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REVIEW ARTICLE

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Recognition and treatment of devastating vasculopathic systemic disorders: Coronavirus disease 2019 and rickettsioses

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Abstract

Cutaneous involvement can be an important sign of both COVID-19 and rickettsioses. Rickettsial infections may be first evident as an exanthem with eschars as a key finding. In contrast, eschars and necrotic lesions can be seen in critically ill COVID-19 patients. Both illnesses share a similar mechanism of infecting endothelial cells resulting in vasculopathy. *Rickettsia parkeri* and *Rickettsia 364D* are both characterized by eschars unlike *Rickettsia rickettsii*. Other eschar causing rickettsioses such as *Rickettsia conorii*, *Rickettsia africae*, and *Orientia tsutsugamushi* are commonly diagnosed in people from or having traveled through endemic areas. While there is no consensus on treatment for COVID-19, rickettsioses are treatable. Due to possibly serious consequences of delayed treatment, doxycycline should be administered given an eschar-presenting patient's travel history and sufficient suspicion of vector exposure. The proliferation of COVID-19 cases has rendered it critical to differentiate between the two, both of which may have overlapping vasculopathic cutaneous findings. We review these diseases, emphasizing the importance of cutaneous involvement, while also discussing possible therapeutic interventions.

KEYWORDS
insect bite, therapy-systemic, urticaria, vasculitis

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is responsible for over 118 million cases globally and over 2.6 million deaths as of March 11, 2021.[1] Aside from pulmonary symptoms, COVID-19 patients can also develop multiple organ dysfunction of the liver, kidney, heart, and immune system.[2] Dermatological manifestations merit considerable scrutiny. Skin lesions linked with COVID-19 have been grouped into six categories with three distinct indicative patterns: vesicular, vasculopathic, and chilblains-like. The vasculopathic lesions in COVID-19 can resemble the changes commonly seen in eschar causing rickettsioses.[3] Some COVID-19 patients present with erythematous maculopapular exanthems at the same time as other symptoms.[4] Rickettsioses are zoonotic infections that utilize ticks and mites as their main vectors. Some rickettsial infections have a mild course irrespective of treatment, while untreated rickettsioses such as Rocky Mountain spotted fever, Mediterranean spotted fever, and scrub typhus can have mortality rates ranging from 20% to 60%.[5] Undiagnosed rickettsial infections and severe acute respiratory coronavirus 2 (SARS-CoV-2) infections can be problematic, as they can lead to severe systemic complications with similar pathophysiology of infecting endothelial cells, resulting in vascular changes.[6,7] However, patients with rickettsioses can be easily treated with tetracyclines, whereas there is no clear consensus on treatment for patients with COVID-19 as yet.[5]

The *Rickettsia* genus consists of obligate, gram-negative intracellular coccobacilli that have been divided into four subgroups: the typhus group, spotted fever group (SFG), ancestral group, and transitional group.[8] Scrub typhus has been included in this review, as its manifestations are similar to many rickettsioses, despite being classified in the *Orientia* genus.[9] All rickettsioses share the following triad of symptoms: fever, rash, and possible eschar. These infections

typically appear as erythematous macules that can develop into petechiae or vesicles. Eschars represent cutaneous necrosis and a pivotal diagnostic clue in most rickettsioses, except for Rocky Mountain spotted fever (RMSF). These lesions can be mistaken for *Staphylococcus aureus* abscesses and other pyogenic infections.[10] Travelers with suspected skin infections and eschars are commonly infected with *Rickettsia*, *S. aureus*, or *S. pyogenes*.[11] When mistaken for another etiology, patients are often treated with beta-lactam antibiotics, which have no efficacy on the gram-negative *Rickettsia*. When not considereing these clinical diagnoses, rickettsial diseases can be missed, leading to severe consequences. There are three main rickettsioses associated with eschars in the United States: *Rickettsia parkeri*, *Rickettsia akari*, and *Rickettsia 364D*. Across the world, *Rickettsia conorii*, *Rickettsia africae*, and *Orientia tsutsugamushi* are common causes of febrile illnesses associated with eschars.[12] Other eschar causing rickettsioses from around the world such as *Rickettsia slovaca*, *Rickettsia sibirica*, *Rickettsia japonica*, *Rickettsia australis*, and *Rickettsia heilongjiangensis* are not included as they are less likely to be encountered in practice.[5,13] Although *Rickettsia rickettsii* does not typically cause an eschar, it has been included in this review.[14]

2 | METHODS

This review includes articles from searching the databases "PubMed" and "Google Scholar" using the keywords "COVID-19", "SARS-CoV-2", "vasculopathic", "endotheliitis", "Rickettsioses", and "eschar". Other keyword terms searched were related to the specific *Rickettsia* discussed in this review. Articles that were released on or prior March 8, 2021 were included.

3 | PATHOGENESIS

Rickettsial species have a unique natural disease course for bacteria. The genus has a high affinity for the endothelium lining of blood vessels, resulting in vascular inflammation and permeability.[7] Bacterium from the SFG escape from the cell and damage the endothelial cell's semi-permeable membrane. The pathogenesis of the cutaneous eschars arises from focal areas of endothelial proliferation and perivascular mononuclear cell infiltration, causing third-spacing. These vascular lesions, along with thrombosis and necrosis of capillaries, form eschars.[13] The human immune response in clearing the infection is largely T-cell mediated. Cell-mediated release of interferon-gamma activates the infected endothelial cells to present intracellular rickettsial antigens to CD8+ T-cells killing the infected cells.[13]

While the pathophysiology of COVID-19 is still being delineated, in vitro studies of blood vessel organoids indicate that SARS-CoV-2 can directly infect endothelial cells.[15] Angiotensin-converting enzyme 2, a receptor expressed in endothelial cells and the epithelial lining in the lungs, small intestine, and heart, acts as the entry point for SARS-CoV-2.[16] Histological analyses from COVID-19 patients show viral inclusion bodies and inflammatory cells within endothelial cells, leading to endotheliitis.[6] This finding indicates that the inflammation is a direct response to the virus infecting the cell and not a secondary response. More specifically, critically ill patients who developed thrombotic retiform purpura had higher SARS-CoV-2 proteins in the endothelium in contrast to those with milder presenting disease that developed chilblains like lesions.[17] This cutaneous manifestation in critically ill patients may be the result of complement activation by the spike proteins of SARS-CoV-2.

As both rickettsial infections and COVID-19 can lead to multiple organ dysfunction, it is critical to examine the role that cytokines play. A lack of anti-inflammatory regulatory cytokines, such as IL-10 in scrub typhus, may contribute to a cytokine storm and the development of acute respiratory distress syndrome (ARDS).[18] Other pro-inflammatory cytokines, such as IL-6, are also produced in patients with rickettsia-infected endothelial cells due to the activation of nuclear factor κB.[13] The role of cytokines has been investigated more in relation to COVID-19 due to the devastating sequelae of these cytokine storms. High levels of IL-6 are affiliated with the secretion of vascular endothelial growth factor and reduced expression of E-cadherin on endothelial cells, resulting in increased vascular permeability. Elevated levels of other chemokines, including but not limited to IL-10, are associated with increased severity of illness and outcomes such as ARDS, sepsis, and multiple organ failure.[16]

4 | COVID-19

While common clinical symptoms of COVID-19 include fever, cough, diarrhea, fatigue, and hyposmia, a variety of cutaneous presentations may be evident. In general, dermatologic findings in patients can be categorized as maculopapular, vesicular, chilblain-like, urticaria, and vascular.[3] Maculopapular exanthems typically arise on the trunk and can spread diffusely while sparing the palms, feet, and face. On histology, lesions have a perivascular lymphocytic infiltrate with variable presentation of eosinophils and histiocytes depending on the time of onset.[19-22] Urticarial lesions, a common skin manifestation of COVID-19, tend to be generalized and present either prior to or simultaneously with other clinical symptoms.[19,20,23] Both urticarial and maculopapular lesions may also be a consequence of adverse drug reactions in patients treated with combination pharmacological therapies consisting of antivirals and antimalarials, with generalized pustular figurate erythema linked specifically with hydroxychloroquine.[3,21,22,24] Therefore, caution should be exercised when diagnosing patients with these mucocutaneous reactions.

There are two presentations of vesicular exanthems: localized and diffuse.[3] Diffuse vesicular rashes are polymorphic while localized vesicular rashes are monomorphic and involve the trunk. These exanthems can be confused with chickenpox or other viral infections.[19-21,25] Chilblain-like eruptions are more commonly found in younger patients and appear erythematous and edematous. They seem to preferentially affect the toes and fingers asymmetrically and indicate a better prognosis.[3,19,21,22] Cases of chilblain-like lesions persisting in patients for over 60 days after initial onset have also

been reported. Despite patients with these lesions having milder infections, their persistence indicates continued inflammation.[26] Vascular manifestations such as livedoid eruptions, necrosis, and dry gangrene are more likely to present in severely ill patients. These lesions can be found in the sacrum region as well as the extremities causing acro-ischemia.[3,19,21,27]

5 | RICKETTSIOSES

Within the SFG, RMSF has the highest mortality rate of up to 40%-50% with delayed initiation of treatment, and has been increasing in incidence within the United States.[14] *R. rickettsii*, the pathogen responsible for RMSF, is most commonly transmitted by *Dermacentor variabilis* east of the Great Plains and *Dermacentor andersoni* in the Rocky Mountains and western states of the United States.[28] RMSF does not typically present with an eschar. Although high fever is the most common symptom, patients also have rash, headaches, nausea, and diarrhea. The rash typically begins as blanching pink macules that often progress to either maculopapular or petechial morphologies due to the leakage of fluid from vasodilated vessels and hemorrhage, respectively. The erythematous macules usually first appear on the wrist and ankles and then progress towards the trunk. Due to non-specific abdominal symptoms, RMSF is often confused with gastroenteritis.[28] Without intervention, RMSF can cause several systemic complications such as septicemia, gangrene, hepatosplenomegaly, and central nervous system abnormalities.[29]

Rickettsialpox is caused by *Rickettsia akari*. Unlike other rickettsioses, it is not transmitted by ticks, but instead by the mouse mite *Liponyssoides sanguineus*, which infests the common house mouse *Mus musculus*. Rickettsialpox was first described in New York City and has since been identified across urban centers in Europe, North America, Asia, and South Africa.[5] Once bitten by the mouse mite, patients develop a high fever, papulovesicular rash, and painless eschar (Figure 1). The rash is relatively sparse, non-pruritic, and monomorphic. Other symptoms such as myalgias, lymphadenopathy, and headaches have also been reported.[30] Rickettsialpox can be misdiagnosed as hand-foot-mouth disease, herpes, and most commonly, chickenpox due to the appearance of vesicules.[31]

Rickettsial parkeri rickettsiosis is mainly transmitted by *Ambylomma maculatam* along the southeastern coastal area of the United States and some inland states.[14,32] Although it has a milder clinical presentation than RMSF, its prevalence may be higher than previously thought due to non-selective assays which cannot sufficiently distinguish between the antigens associated with *R. rickettsii* and *R. parkeri*.[32] Common symptoms include mild fever, exanthemas, and eschars which appear 6 to 10 days after being bitten by an infected tick. Patients can have multiple eschars that are typically crusted, nonpruritic, and surrounded by an indurated, erythematous halo. In addition, some may develop a maculopapular or vesiculopapular eruption.[33]

Pacific Coast tick fever (PCTF) is also endemic to the United States and is caused by *Rickettsia* 364D transmitted by *Dermacentor occidentlis*. Patients with PCTF typically have an eschar, multiple in some cases. Other common symptoms include fever, general malaise, myalgias, headache, and lymphadenopathy. In contrast to RMSF, patients with PCTF often have a milder presentation without a rash. However, some patients may still require hospitalization.[34]

Rickettsia conorii causes Mediterranean Spotted Fever and has several different strains with varying case-fatality rates. Transmitted by the *Rhipicephalus sanguineas*, this pathogen is found throughout Europe, the Indian subcontinent, and Africa. It is typically associated with an eschar as a result of an indurated papule with central necrosis at the inoculation site along with a widespread maculopapular rash. Fever, headaches, and myalgias are other non-specific symptoms.[35]

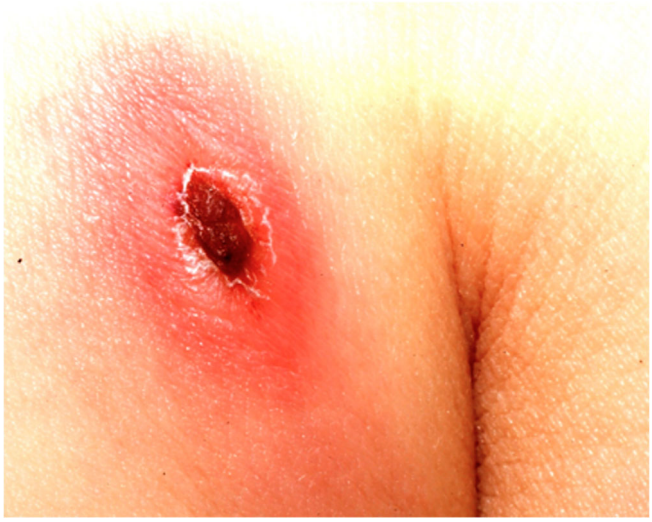

FIGURE 1 Rickettsialpox. Originally misdiagnosed as chickenpox until the discovery of an eschar, Rickettsialpox produces vesicles and is an urban disease

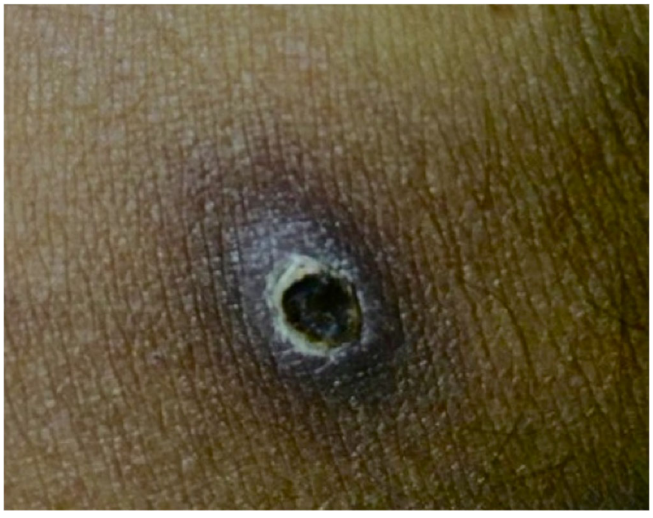

FIGURE 2 African tick bite fever. *Rickettsia africae* infection, mistaken for a common pyogenic abscess, in a person returning from a safari in the Republic of South Africa

An unusual manifestation of this disease is the development of a fern-leaf shaped necrotic skin rash and purpura fulminans, which can progress to necrosis. Some of the most common infectious agents that can also cause purpura fulminans include *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and methicillin-resistant *S. aureus*.[36]

Rickettsia africae causes ATBF (Figure 2). Transmitted by the *Amblyomma herabeum*, *R. africae* resides mainly in sub-Saharan Africa. Despite its name, ATBF is also endemic in the Caribbean, and consideration should extend to those travelers.[5] ATBF is the most common rickettsioses among tourists who have traveled to endemic regions in sub-Saharan Africa on safaris.[37] It commonly presents with multiple eschars, a generalized cutaneous exanthem, fever, myalgias, and headaches. An erythematous halo and maculopapular rash may surround the black crusted inoculation eschar.[38] While this disease typically has a benign course, patients can also develop acute myocarditis or cranial subacute neuropathy.[37]

Scrub typhus, an infection caused by *Orientia tsutsugamushi*, is widespread throughout much of Southeast Asia and can have high mortality rates between 30-70% if left untreated. This organism is transmitted via *Leptotrombidium* mites in more rural areas.[9] While non-specific symptoms include fevers, headaches, myalgias, conjunctivitis, lymphadenopathy, and nausea, many patients also exhibit eschars.[9] The differences in eschar presentation between Asian

TABLE 1 Most common eschar causing rickettsioses

Organism	Disease	Vector(s)	Geographic distribution	Eschar	Rash	Differential diagnoses
Rickettsia rickettsii[14,28,29]	Rocky mountain spotted fever	*Dermacentor variabilis* *Dermacentor andersoni* *Rhipicephalus sanguineas*	East coast of US Rocky Mountain states Mexico	Rare	Initially, maculopapular on wrists, palms, and soles but becomes petechial	Pneumonia Gastrointestinal illness Aseptic meningitis Meningococcemia Appendicitis Acute viral hepatitis Lyme Disease Q Fever COVID-19
Rickettsia africae[5,10]	African tick bite fever	*Ambylomma herbaeum, Ambylomma variegatum*	Sub-Saharan Africa, Caribbean	Common, typically have multiple	May not have a rash but if present, maculopapular or vesicular	Typhoid Malaria Cutaneous leishmaniasis African trypanosomiasis
Rickettsia conorii[35,40]	Mediterranean spotted fever	*Rhipicephalus sanguineas*	Europe, northern Africa, east Asia	Common	Maculopapular rash on palms and soles	Measles Leptospirosis Immune complex vasculitis Toxicoderma
Orientia tsutsugamushi[9,41]	Scrub typhus	*Leptotrombidium* mites	South-east Asia	Common	Maculopapular rash	Typhoid Dengue Leptospirosis Upper respiratory infection Malaria
Rickettsia parkeri[14,32,33]	No defined disease name	*Ambylomma maculatum* *Ambylomma triste*	South-eastern US mainly along the coast South-western US, Mexico, Argentina, Brazil, Uruguay	Common, typically have multiple	Maculopapular or vesiculopapular with non-pruritic lesions	Dengue Rocky Mountain spotted fever Leptospirosis
Rickettsia akari[5,30,31]	Rickettsialpox	*Liponyssoides sanguineas*	Urban centers across US, Europe, Korea	Common	Maculopapular rash that can be vesicular	Chicken pox Cutaneous anthrax Hand, foot, and mouth disease Herpes
Rickettsia 364D[34,42]	Pacific Coast tick fever	*Dermacentor occidentalis*	Southern Oregon through most of California and northern Mexico	Common-typically have multiple	Often does not present with rash	Cutaneous anthrax Boil

countries may be attributed to variability in skin tone and low detection of these eschars.[9] While patients do not typically develop a rash, any rash that does appear is often maculopapular.[39] Complications included jaundice, altered mental status, ARDS, hepatosplenomegaly, myocarditis, and upper gastrointestinal bleeding.[9,39]

6 | DISCUSSION AND TREATMENTS

Given the prevalence of COVID-19 throughout the world, it is critical to distinguish this condition from endemic rickettsioses which may have similar dermatologic findings (See Table 1 and 2). COVID-19 and RMSF both can cause a maculopapular rash, commonly on the trunk and upper limbs, and can progress to ARDS.[3,4,14,16,19] While some incidences of the exanthems may be drug induced, others can be attributed to the virus itself.[19,20] Patients with COVID-19 have also been seen with a pruritic vesicular, varicella-like rash.[3,4,19,25] As chickenpox and rickettsialpox have a similar presentation, it is essential to look for eschars in those with vesicular lesions.[30,31] As both rickettsioses and COVID-19 progress, there can be significant vasculopathy leading to skin necrosis. While COVID-19 is not commonly affiliated with the presence of eschars, black eschars in the sacral region at late stages may be seen.[27] These instances may be explained by pressure from recumbency and the COVID-19 induced hypercoagulable state. There have been reports of patients developing necrotic lesions in the maxillary and acral regions.[4,20] Furthermore, the need for amputations due to irreversible injury has been documented in patients with both COVID-19 or rickettsioses.[14,43] Although disseminated intravascular coagulation (DIC) has been strongly associated with severely ill COVID-19 patients, DIC is rarer in patients with rickettsioses.[3,13] The cutaneous manifestations of DIC in patients with COVID-19 have varied from acro-ischemia to petechial patterns.[44] The multi-organ involvement in RMSF, Mediterranean spotted fever, and scrub typhus may have a similar presentation as in COVID-19, and therefore should be considered when examining patients with fever, rash, and a history of possible exposure to ticks, usually between the months of April to September.[2-4,9,25]

While the clinical presentation of rickettsioses differs based on the organism responsible, there are many similarities. In general, patients are first seen with a high fever and an exanthem. Other symptoms include lymphadenopathy, eschars, hepatosplenomegaly, headaches, nausea, and diarrhea. A full patient history may reveal potential exposure to arthropods such as ticks or mites as well as travel. Co-infections should be carefully considered as they may account for some of the symptoms.[10] Furthermore, due to the non-pruritic nature of eschars, patients may not even notice them and, therefore, a thorough examination of the patients should be conducted in cases of an unspecified febrile illness. Other differential diagnoses for a patient with a fever and eschar include mucormycosis, anthrax, necrotizing fasciitis, and bacterial or fungal sepsis (Figure 3).[45] It is important to start treatment immediately if there is sufficient suspicion of a rickettsial infection, as delayed treatment

TABLE 2 Features of cutaneous exanthems in COVID-19 and rickettsioses

		Maculopapular[4,14,19,33,39]	Urticaria[4,19,20,23]	Chilblain-like lesion[4,19]	Vesicular[4,14,25,30,33]	Vascular (livedo/purpura/necrosis)[4,19,36]
Organism	SARS-CoV-2	SARS-CoV-2 present	SARS-CoV-2 present	SARS-CoV-2 present	SARS-CoV-2 present	SARS-CoV-2 present
	Rickettsia	*R. rickettsii*, *R. conorii*, *R. parkeri*, *O. tsutsugamushi*	Not present	Not present	*R. akari*, *R. africae*, *R. parkeri*	*R. conorii*, *R. rickettsii*
Distribution	SARS-CoV-2	Trunk and extremities sparing palms and soles	Trunk/generalized	Feet and hands	Trunk, extremities	Trunk, extremities
	Rickettsia	Palm and soles but can move towards trunk	Not present	Not present	Face, trunk, extremities	Trunk, extremities sparing the face
Onset compared to other symptoms	SARS-CoV-2	Early or Concurrent	Early or concurrent	Late complication	Concurrent or late	Concurrent
	Rickettsia	Initial presentation of fever followed by maculopapular rash	Not present	Not present	Becomes evident with an eschar followed by vesicular exanthem	Late complication
Prognosis	SARS-CoV-2	Not significant	Not significant, resolves in 1 week	Not significant, resolves in ~2 weeks	Not significant	Late stage complication suggesting severe disease
	Rickettsia	Late onset of rash indicates a poor prognosis in RMSF patients	Not present	Not present	Not significant, typically self-limiting	Late stage complication suggesting severe disease

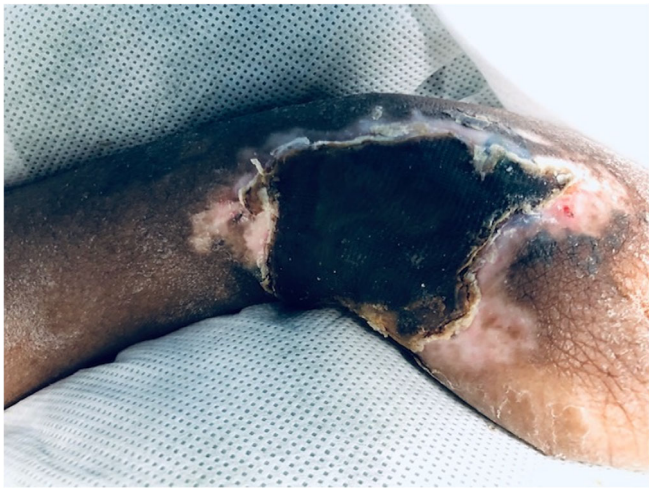

FIGURE 3 Candida eschar (Reprint with permission, Schwartz RA, Kapila R: Cutaneous Manifestations of a 21st Century Worldwide Fungal Epidemic Possibly Complicating the COVID-19 Pandemic to Jointly Menace Mankind. Dermatol Ther 2020:e13481)

is associated with fatalities and complications. Other potential differential diagnoses are included for each eschar-causing rickettsial disease along with its geographic distribution (See Table 1). Irrespective of the age of the patient, doxycycline is the treatment of all rickettsioses.[5]

Although a wide variety of therapeutic agents are being explored for COVID-19, remdesivir, an anti-viral agent, is the only approved drug by the FDA for COVID-19 treatment.[46] Some of the other therapies being investigated include hydroxychloroquine, antivirals such as ritonavir and lopinavir, glucocorticoids, ivermectin, azithromycin, non-steroidal anti-inflammatory drugs, tetracyclines, and thalidomide.[16,24,46] A preliminary clinical trial study indicates the combination of ivermectin and doxycycline reduced the progression of COVID-19, time of recovery, and mortality rate.[47] Although further studies need to be conducted, doxycycline may play an important role in treatment through the downregulation of cytokines responsible for the increased vascular permeability. This potential overlap in treatment further elucidates the similarities in pathophysiology of the two diseases. Iloprost, a prostacyclin receptor agonist, has shown efficacy in managing COVID-19 induced systemic inflammation. Through the vasodilation of vessels and suppression of IL-6 and tumor necrosis factor, Iloprost improved digital ischemia in three patients. Further studies need to be conducted to determine the effect of this anti-inflammatory that is often used to treat other peripheral vasculopathies.[48] Crizanlizumab, a monoclonal antibody against P-selectin, is another pharmacotherapy undergoing clinical trial. By blocking P-selectin, and consequently platelet adherence and leukocyte rolling, Crizanlizumab may be able to prevent vascular inflammation.[49]

Diagnosis of rickettsioses is usually clinical, with epidemiological considerations. Confirmatory testing involves using indirect immunofluorescent assays to detect seroconversion, polymerase chain reaction (PCR), immunohistochemistry (IHC), or culture. Seroconversion refers to a 4-fold change in IgG titers between the 1 week of illness and 2 to 4 weeks later.[50]

7 | CONCLUSION

The dermatological manifestations of COVID-19 and rickettsioses have several overlapping characteristics. For instance, both diseases can cause maculopapular, vesicular, and vascular exanthems. Furthermore, COVID-19 and rickettsial infections cause increased vascular permeability due to endotheliitis and can lead to complications such as ARDS, gangrene, and myocarditis in patients. COVID-19 and rickettsioses can be distinguished by the presentation of an eschar in most cases as necrosis and eschars are a late complication in COVID-19 patients. RMSF, however, does not usually present with an eschar and can be distinguished from COVID-19 by the distribution of the maculopapular rash, as COVID-19 spares the palms and soles while *R. rickettsia* spreads from the palms and soles towards the trunk. In the context of the COVID-19 pandemic, considering these overlooked rickettsioses can lead to improved early recognition, timely therapies, and enhanced patient care in areas with the pertinent tick vectors.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

All four authors made substantial contributions to the conception, design and/or acquisition of the data in this work and approved the final submission.

DATA AVAILABILITY STATEMENT

Data availability statement: Data that supports the following information are available from the first author upon reasonable request.

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