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 africaine*, 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

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.5 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. Travelers with suspected skin infections and eschars are commonly infected with Rickettsia, S. aureus, or S. pyogenes. When mistaken for another etiology, patients are often treated with beta-lactam antibiotics, which have no efficacy on the gram-negative Rickettsia. When considering 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. 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. Although Rickettsia rickettsii does not typically cause an eschar, it has been included in this review.

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

Rickettsia 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. 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. 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.

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. 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. Histological analyses from COVID-19 patients show viral inclusion bodies and inflammatory cells within endothelial cells, leading to endotheliitis. 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. 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). 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 KB. 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.

4 | COVID-19

While common clinical symptoms of COVID-19 include fever, cough, diarrhea, fatigue, and hypoxemia, 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. 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. Urticarial lesions, a common skin manifestation of COVID-19, tend to be generalized and present either prior to or simultaneously with other clinical symptoms. 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 antimicrobials, with generalized pustular figurate erythema linked specifically with hydroxychloroquine. Therefore, caution should be exercised when diagnosing patients with these mucocutaneous reactions.

There are two presentations of vesicular exanthems: localized and diffuse. 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. 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. 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. Vas- 
cular 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.  

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.\(^1^4\) *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.\(^2^8\) 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 
wrists and ankles and then progress towards the trunk. Due to non-
specific abdominal symptoms, RMSF is often confused with gastroen-
teritis.\(^2^8\) Without intervention, RMSF can cause several systemic comp-
lications such as septicemia, gangrene, hepatosplenomegaly, and 
central nervous system abnormalities.\(^2^9\)

*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 mono-
morphic. Other symptoms such as myalgias, lymphadenopathy, and 
headaches have also been reported.\(^3^0\) *Rickettsialpox* can be misdi-
agnosed as hand-foot-mouth disease, herpes, and most commonly, 
chickenpox due to the appearance of vesicles.\(^3^1\)

*Rickettsia parkeri* ricketttsiosis is mainly transmitted by 
*Amblyomma maculatum* along the southeastern coastal area of the 
United States and some inland states.\(^1^4,3^2\) Although it has a milder 
clinical presentation than RMSF, its prevalence may be higher than 
previously thought due to non-selective assays which cannot suffi-
ciently distinguish between the antigens associated with *R. rickettsii* and *R. parkeri*.\(^3^2\) 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.\(^3^3\)

Pacific Coast tick fever (PCTF) is also endemic to the United 
States and is caused by *Rickettsia 364D* transmitted by *Dermacentor 
occidentis*. 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.\(^3^4\)

*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.\(^3^5\)
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 herabaum*, *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

| Organism          | Disease                  | Vector(s)                        | Geographic distribution | Eschar       | Rash                      | Differential diagnoses                          |
|-------------------|--------------------------|----------------------------------|-------------------------|--------------|--------------------------|-----------------------------------------------|
| *Rickettsia rickettsii* | 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* | African tick bite fever | *Amblyomma herabaum*, *Amblyomma 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* | 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* | Scrub typhus | *Leptotrombidium mites* | South-east Asia | Common | Maculopapular rash | Typhoid, Dengue, Leptospirosis, Upper respiratory infection, Malaria |
| *Rickettsia parkeri* | No defined disease name | *Amblyomma maculatum*, *Amblyomma 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* | 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* | 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 |

**TABLE 1** Most common eschar causing rickettsioses
countries may be attributed to variability in skin tone and low detection of these eschars. While patients do not typically develop a rash, any rash that does appear is often maculopapular. Complications included jaundice, altered mental status, ARDS, hepatosplenomegaly, myocarditis, and upper gastrointestinal bleeding.

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. While some incidences of the exanthems may be drug induced, others can be attributed to the virus itself. Patients with COVID-19 have also been seen with a pruritic vesicular, varicella-like rash. As chickenpox and rickettsialpox have a similar presentation, it is essential to look for eschars in those with vesicular lesions. 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. 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. Furthermore, the need for amputations due to irreversible injury has been documented in patients with both COVID-19 or rickettsioses. Although disseminated intravascular coagulation (DIC) has been strongly associated with severely ill COVID-19 patients, DIC is rarer in patients with rickettsioses. The cutaneous manifestations of DIC in patients with COVID-19 have varied from acro-ischemia to petechial patterns. 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.

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. 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). 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 |
| --- | --- | --- | --- | --- |
| **Organism** | SARS-CoV-2 | 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. african, R. parkeri | R. conorii, R. rickettsii |
| **Distribution** | SARS-CoV-2 | Trunk and extremities sparing palms and soles | Trunk/generalized | Feet and hands | Trunk, extremities |
| Rickettsia | Palm and soles but can move towards trunk | Not present | Not present | Face, trunk, extremities | Trunk, extremities |
| **Onset compared to other symptoms** | 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 | 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 |
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 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-inflamma-tory 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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