PICTORIAL ESSAY

Spectrum of Vascular Thrombosis in Critically Ill COVID-19 Patients: From Bench to the Bedside

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Abstract

Proinflammatory cytokines and procoagulant factors released by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lead to thrombosis and ischemia. Pathogenesis and clinical significance of hypercoagulability and an ensuing gamut of vascular complications are explained here.

Keywords: COVID-associated coagulopathy, Prothrombotic milieu, Severe acute respiratory syndrome coronavirus 2, Vascular thrombosis.

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Highlights

- The coronavirus disease-2019 (COVID-19) infection provokes pathology far from the respiratory system it primarily targets.
- Venous, arterial, and micro-thrombosis are seen in multiple organs.
- These can occur singly or concomitantly.
- Thrombosis can occur despite appropriate thromboprophylaxis and even full anticoagulation.
- Anticoagulation *per se* does not have disease-modifying effect but instead viral load with its systemic inflammatory response needs to be attenuated for its dynamism toward prothrombotic state.
- COVID-19-associated thrombotic microangiopathy is a new discrete entity.

Introduction

Thrombosis, *in situ* or embolism, is a serious complication following SARS-CoV-2 infection. Clinical phenotype includes macro- and microvascular venous and arterial thromboses. We look at various thrombotic events caused by SARS-CoV-2. We review pathobiological mechanisms of thrombosis and thrombotic mechanisms following the vaccine. This study was in accordance with ethical standards of the institutional ethics committee (018/2020, 047/2021).

Clinical Scenarios

Case Scenario: Lower Extremity Venous Thrombosis

- *Age/Gender:* 73 years/Female
- *Comorbidities:* Asthma and obesity
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* 11 days
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* Right thigh hematoma
- *Highest D-dimer:* 54,851 ng/mL
- *Absolute Lymphocyte Counts* ($\times 10^3$ cells/μL)*:* Day 1, 0.43; day 2, 0.68; day 3, 0.73; day 4, 0.61; and day 5, 0.54
- *Lowest Platelet Count:* 127,000/μL
- *Imaging Findings:* Figure 1A
- *Maximum Oxygen Support:* Invasively ventilated for COVID-19-associated acute respiratory distress syndrome
- COVID-19 *Treatment Received:* Remdesivir, Methylprednisolone, and Enoxaparin prophylaxis dose
- *Medications for Thrombotic Illness:* Enoxaparin 1-mg/kg subcutaneously 12 hourly (with monitoring of antifactor Xa levels)
- *Interventions:* Inferior vena cava filter
- *Outcomes:* Alive
- *Medication on Discharge:* Apixaban 5 mg by mouth twice daily

Case Scenario: Cerebral Venous Sinus Thrombosis

- *Age/Gender:* 45 years/Male
- *Comorbidities:* Overweight and hypertension
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* Same day (CTs/o COVID-19; swab – negative)
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* Generalized tonic–clonic seizures, new onset
- *Highest D-dimer:* 465 ng/mL
- *Absolute Lymphocyte Counts* ($\times 10^3$ cells/μL)*:* Day 1, 1.8; day 2, 2.2; day 3, 2.1; day 4, 2.4; and day 5, 1.6

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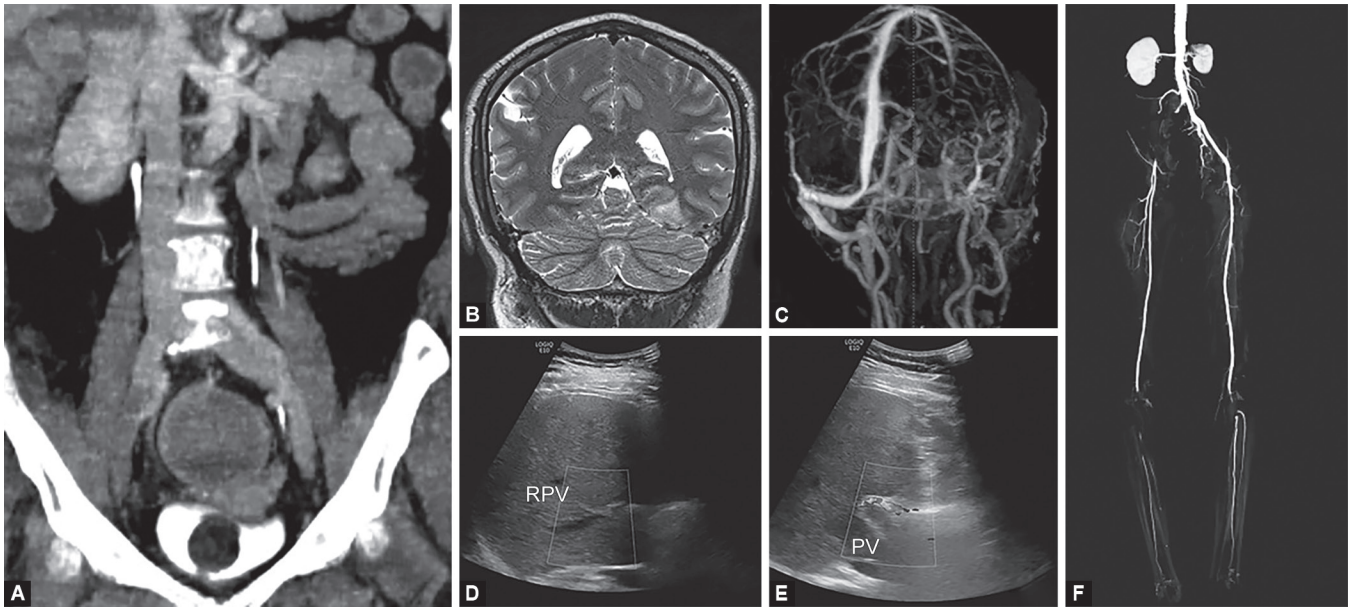


Figs 1A to F: (A) Acute thrombosis of the right external iliac vein extending into right common femoral vein, profunda femoris, and superficial femoral vein up to mid-thigh; (B) An area of signal abnormality in the left posterior temporal/occipital lobe may represent an area of venous ischemia/early developing infarct; (C) Acute dural venous sinus thrombosis involving the left transverse sinus as well as the sigmoid sinus and left internal jugular vein; (D and E) Portal vein thrombosis; (F) Long segment complete lumen occluding thrombus in right common iliac, proximal one-third of the internal iliac, external iliac, and proximal two-thirds of common femoral artery and left popliteal artery thrombosis

- *Lowest Platelet Count:* 1,88,000/μL
- *Imaging Findings:* Figures 1B and C
- *Maximum Oxygen Support:* Room air
- COVID-19 *Treatment Received:* None
- *Medications for Thrombotic Illness:* Dalteparin 5000-mg subcutaneously twice daily
- *Interventions:* none
- *Outcomes:* Alive
- *Medication on Discharge:* Dabigatran 150 mg by mouth twice daily

Case Scenario: Portal Vein Thrombosis

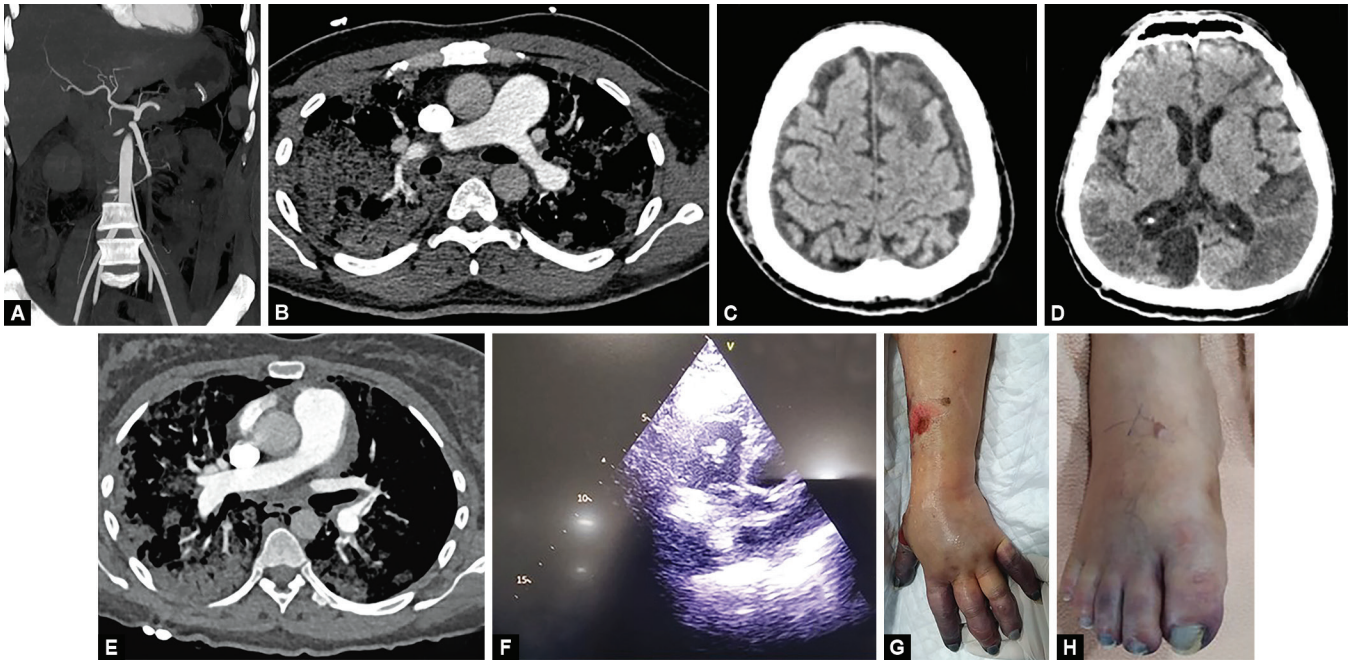
- *Age/Gender:* 38 years/Male
- *Comorbidity:* None
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* 4 months
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* Acute abdominal pain
- Highest D-dimer: 2697 ng/mL
- *Absolute Lymphocyte Count (× 10^3 cells/μL):* Day 1, 1.2
- *Lowest Platelet Count:* 2,85,000/μL
- *Imaging Findings:* Figures 1D and E
- *Maximum Oxygen Support:* Nasal prongs
- COVID-19 *Treatment Received:* Remdesivir, Methylprednisolone, and Enoxaparin prophylaxis dose
- *Medications for Thrombotic Illness:* Enoxaparin 1-mg/kg subcutaneously twice daily
- *Interventions:* None
- *Outcomes:* Alive
- *Medication on Discharge:* Enoxaparin 1-mg/kg subcutaneously twice daily

Case Scenario: Lower Extremity Arterial Thrombosis

- *Age/Gender:* 88 years/Female
- *Comorbidities:* Hypertension, sick sinus syndrome, coronary artery disease, old stroke, and obese
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* 43 days
- *Vaccination History at Time of Presentation:* 2 months prior to presentation
- *Presenting Features of Thrombotic Illness:* Right foot gangrene
- *Highest D-dimer:* 2021 ng/mL
- *Absolute Lymphocyte Count (× 10^3 cells/μL):* Day 1, 0.67; day 2, 0.77; day 3, 0.65; day 4, 1.36; and day 5, 1.13
- *Lowest Platelet Count:* 3,48,000/μL
- *Imaging Findings:* Figure 1F
- *Maximum Oxygen Support:* Nasal prongs
- COVID-19 *Treatment Received:* Remdesivir, Methylprednisolone, and Enoxaparin prophylaxis dose
- *Medications for Thrombotic Illness:* Enoxaparin 1-mg/kg subcutaneously twice daily
- *Interventions:* Right below-knee amputation and retrograde embolectomy
- *Outcomes:* Alive
- *Medication on Discharge:* Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

Case Scenario: Superior Mesenteric Artery Thrombosis

- *Age/Gender:* 35 years/Male
- *Comorbidity:* None
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* 18 days
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* Acute abdominal pain and vomiting
- *Highest D-dimer:* 3207 ng/mL
- *Absolute Lymphocyte Count (× 10^3 cells/μL):* Day 1, 0.44; day 2, 0.52; day 3, 0.69; day 4, 0.83; and day 5, 0.34



Figs 2A to H: (A) Non-opacification of jejunal branches and left internal iliac artery suggestive of thrombosis; (B) CT pulmonary angiography shows focal partially occluding thrombus in segmental arteries of posterior segment right upper lobe; (C and D) Patchy hypo-densities in bilateral cerebral hemispheres in middle cerebral artery (MCA) territories suggestive of acute MCA territory infarction. On right side, involvement of temporal and parietal lobes is seen and on the left side prominent involvement of parietal lobe is seen; (E) CT pulmonary angiography shows pulmonary thrombosis in left main pulmonary artery; (F) 2D Echo shows clot in right ventricle; (G) Gangrenous changes in distal parts of left hand; (H) Gangrenous changes in distal portion of right toes

- *Lowest Platelet Count:* 6000/μL
- *Imaging Findings:* Figure 2A. There were splenic and hepatic infarcts also seen on computed tomography (CT) imaging
- *Maximum Oxygen Support:* Invasively ventilated (following septic shock)
- COVID-19 *Treatment Received:* None
- *Medications for Thrombotic Illness:* Unfractionated heparin infusion followed by Enoxaparin 1-mg/kg subcutaneously twice daily
- *Interventions:* Laparoscopy with small bowel resection
- *Outcomes:* Alive
- *Medication on Discharge:* Enoxaparin 1-mg/kg subcutaneously twice daily

Case Scenario: Pulmonary Thrombosis

- *Age/Gender:* 35 years/Male
- *Comorbidity:* None
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* 10 days
- *Vaccination History at Time of Presentation*: Not received
- *Presenting Features of Thrombotic Illness:* Dyspnea
- *Highest D-dimer:* 35,160 ng/mL
- *Absolute Lymphocyte Count (× 10^3 cells/μL):* Day 1, 0.62; day 2, 1.02; day 3, 0.36; day 4; 0.34; and day 5; 0.38
- *Lowest Platelet Count:* 187,000/μL
- *Imaging Findings:* Figure 2B
- *Maximum Oxygen Support:* High-flow nasal oxygen
- COVID-19 *Treatment Received:* Remdesivir, Methylprednisolone, and Enoxaparin prophylaxis dose
- *Medications for Thrombotic Illness:* Enoxaparin 1-mg/kg subcutaneously twice daily
- *Interventions:* None
- *Outcomes:* Alive
- *Medication on Discharge:* Apixaban 10 mg by mouth twice daily for 7 days followed by 5 mg twice daily by mouth for 3 months

Case Scenario: Thrombotic Microangiopathy

- *Age/Gender:* 70 years/Male
- *Comorbidity:* Hypertension
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* 1 day
- *Vaccination History at Time of Presentation:* Received two doses of Covishield
- *Presenting Features of Thrombotic Illness:* Fever, cough, and diarrhea
- *Highest D-dimer:* 162,049.53 ng/mL
- *Absolute Lymphocyte (× 10^3 cells/μL):* Day 1, 0.36; day 2, 0.41; day 3, 0.69; day 4, 0.39; and day 5, 0.38
- *Lowest Platelet Count:* 14,000/μL
- *Hematological Findings:* Fragmented cells seen on smear
- *Other Blood Investigations:* Serum creatinine 4.8 mg/dL; LDH 2997 IU/L; triglycerides 116 mg/dL; serum ferritin 1925 mg/L; serum haptoglobin below 10 mg/dL; urine for eosinophils – negative; C3-69.6 mg/dL; C4-18.9 mg/dL
- *Imaging Findings:* Figures 2C and D
- *Maximum Oxygen Support:* Invasively ventilated
- COVID-19 *Treatment Received:* Remdesivir and Methylprednisolone
- *Medications/Procedure for Thrombotic Illness:* none
- *Interventions:* Plasmapheresis and hemodialysis
- *Outcomes:* Deceased

Case Scenario: Right Ventricular Thrombus

- *Age/Gender:* 30 years/Female
- *Comorbidity:* None
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* 22 days
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* Tachycardia and tachypnea
- *Highest D-dimer:* 21,423 ng/mL
- *Absolute Lymphocyte Count (× 10^3 cells/μL):* Day 1, 0.24; day 2, 0.4; day 3, 0.52; day 4, 0.73; and day 5, 0.99
- *Lowest Platelet Count:* 372,000/μL
- *Imaging Findings:* Figures 2E and F
- *Maximum O_2 Support:* Invasively ventilated
- COVID-19 *Treatment Received:* Remdesivir, Methylprednisolone, and Enoxaparin prophylaxis dose
- *Medications for Thrombotic Illness:* Enoxaparin 1-mg/kg subcutaneously twice daily
- *Interventions:* none
- *Outcomes:* Alive
- *Medication on Discharge:* Rivaroxaban

Case Scenario: Bilateral Upper Extremity, Lower Extremity, and Pulmonary Arterial Thrombosis

- *Age/Gender:* 58 years/Female
- *Comorbidity:* Obesity
- *Days from COVID-19 Symptom Onset to Thrombotic Infection*: 8 days
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* COVID-19-associated respiratory failure that required invasive ventilation; 8 days into illness bluish discoloration of right toes was noted and the following day, discoloration of tips of left hand occurred
- *Highest D-dimer:* 99,111 ng/mL
- *Absolute Lymphocyte Count (× 10^3 cells/μL):* Day 1, 0.5; day 2; 0.83; day 3, 0.82; day 4, 0.54; and day 5, 0.91
- *Lowest Platelet Count:* 1,25,000/μL
- *Imaging Findings:* The CT peripheral angiography revealed an abrupt cutoff of the proximal right radial artery; the right ulnar artery showed mild irregularity and diffuse narrowing; complete thrombotic occlusion of the left radial artery; thrombus in the right internal jugular vein, right subclavian vein, filling defect in superior vena cava as well as thrombi in right and left pulmonary arteries (Figs 2G and H)
- *Maximum O_2 Support:* Invasively ventilated
- COVID-19 *Treatment Received:* Remdesivir, Methylprednisolone, and Enoxaparin prophylaxis dose
- *Medications for Thrombotic Illness:* Enoxaparin 1-mg/kg subcutaneously twice daily
- *Interventions:* Thrombolysis with rt-PA
- *Outcomes:* Deceased

Case Scenario: Acute Ischemic Stroke Following Rhinocerebral Mucormycosis

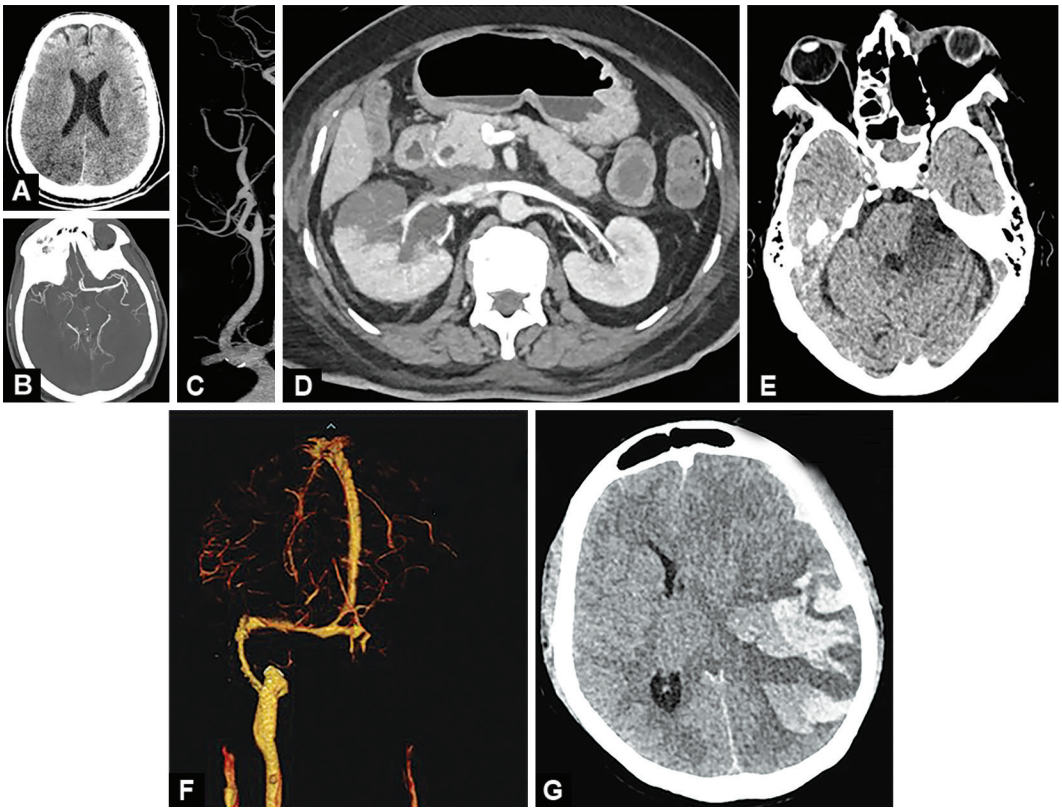
- *Age/Gender:* 60 years/Male
- *Comorbidities:* Hypertension and obesity
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* Same day
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* Acute ischemic stroke
- *Highest D-dimer:* 19,440 ng/mL
- *Absolute Lymphocyte Count (× 10^3 cells/μL)*: (Day 1) 0.25, (Day 2) 0.29, (Day 3) 0.24, (Day 4) 0.17, (Day 5) 0.23
- *Lowest Platelet Count:* 77,000/μL
- *Imaging Findings:* Figures 3A to C
- *Maximum Oxygen Support:* Invasively ventilated (for raised intracranial pressure)
- COVID-19 *Treatment Received:* Remdesivir, Methylprednisolone, and Enoxaparin prophylaxis dose
- *Medications for Thrombotic Illness:* Enoxaparin 1-mg/kg subcutaneously once daily
- *Interventions:* None
- *Outcomes:* Deceased

Case Scenario: Renal Vein Thrombosis with Infarct Secondary to Mucormycosis

- *Age/Gender:* 68 years/Female
- *Comorbidities:* Hypertension, hypothyroidism, and obesity
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* 8 days
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* Abdominal pain
- *Highest D-dimer:* 3,393 ng/mL
- *Absolute Lymphocyte Count (× 10^3 cells/μL):* Day 1, 2.55; day 2, 1.94; day 3, 0.87; day 4 1.19; day 5, 1.67
- *Lowest Platelet Count:* 66,000/μL
- *Imaging Findings:* Figure 3D
- *Maximum Oxygen Support:* Nasal prongs
- COVID-19 *Treatment Received:* Remdesivir, Methylprednisolone, Enoxaparin prophylaxis dose, and Bevacizumab
- *Medications for Thrombotic Illness:* Enoxaparin 1-mg/kg subcutaneously twice daily
- *Interventions:* Laparoscopic total nephrectomy and Whipple's surgery
- *Outcomes:* Alive
- *Medication on Discharge:* No anticoagulants

Case Scenario: Acute Myocardial Infarction

- *Age/Gender:* 72 years/Male
- *Comorbidities:* Diabetes Mellitus, obesity, and hypertension
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* Same day
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* Sudden onset chest pain and cardiogenic shock
- *Highest D-dimer:* Not done
- *Absolute Lymphocyte Count (× 10^3 cells/μL):* Day 1, 0.69; day 2, 0.45; day 3, 0.47; day 4, 0.68; day 5, 0.85
- *Lowest Platelet Count:* 2,23,000/μL
- *Imaging Findings:* Coronary angiography showed double vessel disease
- *Maximum Oxygen Support:* Invasively ventilated
- COVID-19 *Treatment Received:* None
- *Medications for Thrombotic Illness:* Enoxaparin 1-mg/kg subcutaneously twice daily
- *Interventions:* Percutaneous transluminal coronary angioplasty to left anterior descending coronary artery
- *Outcomes:* Alive
- *Medication on Discharge:* Aspirin, clopidogrel, and atorvastatin



Figs 3A to G: (A) Large nonhemorrhagic cortical-subcortical infarcts in the fronto-temporo-parietal and occipital lobes bilaterally involving middle cerebral, anterior cerebral, and posterior cerebral artery territories; (B and C) Both the internal carotid arteries are occluded after short stumps from their origins with a thrombus visualized in the left cervical ICA after its origin; (D) Post-COVID-19 mucormycosis with renal infarct; (E) Subacute infarct involving left superior cerebellar artery territory; (F and G) Cerebral venous sinus thrombosis with venous infarct and hemorrhage

Case Scenario: Stroke in a Patient with Rhino–orbital–cerebal Mucormycosis

- *Age/Gender:* 62 years/Male
- *Comorbidities:* Hypertension, old stroke, and obesity
- *Days from COVID-19 Symptom Onset to Thrombotic Infection:* 53 days
- *Vaccination History at Time of Presentation:* Not received
- *Presenting Features of Thrombotic Illness:* Headache and right hemiparesis
- *D-dimer:* Not done
- *Absolute Lymphocyte (× 10^3 cells/μL):* Day 1, 1.66; day 2, 0.68; day 3, 0.92; day 4, 0.62; day 5, 1.13
- *Lowest Platelet Count:* 35,000/μL
- *Imaging Findings:* Figure 3E
- *Maximum Oxygen Support:* Invasively ventilated
- COVID-19 *Treatment Received:* Remdesivir, Methylprednisolone, and Enoxaparin prophylaxis dose
- *Medications for Thrombotic Illness:* None
- *Interventions:* Left maxillectomy with left eye exenteration
- *Outcomes:* Deceased

Case Scenario: Cerebral Venous Sinus Thrombosis with Hemorrhagic Infarct

- *Age/Gender:* 29 years/Female
- *Comorbidities:* Obese
- *Days from Vaccination to Thrombotic Illness:* Within 2 days
- *Maximum Oxygen Support:* Invasively ventilated (following raised intracranial pressure)
- *Lowest Platelet Count:* 36,000/μL
- *Heparin-induced Thrombocytopenia Panel:* Positive
- *Imaging Findings:* Figures 3F and G
- *Medications for Thrombotic Illness:* None
- *Interventions:* Decompressive craniectomy
- *Outcomes:* Deceased

Discussion

Pathophysiological basis of thrombosis involves endothelial injury, hypercoagulability, and stasis of blood. All three elements operate induced by SARS-CoV-2 following COVID-19 infection.

From the Bench: Infection-associated Thrombosis

Inflammatory cytokines IL- 6 and IL- 8 are increased in patients infected with SARS-CoV-2. Systemic inflammation affects the hemopoietic system *via* angiotensin-converting enzyme (ACE2), cross-reactivity with platelets influencing their quality and quantity, scavenging of these activated platelets by splenic and hepatic macrophages, and thrombotic microangiopathy. Infection with the virus and resultant host inflammatory response leads to endothelial cell inflammation.[1] Decrease in numbers and sensitivity of innate anticoagulants-antithrombin, protein C, and tissue pathway inhibitor on endothelial surface steers thrombosis. Activated monocytes, macrophages, and neutrophils bind to platelets and these activated complexes instigate thrombosis.[2] Hemostasis and immune system provide host defense *via* physiological immunothrombosis and contain spread of the virus. Dysregulation results in generation of immunologically mediated thrombi in the microvessels.[3]

Reported microvascular changes following SARS-CoV-2 infection are more distinct as compared to H1N1 lungs, suggesting a disease-specific effect rather than an epiphenomenon of viral pneumonia.[4,5]

From the Bench: Dysregulated Renin–angiotensin–aldosterone System and Role of ACE2.

COVID-19 induces a prothrombotic state. ACE2 is a functional receptor of SARS-CoV-2. ACE2 suppresses proinflammatory peptides and downregulates the inflammatory state. Downregulation of ACE2 in COVID-19 leads to an increase in angiotensin II contributing to hyperinflammatory and a procoagulant state. Platelets *per se* do not express ACE2 mRNA denoting their activation following COVID-19 is not because of infection but rather following the release of factors from cells that enhance platelet activation and aggregation.[6] Inflammatory cytokine storm, inflammation-mediated endothelial injury, and renin–angiotensin–aldosterone system dysregulation[7] lead to coagulation dysfunction. Release of subendothelial von Willebrand Factor following damage to endothelium activates platelet aggregation and thrombosis. Tropism of SARS-CoV-2 for ACE2 receptors leads to endothelial dysfunction and a procoagulant state.

ACE2 expression increases with age and is reported to be higher in Asian males. This could be a possible explanation for higher disease severity in the elderly and males. ACE2 is present in visceral adipocytes whose expression and activity are reduced by leptin, promulgating proinflammatory effects in the obese.[8]

From the Bench: Dysregulated Immune Response

Excessive activation of complement system (innate immune response) leads to dysregulated immune response. Cellular and molecular mediators in detecting pathogens, induce thrombosis in microvessels. This crosstalk between innate immune system and coagulation is immunothrombosis, a term proposed[9] to denote the physiological role of thrombosis in immune defense. Dysregulated immunothrombosis leads to COVID-associated coagulopathy. SARS-CoV-2-associated endothelial activation, platelet activation, complement activation, cytokine storm, thrombin generation, and neutrophil extracellular traps provide a framework promoting propagation of thrombus.

A decrease in circulating T-lymphocytes and their subsets[10] (CD4+, CD8+, and regulatory T cells) seen following SARS-CoV-2 infection affects antibody production and viral clearance. Ensuing cytokine storm leads to microthrombosis.

From the Bench: The Role of Hemodynamics

Hemodynamic components influencing thrombosis include stasis, turbulent flow, and shear stress[11] in the venous as well as arterial system. Endothelial injury by the virus results in: (1) local thrombus formation and (2) vasoconstriction with a reduction of blood flow causing stasis downstream. Increased flow velocities lead to turbulence, especially in larger vessels. Shear stress in areas of stasis or turbulence acts on the blood leading to the activation of platelets, release of the von Williebrand factor, and platelet aggregation.

From the Bench: Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)

Coronavirus disease of-2019 vaccine induces a prothrombotic state.[12] Four criteria necessary for this diagnosis include[13] (1) COVID-19 vaccine in the prior 42 days, (2) any venous or arterial thrombosis, (3) thrombocytopenia, and (4) positive PF-4 heparin-induced thrombocytopenia by enzyme-linked immunosorbent assay (ELISA) test. Patients presenting with thrombosis without thrombocytopenia following the COVID-19 vaccine may be at an early stage of VITT. This is reported after the CHAdOx1 nCoV-19 vaccine.

To the Bedside

Several risk factors such as elderly, and comorbidities (obesity, cardiovascular disease, diabetes mellitus, atrial fibrillation, and protracted immobility) predispose patients to thromboses (venous, arterial, or microthrombosis). As seen in discussed case scenarios, following are noticed: (1) Venous prothrombotic events occurred in patients even in absence of the usual predisposing risk factors; (2) venous prothrombotic events occurred despite having received venous thromboembolism prophylaxis suggesting inadequacy of current thromboprophylaxis protocols as patients are not entirely safeguarded; (3) pulmonary embolism occurred in the absence of identifiable deep venous thrombosis, probably following crucial *in situ* thrombosis; (4) arterial thromboses also occurred in the absence of usual predisposing risk factors; (5) COVID-19 as a risk factor for acute mesenteric ischemia needs to be included in the differential diagnosis irrespective of age or associated proximate comorbidities; (6) microthrombosis without any risk factors secondary to direct endothelial damage activating intrinsic coagulation pathway; (7) time gap between onset of COVID-19 infection and occurrence of thrombotic event varied amongst patients; (8) cerebrovascular thrombosis can be presenting symptom of COVID-19 as seen in patients described above; (9) consequences of viral infection (fever, dehydration, and hypoxemia) seemed palpable predisposing prothrombotic factors; (10) no correlation between severity of COVID-19 infection and development of thrombosis; (11) none of these patients had clinically significant bleeding even with low platelet counts; (12) lymphopenia that could have augmented formation of cytokines with ensuing microthrombosis; (13) biochemically this is indicated by high levels of d dimer; (14) patients had preserved platelet counts or mild to moderate thrombocytopenia; and (15) congregation of anemia, thrombocytopenia, and schistocytes on peripheral smear with varying degrees of end organ damage typically establishes diagnosis of thrombotic microangiopathy.

As COVID-19 enters its endemicity, it is imperative for treating clinicians to be aware of its thrombotic spectrum. Unraveling its pathophysiologic basis will guide therapeutic possibilities. Mechanisms and phenotype are not yet understood. What is the risk period? For how long would these patients require additional thromboprophylaxis? Whether immunothrombosis can be predicted, prevented, or treated with anticoagulants or targeted interventions, and whether steroids affect immunothrombosis need to be looked into. Anticoagulation *per se* does not have a disease-modifying effect but instead viral load with its systemic inflammatory response needs to be attenuated for its dynamism towards a prothrombotic state.

Conclusion

A key component following SARS-CoV-2-associated coagulopathy is managing the viral infection. Micro- and macrovascular hypercoagulable features are secondary to inflammation following the primary infection. Multiple theories have been proposed, but which triggers are significant and the succession of their occurrence

remains to be studied. Patients should be monitored clinically as well as *via* inflammatory biomarkers. Thromboprophylaxis is recommended in the absence of contraindications and should be advanced to therapeutic anticoagulation as per the patient's clinical evolution. Timely diagnosis helps reduce morbidity and mortality.

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