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Review Article

Skin necrosis in COVID-19 patients: complication of therapy or one of clinical and pathological mechanisms of viral infection?

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ABSTRACT

The coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by a novel coronavirus (SARS-CoV-2, previously known as 2019-nCoV). Dermatological disorders are among the numerous observations in COVID-19 patients that are consistently reported from various clinical sites throughout the world, although their relationship with illness severity is unknown. Urticarial rash, maculopapular or morbilliform rash, papulovesicular lesions, chilblain, livedo reticularis, vasculitis-like picture, and skin necrosis have all been reported with different frequencies and associated circumstances. In this review article, we will highlight reports of skin necrosis, one of the rare skin findings that are associated with COVID, and their clinical and pathophysiological aspects, in addition to attempting to determine whether they are one of the possible outcomes of this virus infection or a complication of various treatment programs. and to discuss the overlap between skin necrosis due to COVID-19-associated coagulopathies and disseminated intravascular coagulation. Cutaneous necrosis in COVID-19 patients during the pandemic period, according to this review, is not rare. possibly It is simple to diagnose and recognize this dermatological condition, but determining the causal variables and their function in pathogenesis is a complex and difficult task. It's also tough to categorize because it affects people of all ages, regardless of gender, ethnicity, or health status. All hypotheses discuss the direct viral role, the immune system's hyperinflammatory state with cytokine storm, the hypercoagulable state with vasculitis, anticoagulant therapy complications, and deep secondary necrotizing infections as possible interactions that lead to necrosis, which can result in serious outcomes such as disseminated intravascular coagulation if not properly treated.

Keywords: COVID-19, Skin necrosis, Coagulopathy, Vasculitis, DIC

INTRODUCTION

During COVID-19, a hypercoagulable state and consumption coagulopathy are identified in some cases, which are associated with severe or fatal illness. The formation of hyaline thrombus in small vessels, mainly in the lungs, also involves damage to the heart, vessels, liver, kidney and other organs, as reported in autopsies of patients who died due to severe infection.[1] Anticoagulant therapy, primarily with low molecular weight heparin, appears to be related with a better prognosis in severe COVID-19 individuals with highly raised D-dimer.[2]

Changes in prothrombin time (PT), D-dimer, antithrombin III, fibrinogen, fibrin degradation products (FDP) and platelet count have all been recorded in COVID-19 patients.[3] Severe COVID-19 infection is connected to disseminated intravascular coagulation (DIC) with a 3% incidence. In intensive care unit (ICU) patients, the prevalence of DIC was greater.[4] In one investigation, violaceous macules with a porcelain-like look, pseudo-chilblain appearance with Raynaud's phenomenon, livedo, nonnecrotic and necrotic purpura, and eruptive cherry angioma were found in seven patients.[5] A retrospective review that included patients with critical COVID-19 with acro-ischemia symptoms such as finger and toe cyanosis, skin bulla and dry gangrene showed D-dimer, fibrinogen and FDP were all considerably high in the majority of patients. Four patients had a prolonged PT. Disseminated intravascular coagulation (DIC) was identified in four cases.[6] A patient with COVID-19 was characterized in another case report as having clinically severe coagulopathy, antiphospholipid antibodies, and numerous infarcts.[7] One case report found COVID-related hypercoagulability in three cases of thrombocytopenia with positive anti-platelet factor 4 (PF4)/heparin antibodies, with Serotonin release assay (SRA) confirmation in one of the three tests.[8] Heparin-induced thrombocytopenia in general is uncommon in critically ill patients, with an estimated incidence of 0.2-0.45%.[9]

DISCUSSION

In an attempt to explain the pathophysiology of the numerous cutaneous manifestations recorded during the COVID-19 pandemic, many theories have been proposed and explored. Some thought the polymorphic erythematous rash was a drug reaction exanthem because it emerged after therapy, and skin biopsies of some of the patients revealed perivascular inflammation with eosinophils and lichenoid reaction. This idea can be supported by improvements in response to medication withdrawal and systemic corticosteroids.[10] Ribavirin, lopinavir ritonavir, intravenous immunoglobulin (IVIG) treatments, colchicine, and hydroxychloroquine are examples of potential COVID-19 drugs. Cytokine storm syndrome, which is characterized by an increase in the production of pro-inflammatory cytokines such as IL1, IL-2, IL6, IL-7, monocyte chemoattractant protein 1, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, interferon-γ inducible protein 10, and tumour necrosis factor-α, could also be a factor.[11] This syndrome provides better explanations for late-onset rash (mean time of 27 days after onset of symptoms) and rash that developed after many days of drug withdrawal.[12] Others have reported that the erythematous rashes clear spontaneously during sickness without the need to stop

treatment, suggesting that the virus plays a direct role in rash etiology.[13] One study analyzed the distribution of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) in relation to viral spike proteins in various sweat glands from skin autopsy samples from five patients with COVID-19, but they were without dermatological changes. SARS-CoV-2 was discovered to target Krt7+ secretory luminal cells of sweat glands, according to the study. Because cell surface receptors are a key determinant of a virus's cell tropism, they discovered that ACE2 and TMPRSS2 were highly expressed in luminal secretory cells, and viral spike protein distribution matched that of ACE2/TMPRSS2.[14] These findings may support the direct viral role in the development of cutaneous lesions (especially in papulovesicular lesions) and may increase the possibility of viral transmission via perspiration and skin contact. It's unknown whether vesicular rash is caused by reactivation of other viral infections or is exclusive to COVID. Some speculated that the lymphopenia associated with COVID-19 infection could have been one of the reasons that predispose people to varicella zoster virus (VZV) infections. Emotional stress, which is commonly associated with SARS-CoV-2 infection, may also play a role in the reduction of immunity, resulting in zoster virus reactivation. In addition to an observation of the Koebner phenomenon occurring in patients infected with SARS-CoV-2, the virus may be causing a local susceptibility to concomitant viral reactivation.[15]

Vascular lesions of the skin were documented to occur with, before, or after COVID-19 infections in many case studies conducted during the COVID pandemic period, in all age groups and with varying degrees of severity and mortality in various geographic areas around the world. These include chilblain-like lesions, livedo reticularis, petechial rashes, retiform purpura, acral ischemia, and dry gangrene. Different histopathological biopsies taken from COVID-19 infected patients with skin lesions suggested vascular involvements as RBC extravasation, fibrinoid necrosis with complement deposition in vessel walls, leukocytoclasia, endothelial injury, micro thrombosis and inflammatory cell recruitment.

Aside from the possibility of the vascular changes being linked to the virus or its treatment modalities, there are a variety of systemic diseases that can manifest as cutaneous vascular manifestations that should be considered during the evaluation of COVID-19 infected patients (Table 1).

Chilblain-like lesions are mostly reported in young age groups with mild to moderate illness, with spontaneous resolution in most cases. Many of them without a history of cold exposure, previous attacks, or extracutaneous changes, with histological pictures showing a lichenoid dermatitis with a perivascular and eccrine mononuclear infiltrate and vascular microthrombi.[16] Other observations described aspects of overlap with chilblain lupus without having the clinical and laboratory characteristics of lupus erythematosus, as histological findings consisted of vacuolar interface dermatitis, basal keratinocytes necrotic, and perivascular infiltrate.[17] Chilblain can also occur as a symptom of lupus and, in rare cases, as a sign

of a familial illness involving interferonopathies. One proposed pathogenesis is the high production of IFN-I associated with moderate cases of COVID-19 infection. IFITM (interferon-induced trans-membrane) 1, 2, and 3 are interferon-induced proteins that impede the early replication of various enveloped RNA viruses, including Middle East respiratory syndrome coronaviruses. In addition to the protective role of the INF-I-mediated inflammatory response in inhibiting virus replication, it has been proposed that this immune mechanism also produces lesions similar to chilblain lupus.[18,19] In patients with severe COVID-19 pneumonia, low type I IFN responses were observed. One review showed antineutrophil cytoplasmic antibodies (ANCA) and lupus anticoagulant antibodies were found in some patients with pseudo-chilblain without any manifestation of ANCA vasculitis or thrombosis.[19] We encountered many cases of COVID-19 infected individuals, especially from children's age groups, that developed pseudo-chilblain lesions during variable periods of illness, most of them with mild to moderate disease.

Table 1: Systemic diseases that can manifest as cutaneous vascular manifestations that should be considered during the evaluation of COVID-19 infected patients.

Cutaneous vascular manifestation	Possible causes
Petechial rashes	Medications (Phenytoin, penicillin), infections (viral bacterial, and fungal), disseminated intravascular coagulation DIC, vasculitis thrombocytopenia, leukemia, scurvy (vitamin C deficiency), vitamin K deficiency
Purpura and ecchymoses	Same causes of petechia in addition to pigmented purpura dermatosis, senile purpura, Steroid purpura, connective tissue diseases (systemic lupus erythematosus), hemolytic uremic syndrome and primary (idiopathic) thrombocytopenic purpura
Chilblain-like lesions	Connective tissue disorders (chilblain lupus), chronic myelomonocytic leukemia, primary or secondary Raynaud phenomenon, Buerger's disease, familial tendency to chilblains which induced by cold exposure smoking and vasoconstrictors
Livedo reticularis	Antiphospholipid syndrome, Sneddon syndrome, cryoglobulinemia, multiple myeloma, protein C and S deficiency, antithrombin III deficiency, disseminated intravascular coagulation, hemolytic uremic syndrome, deep venous thrombosis, systemic lupus erythematosus and other CTD, vasculitis (Polyarteritis nodosa, granulomatosis with polyangiitis and other), multiple sclerosis, Parkinson disease, infections, renal cell carcinoma, lymphoma, leukemia, drugs (Amantadine, minocycline, and non-steroidal anti-inflammatory drugs), cholesterol emboli, septic emboli, hypercalcemia, and thromboangiitis obliterans (Buerger disease)
Acral ischemia and necrosis	Peripheral arterial disease, atherosclerosis, venous insufficiency, peripheral neuropathy, embolus (Cholesterol, fat and septic), Buerger's disease, frost bite, hypotension, low cardiac output, vascular obstruction (hyper viscosity syndromes and cryoglobulins), and ypass graft (a surgical procedure)

The presence of serum antibodies of the IgA isotype in acro-ischemia in certain children with COVID shows that their immune response is based on strong mucosal protection, which could even impair the activation of an IgG response.[17] Patients with a severe and serious disease had the greatest levels of IgA.[20] Only IgA levels were statistically substantially connected with critical disease in repeated regression analyses, regardless of age, sex, or duration of symptoms.[20]

In our attempt to understand the link between COVID-19 infection and vasculitis-like changes with thrombotic events, we illustrated the general pathological mechanisms of these vascular changes. Many studies' findings suggest a link between inflammation and thrombosis in patients with thrombotic events but no underlying inflammatory disease, like deep vein thrombosis, as the thrombosis is followed by elevations of inflammatory markers that lead to further progression, or in patients with inflammatory diseases but no clinical thrombotic events like inflammatory bowel disease (IBD), as platelet activation and coagulation have been found to correlate with the activity of the disease. The disruption and damage of the endothelial layer leads to the expression of active tissue factor (TF) and consequent release of von Willebrand factor (VWF) and thrombin, in addition to decreased protein C, thrombomodulin, and other anticoagulant factors, which lead to the activation of coagulation factors and ultimately end in fibrin deposition and thrombus formation.[21] Th1 cell proinflammatory cytokines such as interleukin IL1, IL6, IL8, IL12, tumor necrosis factor (TNF) and interferon-gamma (IFN), in addition to Th17 cell cytokines like IL17 and IL22, have been proposed as immunological factors that contribute to endothelial dysfunction in inflammatory diseases like vasculitis.[22] In thrombus formation, the main event is platelet activation, which leads to release of ligand (CD40L) and vascular endothelial growth factor (VEGF), which further stimulates coagulation by induction of TF expression on both monocytes and endothelial cells, in addition to

chemokine production like MCP-1 and IL-8, which recruit neutrophils.[23]

The main extrapulmonary targets of COVID-19 infection are the immune system and systemic and cutaneous blood vessels. In critically ill COVID-19 patients, increased immune responses and cytokine storms were found to cause thrombotic disorders. In some cases of severe COVID-19 characterized by respiratory failure and purpuric skin rash, The pathophysiology was suggested to be a microvascular damage syndrome caused by complement pathway activation and an accompanying hypercoagulable state. Purpuric skin lesions revealed a pauci-inflammatory thrombogenic vasculopathy, with C5b-9 and C4d deposition in both affected and normal skin.[24] COVID-19 spike glycoproteins were also found in the cutaneous microvasculature of two of the cases studied, along with C4d and C5b-9.[24] A number of complement regulatory factor polymorphisms, as well as coagulation pathway alterations, can increase a person's sensitivity to increased complement activation and thrombosis.[25]

Livedo racemose and acral ischemia seem to be signs of the procoagulant status and thrombosis correlated to COVID-19 severity because both lesions showed thrombotic vasculopathy in the skin vasculature and deposition of IgM, fibrin, C3 and C5b-C9, which indicate an active complement pathway. Lab findings that consist of elevation of D-dimer, INR and fibrinogen levels support this hypothesis.[26]

Multisystem inflammatory syndrome (MIS), this syndrome is seldom associated with Kawasaki disease-related coronary artery aneurysms, which occur in less than 10% of cases.[27] MIS-C typically affects children over the age of seven who are of African or Hispanic origin and has a higher level of inflammatory markers.[28] Many cases of MIS have been linked to coagulopathy, as neutrophil extracellular traps (NETs) play a key role in inducing thrombosis.[29] The latency between the peak of COVID-19 cases and the rise of MIS-C cases was several weeks in most investigations, suggesting that MIS-C may be an immune-mediated complication rather than a direct viral role in pathogenesis.[30]

Overactivation of the innate immune system results in a hyperinflammation syndrome with massive cytokine release, which is manifested by multiorgan damage and generalized systemic micro thrombosis, which is similar to antiphospholipid syndrome, disseminated intravascular coagulation, and thrombotic microangiopathy. The presence of anticardiolipin, anti-2 glycoprotein I antibodies, and lupus anticoagulant target phospholipid proteins was documented in many cases of COVID-19 affected individuals which can be explained by the fact that the S1 and S2 subunits of the S protein of the virus might form a phospholipid-like epitope that induces the generation of antiphospholipid antibodies (molecular mimicry).[7,31,32] Another possibility is that oxidative stress caused by SARS-CoV-2 changes the conformation of 2-glycoprotein I in host cells, creating a neoepitope for antibody generation.[33] The release of tissue factor from endothelial cells ,platelet activation, mitochondrial dysfunction, oxidative stress, complement activation ,and increased expression of a glycoprotein IIb–IIIa, All of these potential mechanisms could explain the pathogenesis similarities between COVID-19-induced coagulopathy and other systemic microangiopathies.

Severe COVID-19 infection is connected to disseminated intravascular coagulation (DIC) with a 3% incidence.[4] DIC can occur with infections (sepsis), burns, malignancy, vasculopathies, and autoimmune diseases. Ist is characterized by widespread coagulation activation, which results in fibrin buildup in the vasculature, organ failure, clotting factor and platelet consumption, and life-threatening bleeding. DIC has various presentations in the skin: purpura (83%), petechiae (61%), bleeding from IV sites (39%), palpable purpura (32%), hematomas (31%), acral cyanosis (25%), hemorrhagic bullae (19%), gangrene (17%), and purpura fulminans, which results from both hemorrhagic and thrombotic mechanisms.[34] On histological examination, fibrin thrombi in capillaries do not have the inflammation associated with vasculitis.

COVID-19 associated coagulopathy (CAC) and DIC overlap is not uncommon, but increased levels of both fibrinogen and D-dimer, as well as normal platelet count in CAC, are general measures to differentiate. In addition to that, bleeding tendency is a feature of DIC, not CAC. But this is not constant, as in the thrombotic phenotype of DIC, the bleeding event is uncommon. The diagnostic criteria of CAC are proposed as (A) proven COVID-19 and (B) two or more of the following criteria: (1) decrease in platelet count (less than 150×109/l); (2) increase in D-dimer (more than two times the upper limit of normal); (3) >1 s prolonged prothrombin time or International normalized ratio (INR) >1.2; (4) decrease in fibrinogen level; (5) presence of thrombosis (macro thrombosis including deep vein thrombosis/venous thromboembolism, thrombotic stroke, acute coronary syndrome, limb artery thrombosis, mesenteric artery thrombosis, etc., and/or micro thrombosis including skin, acral lesions, etc.). “Risk of CAC” is defined as one of above five criteria and one of following criteria: (i) increase in fibrinogen level; (ii) increased von Willebrand factor (VWF) (more than two times the upper normal limit); (iii) presence of lupus anticoagulant and/or high-titer antiphospholipid antibodies.[34] COVID-19 associated coagulopathy (CAC) is localized initially but can progress to disseminated intravascular coagulation (DIC) when the disease progresses.[34] Diagnostic criteria for overt DIC: Platelet count, cells x 109/l, ≥100 (0), 50 to <100 (+1), <50 (+2), elevated levels of a fibrin-related marker (e.g. D-dimer, fibrin degradation products No increase (0), moderate increase (+2), severe increase (+3), prolonged PT, seconds <3 (0), 3 to <6 (+1), ≥6 (+2), fibrinogen level, g/l ≥1 (0), <1 (+1) [35].

In our practice, we encountered this overlap between CAC and DIC in a 12-year-old male child with no previous medical history, who was infected with COVID-19, as confirmed by PCR and serology, and developed retiform purpura on his right thigh and leg after 4 days, which progressed to painful cutaneous necrosis (Figure 1 A and B). The presence of thrombocytopenia (138 per microliter), very high D dimer (3325 ng/ml), normal fibrinogen level (3.6 g/l), short thrombin and prothrombin times, and normal activated partial thromboplastin time, all may support the diagnosis of COVID-19 associated coagulation (CAC). Furthermore, low levels of antithrombin 3 (64% range (90-115%)) may be involved in the pathogenesis of thrombus formation in this case. The hemodynamic instability of the patient with multiorgan involvement, in addition to negative blood cultures and bacterial toxins, and the absence of bleeding tendency, all make the thrombotic phenotype of DIC an acceptable description of this condition.

Heparin-induced thrombocytopenia with thrombosis also have been reported in literature during COVID19 pandemic, with the positive standard platelet activation assays like anti-platelet factor 4 (PF4)/heparin antibodies, with Serotonin release assay SRA, despite absence of risk factors in some patients like female gander or recent surgical interventions.[8,36,37] The incidence of HIT in COVID-19 patients was estimated to be 0.2% and raised up to 2.2% in critically ill patients. The median period from the start of heparin to the diagnosis of HIT was 13.5 days (10.75-16.25 days).[38] Heparin's widespread use may increase the risk of HIT, complicating patient management by exacerbating thrombocytopenia and heightening thrombotic hazards. Early detection is critical for treatment programs (avoidance of platelet transfusion and use of anticoagulants other than heparin). The immune system's exaggerated response to COVID-19 leads to platelet activation and PF4 release, which may stimulate anti-PF4/H Ab production.[39] Heparin (low molecular weight and unfractionated) skin necrosis with normal platelet count has also been reported.

Calciphylaxis and warfarin induced necrosis, especially in high-risk populations, are two more unusual connections to consider when evaluating retiform purpura and skin necrosis in COVID-19 infected patients. The presence of comorbidities in COVID-19 patients like longstanding end stage kidney disease, female gender, secondary hyperparathyroidism due to autoimmune hypothyroidism, hypercalcemia, hyperphosphatemia, use of warfarin and chronic prednisone use, in addition to the hypercoagulable state of this virus infection, can increase the possibility of calciphylaxis.[40,41] The median period from drug beginning to the onset of warfarin-induced skin necrosis (WISN) is 5 days (range 3 to 10 days).[42] There was also evidence of a late-onset necrosis that occurred months to years after commencing warfarin. It may also occur in people who have previously tolerated warfarin and are starting medication again. There have also been reports of cases arising within days of stopping warfarin. WISN is thought to be due to high loading doses of warfarin, paradoxical induction of hypercoagulability (due to a drop in protein C levels), and inadequate heparinization prior to warfarin initiation. Inherited or acquired protein C deficiency, antithrombin III deficiency, and factor V Leiden mutations predispose to WISN. Concurrent exits of HIT and WISN have also been reported.[42]

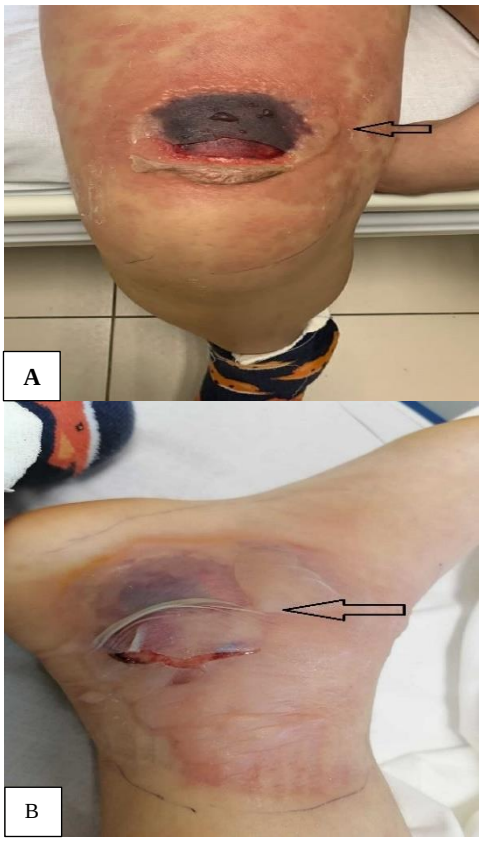

Figure 1 (A and B): A 12-year-old male with a COVID-19 infection who presented with skin necrosis. The image shows a skin lesion on the lower third of the right thigh, a circular patch of black eschar with a 7 cm diameter surrounded by a rim of flaccid blisters, skin sloughing, and hyperemia (arrow). with diffuse erythema and slight scaling of surrounding areas; the image shows an acute inflammatory process of skin located on the medial side of the right lower leg, represented by a large irregular patch with well-defined borders, up to 15 cm in diameter; with surrounding hyperemia and erythema, the central black necrosis (arrow) is covered with flaccid blisters and sloughed epidermis.

Another cause of skin necrosis in COVID-19 patients is necrotizing fasciitis, a life-threatening infection that is characterized by a rapid evolving necrosis of soft tissue. The patient will be hemodynamically unstable, toxic, with a fever and severe out of proportional pain. The relationship between necrotizing fasciitis and COVID-19 infection has not been well defined in the literature, but some authors speculated that the lymphopenia associated

with COVID-19 infection may play a role in secondary bacterial superinfection development.[43,44] It is a bacterial infection caused by multiple microorganisms such as group A *Streptococcus*, *Staphylococci*, *Clostridium perfringens*, and anaerobic strains (*Escherichia coli*, *Bacteroides fragilis*). Bacteria multiply and produce toxins and enzymes that cause thrombosis in blood vessels.

CONCLUSIONS

Cutaneous necrosis in COVID-19 patients during the pandemic period, according to this review, is not rare. possibly It is simple to diagnose and recognize this dermatological condition, but determining the causal variables and their function in pathogenesis is a complex and difficult task. It's also tough to categorize because it affects people of all ages, regardless of gender, ethnicity, or health status. All hypotheses discuss the direct viral role, the immune system's hyperinflammatory state with cytokine storm, the hypercoagulable state with vasculitis, anticoagulant therapy complications, and deep secondary necrotizing infections as possible interactions that lead to necrosis, which can result in serious outcomes such as disseminated intravascular coagulation if not properly treated.

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