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Case Report

# First case of Mediterranean spotted fever-associated rhabdomyolysis leading to fatal acute renal failure and encephalitis

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SUMMARY

Mediterranean spotted fever (MSF) is a tick-borne zoonosis caused by *Rickettsia conorii*. In Italy, about 400 cases are reported every year and nearly half of them occur in Sicily, which is one of the most endemic regions. Although MSF is mostly a self-limited disease characterized by fever, skin rash, and a dark eschar at the site of the tick bite called a 'tache noire', serious complications are described, mainly in adult patients. Nevertheless, severe forms of the disease with major morbidity and a higher mortality risk have been described. We report a fatal case of MSF complicated by rhabdomyolysis, acute renal failure, and encephalitis in an elderly woman.



## 1. Introduction

Mediterranean spotted fever (MSF) is a tick-borne zoonosis. The etiological agent is *Rickettsia conorii*, an obligate intracellular Gram-negative, rod-shaped bacterium. In Italy, about 400 cases are reported every year and nearly half of them occur in Sicily, which is one of the most endemic regions.[1]

Although MSF is mostly a self-limited disease characterized by fever, skin rash, and a dark eschar at the site of the tick bite called a 'tache noire', serious complications are described, mainly in adult patients.[1,2] Diagnosis is based on epidemiological, clinical, and laboratory criteria. Concerning therapy, doxycycline is considered the safest and most efficacious treatment; clarithromycin is considered a valid alternative, especially in patients with hypersensitivity to tetracyclines, in pregnant women, and in children.[3,4]

We report a fatal case of MSF complicated by rhabdomyolysis, acute renal failure, and encephalitis.

## 2. Case report

A 78-year-old woman was admitted to the Infectious Diseases Unit of the University Hospital of Palermo, Italy, in August 2013, because of clinical symptoms of continuous–remittent fever (max 38.5 °C), generalized rash, acute renal failure, and progressive loss of consciousness over 48 h. Her medical history was significant for type II diabetes mellitus and arterial hypertension. The patient also had a history of acute myocardial infarction and ischemic stroke.

On admission the patient was in a serious clinical condition with neurological impairment. Her Glasgow Coma Scale (GCS) score was 3. Her body temperature was 38 °C, blood pressure was 90/50 mmHg, and she presented an arrhythmic pulse at a high frequency (heart rate 128 beats/min) and an oxygen saturation of 97%.

On physical examination, she presented a general maculopapular rash with rare petechial elements that involved the palms of the hands and the soles of the feet. Furthermore we noticed two dark crusted lesions with a diameter of 50 mm like a 'tache noire' on the left thigh. On chest auscultation the patient had normal vesicular breathing sounds. Cardiac auscultation detected an arrhythmic pulse and there was evidence of atrial fibrillation on electrocardiogram. Abdominal examination revealed just hepatomegaly.

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Laboratory tests showed neutrophil leukocytosis (white blood cell (WBC) count $12.04 \times 10^9$/l with 87.4% polymorphonuclear neutrophils), acute renal failure (uremia 216 mg/dl, creatinine 3.13 mg/dl, hyperkalemia, and hypoalbuminemia), increased creatine kinase (>1400 U/l) and myoglobin (>2000 mg/dl), elevated transaminase blood levels (aspartate aminotransferase 176 U/l, alanine aminotransferase 79 U/l), increased lactate dehydrogenase (LDH; 1041 U/l) and D-dimer (8238 ng/ml), an international normalized ratio (INR) of 0.9, activated partial thromboplastin time (APTT) of 33 s, and C-reactive protein >27 mg/dl.

Brain computed tomography (CT) scans taken at admission and after 48 h were normal. A chest and abdomen CT scan was normal. As meningoencephalitis was suspected, a lumbar puncture was done on the first day of admission and revealed clear cerebrospinal fluid (CSF) with a normal liquor tension, containing $5 \times 10^6$ WBC/l, an elevated sugar content of 96 mg/dl, and negative Pandy reaction.

Routine microbiological cultures and PCR for herpes simplex virus from the CSF were negative, as were two blood culture sets. Rickettsia PCRs on blood and CSF were negative. Serological tests to detect *R. conorii* IgM and IgG (indirect immunofluorescence assay (IFI) and ELISA) gave negative results. The *R. conorii* IFI and ELISA were repeated after 1 week, showing elevated IgM and IgG titers (IFI IgM–IgG 1/320–1/640; ELISA IgM–IgG 1/200–1/800).

Empiric antibiotic therapy was started with intravenous (IV) chloramphenicol and IV levofloxacin. After 3 days of hospitalization the fever disappeared and the maculopapular rash improved. Therapy with corticosteroids and mannitol was started with an initial slight improvement revealed by neurological examination. Because of the progressive acute renal failure, hemodialysis sessions were initiated in agreement with the nephrologist. On the fifth day of hospitalization her clinical condition worsened and the patient died after 10 days of hospitalization due to cardiac arrest during a hemodialysis session.

## 3. Discussion

Most cases of MSF follow a benign course. However, severe forms of the disease with major morbidity and a higher mortality risk have been described.[1,2,5] Few cases of spotted fever rickettsiosis have been reported in HIV-positive patients.[6]

The pathogenesis of MSF complications results from vascular injury, which may be responsible for organ dysfunction of different organs. Renal impairment has been described frequently as a consequence of severe MSF. Several mechanisms of renal damage during MSF have been reported and the prognosis is determined by the type of renal disease and by early treatment.[7]

Rhabdomyolysis is a syndrome characterized by elevated serum concentrations of creatine phosphokinase (CPK) and myoglobin, as well as myoglobinuria, which can lead to renal dysfunction. There are several causes of rhabdomyolysis: the use of statins, trauma, prolonged immobilization, infection, electrolyte and endocrine abnormalities, and genetic or connective tissue disorders. A viral etiology is the most frequent among the possible infectious causes.[8] Benign acute myositis secondary to *R. conorii* infection has been described in the literature, as well as histologically documented pictures of myositis, but no case of rhabdomyolysis in the course of MSF has been described. Rhabdomyolysis due to *R. conorii* infection linked with acute renal failure has not been reported previously.

In our case report, the patient was not taking any drug or going through any situation that could explain the appearance of rhabdomyolysis.[9] The exact pathogenesis of Rickettsia-induced myopathy remains unclear, but we are led to believe that *R. conorii*, like the influenza virus, may act by direct invasion and immune-mediated mechanisms.[8]

Neurological complications of MSF include clinical pictures of meningitis and meningoencephalitis.[10,11] The pathogenetic mechanism responsible for the brain damage is thought to be the invasion and multiplication in vascular endothelial cells, resulting in widespread vasculitis of capillaries, arterioles, and small arteries. Our patient had a clinical presentation of meningoencephalitis, but the chemical–physical characteristics of the CSF, as well as the search for Rickettsia by PCR, were negative.

An early diagnosis and prompt initiation of antibiotic therapy are crucial to the outcome of the disease. Doxycycline is the gold standard treatment for MSF in adults. In severe and complicated cases, the use of high doses of doxycycline (200 mg twice daily) is reported to give good results, as well as the use of chloramphenicol in cases of neurological involvement.

Our case demonstrates the importance of recognizing rhabdomyolysis as a complication of *R. conorii* infection and its potential association with life-threatening acute renal failure and electrolyte imbalances. Furthermore we recommend close monitoring of CPK and symptoms of myopathy in all patients with MSF.

*Conflict of interest:* The authors declare that they have no competing interests or funding.

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