Received: 11 June 2020 | Accepted: 30 July 2020

DOI: 10.1111/iwj.13483

ORIGINAL ARTICLE

IWJ WILEY

Pathophysiology of coronavirus disease 2019 for wound care professionals

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Abstract

There is pressing urgency to understand the pathogenesis of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes Coronavirus disease 2019 (COVID-19). The tissue tropism of SARS-CoV-2 includes not only the lung but also the vascular and integumentary systems. Angiotensin-converting enzyme 2 (ACE2) appears to be the key functional receptor for the virus. There is a prominent innate immune response to SARS-CoV-2 infection, including inflammatory cytokines, chemokines, the complement system, and acute phase proteins. The pathophysiologic significance of SARS-COV-2 and host immune system interaction, and COVID-19-associated coagulopathy instigating microvascular injury syndrome mediated by activation of complement pathways, and an associated procoagulant state is important for wound care professionals to understand.

KEYWORDS

acute phase proteins, blood coagulation disorders, complement system proteins, COVID-19, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

The recent emergence of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly developed into a global pandemic and public health emergency.[1,2] As of 11th June 2020, a total of 7 476 361 accumulated cases and 419 368 deaths have been reported worldwide in 215 countries and regions, with an overall mortality rate of about 1%.[3] Coronavirus disease 2019 (COVID-19) primarily produces fever and respiratory symptoms, although involvement of other organ systems has been reported, including cardiovascular and skin manifestations.[3] With any emerging disease, clinicians must integrate a rapidly evolving evidence base into our understanding of the illness.[4-6] Wound care professionals must be particularly attentive of the pathophysiology of COVID-19 on the vascular and integumentary systems as they may influence patient care outcomes. This study reviews the known literature on SARS-CoV-2 infection and COVID-19-related vascular skin and dermatologic manifestations with regards to wound care.

2 | SARS-COV-2 AND HOST IMMUNE SYSTEM INTERACTION

The main vector of SARS-COV-2 spread by droplets that come into contact with mucous membranes.[6] Intriguingly, not all individuals who are exposed acquire the infection. Once infected, the disease progresses through 3 main stages. Stage 1 is an asymptomatic-pauci-symptomatic incubation period where the virus may or may not be clinically detectable. Stage 2 is a period of non-severe symptomatic illness with detectable virus that may resolve or progress. In infected individuals, approximately 80% will end in stage

2. Finally, stage 3 is characterised by severe respiratory illness with progressive pneumonitis that may or may not lead to respiratory failure, which in its final stages, causes diffuse alveolar damage. This last stage is characterised by a state of high levels of inflammation leading to further clinical deterioration and potential involvement of extrapulmonary sites such as cardiac, vascular, and cutaneous tissue.[7] Immunologically, SARS-COV-2 infects cells of the respiratory tract and likely infects endothelial cells and macrophages based on our knowledge of SARS-CoV, which shares considerable homology. Infection triggers innate immunity followed by adaptive humoral and cellular immune responses. The development of neutralising antibodies is believed to be a critical event in recovery as well as the generation of virus-specific T-cell responses, ultimately leading to viral clearance.[8] Unfortunately, the process is not linear, and it is uncertain why adaptive immunity fails and many infected individuals continue to be carriers of the virus.[9] Studies to correlate these three clinical disease stages with SARS-COV-2 viral loads from respiratory secretions, blood, and tissues have produced contradictory results: some patients with advanced disease have high viral loads while others do not.[10] Recent attempts to reconcile these findings suggest that cytokine production belies many of the late-stage disease manifestations in COVID-19 disease, and this may be driven by viral infection or non-infective sources such as collateral tissue destruction.[11] In patients with advancing disease, a syndrome has been reported characterised by hypercytokinemic inflammation, as macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH).[12] In COVID-19, and unlike MAS or sHLH, the primary target organ is the lung, leading to an acute respiratory distress syndrome with some shared features to the idiopathic form both clinically and pathologically.[12] Laboratory features are quite similar among these disorders, with marked elevations of acute phase reactants (ie, C-reactive protein, ferritin), lymphopaenia, coagulation defects, and elevated levels of numerous inflammatory cytokines; prominent among them are interleukins 6 (IL-6), 1 (IL-1), 2 (IL-2), 7 (IL-7), and 17 (IL-17), granulocyte macrophage-colony stimulating factor, and tumour necrosis factor (TNF).[12] Why there is an increased incidence of this inflammatory late-stage complication in select young individuals and more frequently in elderly patients and in those with comorbidities is insufficiently comprehended. Inflammation commonly predisposes patients to thrombosis.

Key messages

- SARS-CoV-2 is a respiratory virus that also has tissue tropism to the vascular and integumentary systems
- ACE2 appears to be the key functional receptor for the virus
- the innate immune response to SARS-CoV-2 infection includes inflammatory cytokines, chemokines, the complement system, and acute phase proteins
- the host immune system interaction and COVID-19-associated coagulopathy instigating microvascular injury syndrome are important for wound care professionals to understand

3 | COVID-19-ASSOCIATED COAGULOPATHY

The clinical presentation of COVID-19-associated coagulopathy is that of a highly prothrombotic state.[13,14] Two recent studies from China and the Netherlands and our own initial experience indicate that critically ill COVID-19 patients without other risk factors for thrombosis manifest with various thrombotic events including microvascular thrombosis, venous and pulmonary thromboembolism, and acute arterial thrombosis.[13,14] The study from China reported a 25% incidence venous thromboembolism.[13] The study from the Netherlands has 31% incidence of thrombotic complications (deep vein thrombosis, pulmonary embolism, and arterial thrombosis) of which 81% of events were pulmonary thromboemboli.[14] The most common pattern of coagulopathy observed in patients hospitalised with COVID-19 is characterised by elevations in fibrinogen and D-dimer levels, painting a picture of a highly prothrombotic state with high fibrin turnover.[13,14]

This correlates with a parallel rise in markers of inflammation, for example, C-Reactive Protein.[12-14] Unlike the pattern seen in classic disseminated intravascular coagulopathy (DIC) from bacterial sepsis or trauma, prolongation of the activated partial thromboplastin time (APTT) and/or prothrombin time (PT) is minimal, thrombocytopenia is mild (platelet count ~100 $\times 10^9$/L), and lab results supporting microangiopathy are unlikely. Rarely patients with severe COVID-19 infection and multiorgan failure progress to a coagulopathy meeting criteria for overt DIC.[13,14] This is reflected by moderate to severe thrombocytopenia (platelet count <50 $\times 10^9$/L), prolongation of the PT and aPTT, extreme elevation of D-dimer, and decreased fibrinogen (<1.0 g/L).

Lupus-like inhibitors have been reported in some patients with COVID-19 as the reason for APTT prolongation.[15,16] Generally lupus anticoagulants are not

associated with bleeding unless they are masking an underlying bleeding tendency or have associated hypoprothrombinemia in which case the PT will be prolonged.[15,16] The artefactual APTT prolongation may necessitate monitoring of unfractionated heparin with anti-Xa activity.[15,16] Patients with COVID-19 and a lupus-like inhibitors should be treated with prophylactic anticoagulation similar to other hospitalised patients.[15,16]

DIC is much less common in those with mild COVID-19 infection, affecting only 0.6% of survivors as opposed to 71.4% of non-survivors in one study.[17] Similarly, the majority of reports of large vessel thromboses and microemboli in COVID-19 are in those with severe illness. Supporting this observation is a retrospective study demonstrating that thromboprophylaxis has a mortality benefit in only severely ill COVID-19 patients with a high sepsis-induced coagulopathy score.[18] Although studies in mild disease are limited, these combined data suggest that DIC and macrothromboses may be restricted to severe COVID-19 infections. This is not unexpected given that severe infection is accompanied by features of Virchow's triad including venous stasis in the setting of immobility, hypercoagulability as a result of cytokine storm, and endothelial cell dysfunction because of sepsis and inflammation. With this in mind, what then accounts for the vaso-occlusive phenomena that preferentially affect cutaneous small vessels in mild cases of COVID-19? Based on emerging data, several other potential factors may play a role in microthrombi formation in less severe disease.

Pathology has demonstrated diffuse alveolar damage with profound inflammation, thrombosis, and thrombotic microangiopathy of small vessels and capillaries of the lung.[19] Megakaryocytes within pulmonary capillaries with nuclear hyperchromasia and atypia, as well as neutrophils partially degenerated and entrapped in fibres, suggesting neutrophil extracellular traps, have also been noted.[17] Endothelial cell injury and diffuse microvascular thrombosis suggestive of thrombotic microangiopathy is also reported in extrapulmonary organs and may explain acute onset of multiorgan failure without an otherwise obvious aetiology.[20]

COVID-19-associated coagulopathy is likely multifactorial, and COVID-19 patients share many of the classic venous thromboembolism risk factors seen in adult respiratory distress syndrome (ARDS) from other causes, ie, immobilisation, large vascular-access catheters, and systemic inflammation. The hallmark of COVID-19 is hypercytokinemic inflammation, characterised by high levels of Il-1, Il-6, TNF-alpha, and other inflammatory cytokines.[12,17] Inflammation is known to promote thrombosis through various mechanisms, including activation of the endothelium, platelets, monocytes, and the tissue factor/factor VIIa pathway, as well as altering fibrinolysis and natural anticoagulant pathways (thrombomodulin, proteins C and S, tissue-factor-pathway inhibitor).[21,22] A retrospective study demonstrated that severe COVID-19 patients have high levels of inflammatory cytokines including IL-1β, IL-8, IL-9, IFN-γ, and TNF-α among others.[23] Although less profoundly elevated than in severe illness, levels remain moderately elevated in non-severe disease.[24] Many of these involved cytokines are thought to promote thrombogenesis, and even mild cytokine elevations in non-severe disease could theoretically contribute to thrombosis.[21-24] Intense inflammation with thrombosis of pulmonary vessels is also seen in ARDS of other etiologies, and it remains to be seen if these findings represent a distinct phenotype unique to COVID-19, or are a general indicator of the severity of inflammation of COVID-19.[24]

Serum proteomic profiling of patients with SARS identified an N-terminal fragment of complement C3C-alpha, a central component of the complement pathway, as a sensitive biomarker of early SARS.[25] Murine models of SARS-CoV and Middle East respiratory syndrome coronavirus have shown that complement activation is a major contributor to lung injury and other organ failure. Complement inhibition in these models reduced organ damage and inflammation.[25-27] Therapeutic use of complement blockade in COVID-19 has been suggested, but clinical data are not yet available.[28]

Another potential reason for microvascular thrombosis that may be specific for SARS-CoV-2 infection in non-severe COVID-19 infection is because of the mechanism of viral entry into cells. SARS-CoV-2 is known for its affinity to bind to ACE2, a transmembrane enzyme, allowing entry into the cell. ACE2 is expressed on alveolar epithelial type II cells and various extrapulmonary tissues including endothelial cells. ACE2 binding results in decreased expression of ACE2, activation of the renin-angiotensin system, promotion of platelet aggregation, and thrombus formation. As endothelial cells also express ACE2, SARS-CoV-2 may additionally cause direct endothelial dysfunction after binding to ACE2, leading to subsequent thrombosis. This endothelial cell activation may represent a unique mechanism of COVID-19-mediated microvascular injury, thrombosis, and subsequent multisystem organ failure.[29-31] In the setting of mild disease where profound coagulopathy is unlikely, mild elevations in prothrombotic cytokines and direct endothelial cell damage by SARS-COV-2 may theoretically contribute to the small vessel occlusive phenomena noted in the skin. Other potential mechanisms include complement activation, antiphospholipid antibody production, and tissue factor expression on endothelial cells.

An additional factor that could contribute to thrombosis is the presence of a positive lupus anticoagulant

that was detected in 50 patients out of the 57 tested (87.7%) in a French study. This once more points to an important role of endothelial injury as a key mechanism of multiorgan failure and coagulopathy of COVID-19.[16] The "two-hit" model of thrombosis associated with antiphospholipid syndrome proposes that after a first hit causes injury to the endothelium, antiphospho-lipid antibodies potentiate thrombus formation as a second hit.[32] Activation of the contact system because of increased vascular permeability and thrombotic microangiopathy warrant further exploration.[33]

4 | COVID-19 AND SKIN

A range of cutaneous manifestations, such as such as chilblain, livedo reticularis, mottling, petechiae, and purpura, are associated with COVID-19.[34] These aforementioned manifestations could be secondary findings associated with a series of thrombotic events such as DIC, hyaline thrombus formation, acral ischaemia, and thrombocytopenia. Immune dysregulation, vasculitis, or neoangiogenesis might also be associated with the pathophysiology of these cutaneous manifestations.[34]

The pathophysiological mechanisms of COVID-19 cutaneous manifestations remains uncertain, but some common theories are prevalent. Viral particles, in particular viral nucleotides, present in the cutaneous blood vessels in patients with COVID-19 infection may instigate an immune response in the manner of lymphocytic vasculitis similar to those observed in thrombophilic arteritis induced by blood immune complexes that activate cytokines. Keratinocytes may be a secondary target after Langerhans cells activation, inducing a spectrum of different clinical manifestation.[35,36] It can be postulated that the virus does not target the keratinocyte, but rather immune response to infection leads to Langerhans cells activation, resulting in a state of vasodilation and spongiosis.[36] Further theories suggest livedo reticularis-resembling manifestations can result due the accumulation of microthromboses originating in other organs, thus reducing blood flow to the cutaneous microvasculature system.[37] Similarly, low-grade DIC and hypoxia-related accumulation of deoxygenated blood in venous plexes may further explain such manifestations.[37] In addition, pauci-inflammatory thrombogenic vasculopathy with deposition of C5b-9 and C4d as well as colocalization of these with COVID-19 spike glycoproteins was reported.[38] It is still unclear whether cutaneous symptoms are a secondary consequence of respiratory-related infection or a primary infection of the skin itself. It is more likely that a combination of such mechanisms is responsible for the cutaneous manifestations found in COVID-19 positive individuals. Skin biopsies have demonstrated a striking thrombogenic vasculopathy accompanied by extensive necrosis of the epidermis and adnexal structures, including the eccrine coil.[38] There was a significant degree of interstitial and perivascular neutrophilia with prominent leukocytoclasia. The vasculopathy included fibrin deposition within capillary lumens and walls accompanied by endothelial cell necrosis, consistent with a thrombotic necrotizing capillary injury syndrome. In the superficial dermis, there was a perivascular lymphocytic infiltrate along with deeper-seated small thrombi within venules of the deep dermis, in the absence of a clear vasculitis. Immunohistochemistry demonstrated showed extensive deposition of C5b-9 within the microvasculature. In summary, at least a subset of sustained, severe COVID-19 may define a type of catastrophic microvascular injury syndrome mediated by activation of complement pathways and an associated procoagulant state. To clarify the underlying mechanisms, large-scale prospective studies with biopsies, serological tests showing antibody response to virus infection and PCR analysis of suspected patients are warranted. Since the time kinetics of skin and vascular manifestation, and viremia probably vary among different infections, it may be significant to measure blood viral load at different time points (before, during, or after lesions onset), thereby determine the appropriate time of biopsies for molecular identification.

5 | HEPARIN AND COVID-19

Heparin anticoagulation appears to be the obvious response to such a hypercoagulable process. In addition to its antithrombotic effect, heparin may have anti-inflammatory, anti-complement, and direct antiviral effects that may be beneficial in COVID-19.[39] Heparin inhibits neutrophil activation, binds inflammatory cytokines, and reduces endothelial activation.[40] Experimental models have also shown that heparin directly binds to SARS-CoV spike-protein1, which acts as the viral anchor site for SARS-CoV-ACE2 interaction, and thereby blocks cell entry.[41] While promising, these effects have yet to be demonstrated in clinical practice.

6 | DISCUSSION

The pathophysiologic importance of SARS-COV-2 and host immune system interaction, and COVID-19-associated coagulopathy instigating microvascular injury syndrome mediated by activation of complement pathways, and an associated procoagulant state is important for wound care professionals and could have translational implications. At least a subset of sustained, severe

COVID-19 may define a type of catastrophic microvascular injury syndrome mediated by activation of complement pathways and an associated procoagulant state. It provides a foundation for further exploration and may indicate targets for specific intervention. While evidence is rapidly emerging about COVID-19-associated coagulopathy, at present, the skin appears to possibly represent an innocent bystander in the prothrombotic milieu of SARS-CoV-2 infection. In pauci-symptomatic COVID-19 patients, under-expression of angiotensin-converting enzyme 2 receptor necessary for SARS-Cov2 binding and infection, a milder inflammatory cascade resulting in lesser activation of the complement cascade, within the capacity of complement regulatory proteins, both soluble and normally present in abundance on the microvasculature may result in lesser vascular/microvascular injury with minor procoagulant state. However, further research is required to elucidate and validate the pathophysiology in order to safely prevent and/or treat COVID-19-related inflammatory skin complications including the cytokine response and the coagulopathy.

CONFLICT OF INTEREST

The author declares no potential conflict of interest.

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How to cite this article: Al-Benna S. Pathophysiology of coronavirus disease 2019 for wound care professionals. *Int Wound J*. 2020;17: 1935–1940. https://doi.org/10.1111/iwj.13483