, ICU: Intensive care unit, FDP: Fibrin degradation products

and ischemic hepatitis (shock liver) being poor prognostic markers. Most deaths are reported to occur between 5 and 21 days after the onset of gangrene.[11]

According to Huang *et al*. and Zhou *et al*., COVID-19 patients admitted to the ICU have considerably higher levels of D-dimer than COVID-19 patients not admitted to the ICU, and higher D-dimer levels are related to an increase in inhospital mortality.[12,13] Tay *et al*. reported that nonsurvivors had considerably longer PTs than survivors.[14] Similarly, Huang *et al*. observed that PT was significantly longer in ICU COVID-19 patients when compared to non-ICU COVID-19 patients; however, the absolute difference was small.[12] All three patients of peripheral gangrene in the current study had thrombocytopenia. Two of those affected had severe thrombocytopenia (50,000/L) and died. Other studies have shown similar results. Guan *et al*. reported a 36.2% incidence of thrombocytopenia 150 X 10 9 /L, which increased to 57.7% in ICU patients.[15] Thrombocytopenia, often mild in COVID-19, is a sign of disease severity. Consumption of platelets that generate pulmonary thrombi is a likely cause of thrombocytopenia and associated poor prognosis.[7] APTT was not significantly altered in the current study. In another

study, Bowles *et al*. found that in 216 patients, the APTT was prolonged. As a result, determining the relevance of this illness is challenging.[16]

Evidence supports the use of prophylactic anticoagulation for venous thromboembolism; however, whether prophylactic or full anticoagulation will benefit arterial thrombosis caused by COVID-19 is unknown. Patients with viable tissue and marginally threatened limbs undergo vascular intervention for arterial thrombolysis and thrombectomy. As in our clinical case, the limbs with irreversible ischemia must be amputated.

Ethical consideration

The Institutional Ethics Committee approved this study (MGIMS/IEC/SUR/03/2023 dated January 21, 2023). Patient confidentiality was maintained throughout all research procedures. All procedures performed in studies involving the human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards mentioned in these lines in ethics as Helsinki Declaration.

Conclusions

Monitoring thromboembolic events are critical, especially in patients with high-risk characteristics. More research is needed to determine the role of amputation surgery and its effect on survival when initial revascularization interventions fail to restore blood flow. Peripheral gangrene cases in the background of COVID-19 portend a fatal outcome and need strict monitoring of the D-dimer, procalcitonin, and PT levels, and a marked variation in these values could be alarming and used as a marker for predicting survival in cases of COVID-19 with peripheral gangrene and also highlighted the limited role of amputation in reducing mortality.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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