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Letter to the Editor

Rash in a febrile returned traveler from Greece: A case of Mediterranean spotted fever

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Dear Editor,

We herein describe a patient who travelled to Greece and developed fever, rash and multiple eschars on the lower legs and feet bilaterally upon return. Skin biopsy was notable for leukocytoclastic vasculitis with eosinophils. He was empirically treated for presumed rickettsial infection with doxycycline and made a full recovery. While initial rickettsial serology was negative, repeat testing at 2- and 3-weeks post-symptom onset demonstrated sero-reactivity. A full description of his travel, clinical symptomatology, and illness evolution follows.

1. Case

A previously healthy 45-year-old man travelled to Athens, Sparta and Chios Island in Greece for 27 days over the summer for the purpose of visiting friends and relatives (VFR). He noted multiple bites on his lower legs, acquired near a beach. On return to Canada, he developed fever and rash, which started on his legs bilaterally and then spread to his abdomen, thorax, arms, and soles. He was referred from the Emergency Department to our Unit with persistent rash, fever, myalgia and arthralgia. Physical examination revealed a diffuse pruritic and tender maculopapular rash with petechiae and multiple eschars noted on bilateral legs and feet (Fig. 1). Based on initial clinical presentation, rickettsiosis was suspected and doxycycline 100 mg PO BID x 7 days was initiated empirically. Initial rickettsial serology performed at initial consultation during the early acute period of illness was negative, but *Rickettsia* serologies repeated at 2- and 3-weeks post-symptom onset were IgG antibody reactive at a titre of 1:64. A punch biopsy taken from the lower extremity revealed leukocytoclastic vasculitis with the presence of eosinophils.

The patient developed severe abdominal pain while taking doxycycline, and given the drug intolerance, treatment was switched to complete a 1-week course azithromycin, after which all symptoms resolved.

2. Discussion

Mediterranean Spotted Fever (MSF) is an acute febrile illness resulting from infection by the bacterium *Rickettsia conorii*. *R. conorii* is transmitted to humans through contact with the brown dog tick *Rhipicephalus sanguineus*. [1] MSF is endemic to southern Europe, sub-Saharan Africa, the Middle East, the areas surrounding the Black and Caspian Seas, and the Indian subcontinent [1]. *R. sanguineus* is the most common tick in the Mediterranean basin [1]. Approximately 88 % of cases of MSF are diagnosed between the months of June and September [2]. Cases of MSF have been increasing within the Mediterranean, with an incidence of 50 per 100,000 inhabitants, and increasing cases reported in travelers [1]. This case highlights the need for prompt clinical diagnosis and empiric initiation of appropriate treatment antimicrobials given delayed turnaround time and low sensitivity of serology performed in the acutely unwell traveler.

Diagnosis of MSF is based on a combination of high-yield clinical symptoms, such as fever and 'spotted' rash with eschar(s), laboratory investigations, and epidemiological criteria (Table 1) and is commonly treated using doxycycline [1–3]. As in other tick-borne spotted fever rickettsioses, there is an initial asymptomatic incubation period of 6–10 days after which a flu-like illness develops [1]. Over the subsequent 3–5 days, there is development of a diffuse rash involving the palms and soles. The rash is maculopapular in 97 % of cases, but may be petechial in approximately 10 % of cases or rarely, papulovesicular [1]. In an estimated 70 % of cases, there is a characteristic black eschar, also known as *tache noire* at the site of the initial tick bite inoculation [1]. As illustrated by the histopathology on biopsy, once introduced through the saliva of a tick bite, *R. conorii* invades and proliferates in the endothelial cells of small vessels causing endothelial injury, vasculitis, capillary leakage and tissue necrosis.

In addition to the classic triad of fever, rash and headache, other associated symptoms and signs include conjunctivitis, lymphadenopathy and gastrointestinal symptoms, mild transaminitis and acute kidney injury [1–3]. Malignant forms of MSF are more commonly reported in higher risk patient populations such as the elderly, persons with diabetes mellitus, and those with immunosuppression [1]. Complications can affect major organ systems causing encephalitis, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), liver failure, pancreatitis, and peripheral gangrene, with

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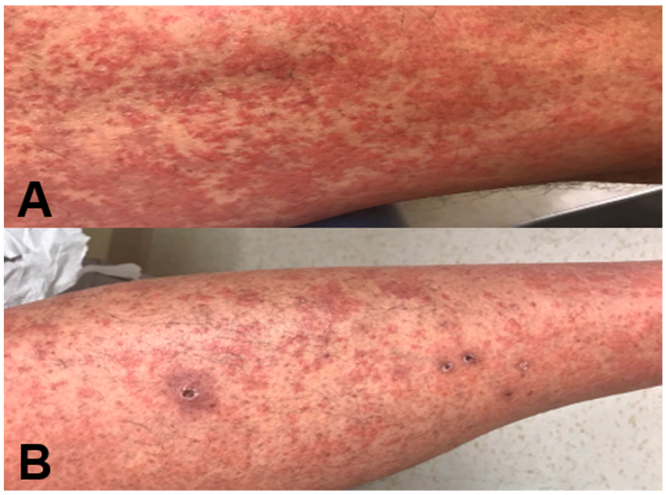

Fig. 1A and B. Maculopapular petechial rash on legs with multiple eschars.

underlying vasculopathy and systemic immune dysregulation from the infection thought to drive multi-organ failure [1]. The diagnosis of MSF is no longer necessarily considered benign as it carries a case fatality of 1–3% in those who are untreated.

3. Diagnosis & treatment

The initial diagnosis of MSF is clinical and treatment should not be delayed for laboratory confirmation. Differential diagnosis is outlined in Table 1. Serologic tests are simple and the most widely used form of testing, with available tests having cross reactivity with various *Rickettsia* species, as illustrated by our patient's seroreactivity to Rickettsia serology. Depending on availability, there are current serologic assays based on micro-immunofluorescence or western blotting which can differentiate between the different species of spotted fever infections [1,4]. When ordering serology, it is important to remember that seroconversion occurs 7–15 days following symptom onset and therefore, repeat testing may be warranted if initially negative [1]. Cell cultures can also be used for diagnosis, but samples should be collected prior to initiation of antibiotics for validity of results [1]. Molecular methods such as polymerase chain reaction (PCR) testing on samples taken from eschar swabs or crust, and from blood or tissue biopsy are the most novel method of diagnosis and can provide species-level diagnosis [1,4]. Tick speciation, if available, may provide information on other diseases potentially transmissible by the vector.

The microbiological diagnosis of MSF is confirmed retrospectively by demonstrating a four-fold or greater rise in convalescent antibody titres compared to acute titres. Typically, an immunofluorescence assay (IFA) for *R. rickettsii* IgG antibodies is applied as evidence for any of the rickettsioses in the spotted fever group, including *R. conorii.* [1] As in the case outlined here, initial serology may be negative, with seroconversion occurring within 7–15 days and lasting for months to years following infection [1,4]. In our case, biopsy revealing leukocytoclastic vasculitis further supported and confirmed the pathophysiology resulting in endothelial damage.

When MSF is suspected, antimicrobial therapy should be started promptly while awaiting confirmatory acute and convalescent serologies. Tickborne rickettsiosis are treated with doxycycline 100 mg orally every 12 hours until afebrile for at least 3 days, with a total duration of at least 5–7 days [1]. Macrolides such as azithromycin may be a reasonable alternative to doxycycline, and should be considered in cases of doxycycline contraindication, intolerance, in children, or pregnancy [1,5]. Fluoroquinolones should be avoided due to possibly more severe clinical course [1].

We have presented a case of a VFR traveler who returned from Greece with a classic clinical presentation of multi-eschar Mediterranean Spotted Fever (MSF) and was successfully treated with azithromycin. The triad of fever, rash, and eschar, along with a compatible travel history, should prompt consideration of rickettsiosis. Persons traveling to endemic regions should practice protective measures such as wearing long sleeved and/or permethrin-impregnated clothing,

Table 1
Major infectious differential diagnosis of fever with diffuse rash in a returned traveler from the Mediterranean.

Infectious Disease	Causative agent, mean incubation period	Key distinguishing features by history and examination	Appropriate diagnostic specimens and microbiological testing	Therapy
Erythema infectiosum	Parvovirus B19, 4–21 days to symptom onset	"Slapped cheek" rash, childhood exanthem, pruritic rash of soles, associated arthropathy and/or arthritis	Primarily a Clinical diagnosis, Serum antibody testing available	Supportive
Measles	Measles paramyxovirus, 10–12 days to prodrome; 14 days to rash	Absence of immunization history; rash beginning on face; Koplik spots	Serum antibody testing, Throat and/or nasopharyngeal swab for PCR	Supportive; vitamin A if critically ill
Mononucleosis	Epstein-Barr virus (EBV), 6-weeks to symptom onset in primary EBV; antibiotic-associated rash can occur 1–4 days after antibiotics initiated	Antecedent use of antibiotics for group A streptococcal infection	Serum heterophile antibody, serum EBV-specific antibody testing	Supportive; exclusion from contact sports x 12-weeks
Mpox	Mpox *Orthopoxvirus,*	Well-circumscribed centrally umbilicated lesions, with morphological progression from macules through to pustules, history of sex-on-premises establishment	Molecular testing of lesion exudate or aspirate (by PCR or next-generation sequencing); Culture of lesion exudate or aspirate	Supportive Pain control Tecovirimat as a first-line counter-measure for those at risk of severe Mpox; Tecovirimat, brincidofovir, and/or vaccinia immune globulin for those with severe disease
Scarlet fever	Group A *Streptococcus* (*S. pyogenes*), rash onset 1–7 days from development of fever and sore throat	Childhood exanthem mostly in those aged 5–15 years, sore throat, "sandpaper" rash, "strawberry" tongue	Throat swab for culture or rapid antigen testing Anti-streptolysin-O titre by serum testing	Beta-lactam antibiotics
Syphilis, secondary	*Treponema pallidum*, 4–10 weeks following primary infection	Sexual exposure; palmar and plantar rash	Dark-field microscopy of lesion Serum antibody testing	Penicillin
VZV	Varicella zoster virus, 10–21 days to symptoms	Lack of immunization history, exposure to person with chickenpox or shingles	Lesion PCR Serum antibody testing	Supportive

Abbreviations: EBV, Epstein-Barr virus; MSF, Mediterranean spotted fever; PCR, polymerase chain reaction; VZV, varicella zoster virus.

performing tick checks, and using DEET- or icaridin-based repellents. While endemic to a number of countries, the disease is likely underestimated in Greece. Reported cases of multiple eschars from suspected MSF patients have partially been attributed to a new emerging spotted fever rickettsiosis known as *R. aeschlimannii* [1]. Further studies of MSF will enable a better understanding of its epidemiology and pathophysiology, and potentially improve clinical outcomes.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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