CLINICAL PRACTICE

Clinical Vignettes

Life and Limb: a Case of COVID-19-Associated Multisystem Thrombosis and Review of the Literature

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CASE PRESENTATION

A 63-year-old non-smoking woman with a past medical history of hypertension and myasthenia gravis status post thy- mectomy presented for care at our institution with a 9-day history of cough, fever, and weakness. On presentation, she was hypoxic with an oxygen saturation of 85% on ambient air and had a positive nasopharyngeal polymerase chain reaction assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Due to rapidly progressive respiratory failure and hypotension, she was admitted to the Intensive Care Unit (ICU) and was intubated on the same day and an internal jugular central venous catheter was inserted for vasopressor infusion. A right radial arterial catheter was also placed for hemodynamic monitoring. On admission, she was treated with prophylactic anticoagulation for venous thromboembolism (VTE), with dalteparin 5000 units subcutaneously daily. In the ICU, her condition rapidly deteriorated. Her oxygenation and lung mechanics worsened, and she developed circulatory collapse, consistent with acute respiratory distress syndrome (ARDS) with systemic hyperinflammation. Empiric antimicrobial therapy with intravenous piperacillin-tazobactam and vancomycin as well as intravenous hydrocortone 100 mg every 8 h was initiated. A right radial arterial catheter was also placed for hemodynamic monitoring. On admission, she was treated with prophylactic anticoagulation for venous thromboembolism (VTE), with dalteparin 5000 units subcutaneously daily. In the ICU, her condition rapidly deteriorated. Her oxygenation and lung mechanics worsened, and she developed circulatory collapse, consistent with acute respiratory distress syndrome (ARDS) with systemic hyperinflammation. Empiric antimicrobial therapy with intravenous piperacillin-tazobactam and vancomycin as well as intravenous hydrocortisone 100 mg every 8 h was initiated. Initial investigations revealed an elevated C-reactive protein (637 mg/L, normal 0–4) as well as an elevated D-dimer level (1498 μg/L, normal < 500). Platelets and fibrinogen were within normal limits. Within 72 h of admission, the patient required high doses of vasopressors including a norepinephrine infusion at 25 mcg/min and vasopressin at 0.04 unit/min as well as ionotropic support with dobutamine 5 mcg/kg/min. She was started on inhaled nitric oxide at 20 parts per million for refractory hypoxia. On the fourth day of admission, the interleukin-6 serum level was elevated at 2948 ng/L and she received a dose of intravenous tocilizumab 8 mg/kg.

On day 5, acute marbling of the entire right forearm was noted, and her right radial arterial catheter was removed. The following day, her forearm was cyanotic, without detectable radial or ulnar pulses by bedside Doppler ultrasound. Vascular surgery was urgently consulted, and the patient was started on therapeutic anticoagulation with unfractionated heparin which was consistently within the therapeutic range. Her hand nevertheless remained ischemic and she was taken to the operating room on day 7 of admission for an urgent thrombectomy. A 3.0 × 0.2 × 0.1-cm bland arterial thrombus was removed from the radial artery near the bifurcation of the brachial artery, and far from the previously inserted distal radial catheter. The next day, the patient’s unfractionated heparin was changed to therapeutic subcutaneous dalteparin 200 units/kg, which was continued thereafter.

Her condition gradually stabilized, and the patient was successfully extubated on day 21 of admission. The patient was found to be somnolent upon extubation, which was initially attributed to the sedation she had received while intubated. When her mental status did not significantly improve off sedation, a magnetic resonance image (MRI) of the brain performed 48 h later revealed bilateral subcortical microinfarctions and abnormal white matter changes in the right parietal and occipital lobes. These findings were interpreted by the radiologist as being suggestive of cortical vein thrombosis. Furthermore, there was no atrial fibrillation nor evidence of heparin-induced thrombocytopenia during her illness. On day 25, the patient had a sudden hypoxic event and was urgently reintubated. Despite being on therapeutic anticoagulation with low-molecular-weight heparin for over 2 weeks, the patient was sent for a computed tomography (CT) pulmonary angiogram, which showed multiple right upper lung acute and subacute segmental pulmonary emboli. At this time, lupus anticoagulant and anticardiolipin antibodies were negative; additional thrombophilia workup was deferred given acute thrombosis and ongoing receipt of heparin products, which would affect the reliability of these tests. She slowly improved clinically from both a respiratory and neurological standpoint and she was transferred from the ICU to the ward 52 days following her admission. She unfortunately had
ischemic necrosis of the fingertips in her right hand (Fig. 1),
though the rest of the hand and arm were spared. The patient
was discharged in stable condition to a rehabilitation center on
day 97 of admission.

DISCUSSION

Thrombotic complications in COVID-19 infection, both macro-
and micro-vascular, are an emerging cause of morbidity and
mortality in patients with severe disease. The mechanism for
this is likely multifactorial, though it appears to be mediated by
the interplay between inflammation and the coagulation system,
or thromboinflammation. This hypercoagulable state has been
described by Tang et al. with observational data showing ab-
normal coagulation parameters such as elevated D-dimer level
and fibrin degradation products. Elevated D-dimer has been
identified as a predictor of mortality. High plasma levels of
proinflammatory cytokines have also been observed in
COVID-19 patients admitted to the ICU. Moreover, endothe-
lial injury has been suggested to play an important role in the
pathogenesis of COVID-19-associated thrombosis, with reports
of elevated von Willebrand factor and factor VIII levels, which
suggests endothelial stimulation and damage. Endothelial cells
also express ACE2, the receptor for SARS-CoV-2, which possi-
bly mediates endothelial injury. In addition, the high levels of
positive end-expiratory pressure (PEEP), commonly required to
help manage COVID-19 patients on mechanical ventilation,
may lead to a decrease in pulmonary blood flow, leading to
stasis and microthrombosis.

In a retrospective cohort study of 184 ICU patients with
COVID-19, Klok et al. found a cumulative incidence of 31% of
a composite outcome of symptomatic pulmonary embolism
(PE), deep vein thrombosis (DVT), ischemic stroke, myocardial
infarction, or systemic arterial embolism. In that cohort,
only three patients (4.3%) had arterial thrombotic events, all of
which were ischemic strokes. Despite routine prophylactic
anticoagulation, the study by Middeldorp et al. showed an
incidence of VTE of 34% at 14 days of admission and the
proportion of patients with VTE was significantly higher in the
ICU population (48%). Since then, the increased incidence of
thrombotic complications associated with COVID-19, specif-
ically with severe disease, has been reported (Table 1).

Early reports suggest that the incidence of thrombotic com-
plications may be higher in COVID-19 patients compared to
non-COVID-19 hospitalized patients with similar degrees of
illness. Some centers have opted to increase prophylactic
anticoagulation to intermediate or full dose, based either on the
severity of the disease or on an elevated D-dimer level. How-
ever, due to the lack of high-quality evidence, most guideline
statements either recommend against the use of empiric inter-
mediate or therapeutic doses of anticoagulation for VTE.
prophylaxis, or strictly recommend prophylactic anticoagulation for all admitted patients with COVID-19. It is unclear whether critically ill COVID-19 patients are at increased bleeding risk, and any increased risk may be in the setting of thrombocytopenia and other associated factors, but this is another area of ongoing research. On the balance, preliminary data more firmly supports increased thrombotic risk than bleeding risk at this time.

Our patient had been started on prophylactic anticoagulation on admission and later found to have bilateral pulmonary emboli despite over 2 weeks of therapeutic anticoagulation. While delayed diagnosis of the thrombotic event is possible, treatment failure of therapeutic anticoagulation has been reported in patients with severe COVID-19 disease. White et al. demonstrated heparin resistance and suboptimal peak anti-Xa levels following therapeutic anticoagulation and hypothesize that this may contribute to the increased thrombotic risk in critically ill patients with COVID-19. There are a number of possible confounders that may have contributed to our patient’s risk of multisystem thrombosis. Although myasthenia gravis has also been associated with increased rates of VTE, our patient’s disease was well-controlled following her thymectomy, and a panel to test for circulating anti-acetylcholine receptor antibodies was negative. Furthermore, we cannot definitively exclude that the patient does not have another underlying thrombophilia. An extended workup was not sent during her hospitalization given that many of these tests could be markedly confounded by her receipt of anticoagulation and her ongoing acute thrombosis. However, because she had no personal nor family history of bleeding dyscrasia or thrombosis prior to this illness, the unanimous consensus of her treating physicians was that an acquired prothrombotic state secondary to COVID-19 infection was the most likely cause of her multisystem thrombosis.

Tocilizumab, an interleukin-6 inhibitor, has been reported to decrease factor VIII, which may cause fibrin clot instability, causing microthrombi to dislodge. Tocilizumab has been used in the COVID-19 pandemic, but its association with thrombosis is not clearly understood and further research is warranted. The use of corticosteroids has also been linked to an increase risk of venous thromboembolism, although the risk of thrombotic complications in the COVID-19 population appears disproportionate. Overall, we do not feel that these confounding factors explain her severe, multisystem venous and arterial thromboses.

In addition to VTE, arterial thromboses including myocardial infarction and ischemic stroke have been reported in COVID-19 disease. Critical limb ischemia is a rare arterial complication that has been reported in COVID-19 patients by means of case reports and case series (Table 2). An observational single-center study of COVID-19 patients by Bellosta et al. showed a significant increase in the incidence of acute limb ischemia from January to March 2020 compared to the same months in 2019. The study showed that patients with COVID-19 undergoing surgical revascularization for acute limb ischemia had a high rate of technical failure, which might have resulted from an inherent virus-related hypercoagulable state. Prior to the COVID-19 pandemic, a known hypercoagulable state without atherosclerotic disease was an uncommon etiology of acute limb ischemia, but it is known to confer...
a worse prognosis. The majority of published cases of limb ischemia in COVID-19 occur in patients without known peripheral atherosclerotic disease, in patients either on prophylactic anticoagulation or on antiplatelet therapy at baseline. With the exception of a case complicated by a retroperitoneal hematoma, all cases were treated with therapeutic anticoagulation. A proportion of patients required surgical intervention with either surgical thrombectomy or amputation, in two cases to attempt revascularization.

Of the 12 patients who survived and had a reported outcome, 7 had a successful revascularization intervention, while 5 had irreversible ischemia. This highlights that while cases of critical limb ischemia have been reported in this population, limited data exists on the appropriate course and optimal therapy.

In summary, thrombotic complications seen in patients with COVID-19 contribute to morbidity, multiorgan failure, and mortality. While more intensive prophylactic anticoagulation strategies have been suggested, best clinical practices to prevent and manage complications of this severe illness are yet to be determined. A randomized controlled trial such as the upcoming ATTACC trial (ClinicalTrials.gov identifier: NCT04372589) comparing therapeutic anticoagulation to usual care should help guide our future management of this complex condition.

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Compliance with ethical standards:

Conflict of Interest: The authors have no conflict of interest to declare.

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Table 2 Arterial Thrombosis in COVID-19

| Author1, 2, 3 | Age, sex | Known PAD | Arterial thrombus localization | Antithrombotic at time of event | VTE Peak D-dimer (μg/L) | Treatment | Outcome |
|-------------|-----------|-----------|-------------------------------|-----------------------------|------------------------|-----------|---------|
| Andrea26    | 58, M     | No        | R tibial, abdominal aorta     | NA                          | NA > 595               | Medical, surgical embolectomy | Revascularization |
| Baccellier27 | 67, M     | No        | R iliac, femoro-popliteal, R  | PPX                         | NA > 20,000            | Medical, surgical thrombectomy | Revascularization |
| Galanis28    | 80, M     | No        | R radial                      | PPX, ASA                    | NA 13,600              | Medical                             | Death |
| Giacomelli29 | 67, M     | AAA repair | Aortic graft at femoral level  | NA                          | NA 52,411              | Medical                             | Death |
| Kashi1, 30  | 67, F     | No        | NA                           | No                          | No NA                  | Medical                             | Irreversible ischemia |
| Kashi2, 30  | 58, F     | No        | Descending thoracic aorta     | PPX, ASA                    | No 1200                | Medical                             | NA     |
| Kashi3, 30  | 69, M     | No        | Aortic arch, descending      | PPX, ASA                    | PE 3700                | Medical                             | NA     |
| Kashi4, 30  | 71, M     | No        | Right popliteal               | DOAC                        | DVT > 20,000           | Medical                             | Irreversible ischemia |
| Kashi5, 30  | 59, M     | No        | L common femoral              | DOAC                        | No > 20,000            | Medical                             | Irreversible ischemia |
| Kashi6, 30  | 82, M     | Yes       | R iliac, L deep femoral       | PPX, ASA                    | No 367,000             | Medical, thrombectomy, amputation   | Irreversible ischemia |
| Kashi7, 30  | 64, M     | Yes       | R femoro-popliteal bypass     | ASA                         | No 173,000             | Medical, amputation                 | Irreversible ischemia |
| Kaur2, 31   | 43, M     | No        | R superficial femoral, popliteal, | NA                          | No > 20,000            | Medical                             | Death    |
| Kaur32      | 71, M     | No        | R brachio-cephalic trunk,     | NA                          | NA 1850                | Medical, surgical thrombectomy      | Revascularization |
| Perini1, 33 | 53, M     | No        | Bilateral lower limb          | PPX                         | NA > 450,000           | Surgical thrombectomy               | Death    |
| Perini2, 33 | 37, M     | No        | Humeral                       | PPX                         | NA                      | Medical                             | Revascularization |
| Schultz2, 34 | 70, F     | No        | R radial and ulnar (digital)  | NA                          | DVT > 10,000           | Medical                             | Revascularization |
| Schultz3, 34 | 43, M     | No        | R distal radial               | NA                          | DVT 4110               | Medical                             | Revascularization |
| Warrior35    | 59, F     | No        | R popliteal                   | NA                          | NA 39,753              | Medical, surgical thrombectomy      | Revascularization |

AAA abdominal aortic aneurysm, ASA acetylsalicylic acid, DOAC direct oral anticoagulant, DVT deep vein thrombosis, F female, L left, M male, NA not available, PAD peripheral arterial disease, PE pulmonary embolism, PPX prophylactic anticoagulation, R right, VTE venous thromboembolism

AA a worse prognosis. The majority of published cases of limb ischemia in COVID-19 occur in patients without known peripheral atherosclerotic disease, in patients either on prophylactic anticoagulation or on antiplatelet therapy at baseline. With the exception of a case complicated by a retroperitoneal hematoma, all cases were treated with therapeutic anticoagulation. A proportion of patients required surgical intervention with either surgical thrombectomy or amputation, in two cases to attempt revascularization.

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