

# An Infant with Mediterranean Spotted Fever in Palestine: A Case Report

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**Abstract Introduction:** Mediterranean spotted fever (MSF) is an emerging and zoonotic disease caused by *Rickettsia conorii*. The main arthropod vector of this bacterium is *Rhipicephalus sanguineus*, also called “brown dog tick”. We report a 3-month-old infant affected by MSF as the first reported case of the condition in Palestine. **Clinical report:** in July 2022, a previously healthy 3-month-old child was admitted to the hospital due to fever, diffuse maculopapular rash and a black spot on his leg. Laboratory assessment revealed thrombocytopenia, hypoalbuminemia, and elevated liver enzymes. Polymerase chain reaction (PCR) testing was positive for *Rickettsia conorii* and a diagnosis MSF was ascertained. The patient was completely recovered with doxycycline treatment. **Conclusion:** Mediterranean spotted fever (MSF) is endemic in Africa, India, Europe and Mediterranean countries; including Palestine. In this case study, we affirm the significance of suspecting MSF in patients presenting with fever and rash even in those who stay in their homes apart from environments with high tick-exposure possibility.

**Keywords:** *Mediterranean spotted fever, Palestine, Rickettsia conorii, Rhipicephalus sanguineus, doxycycline*

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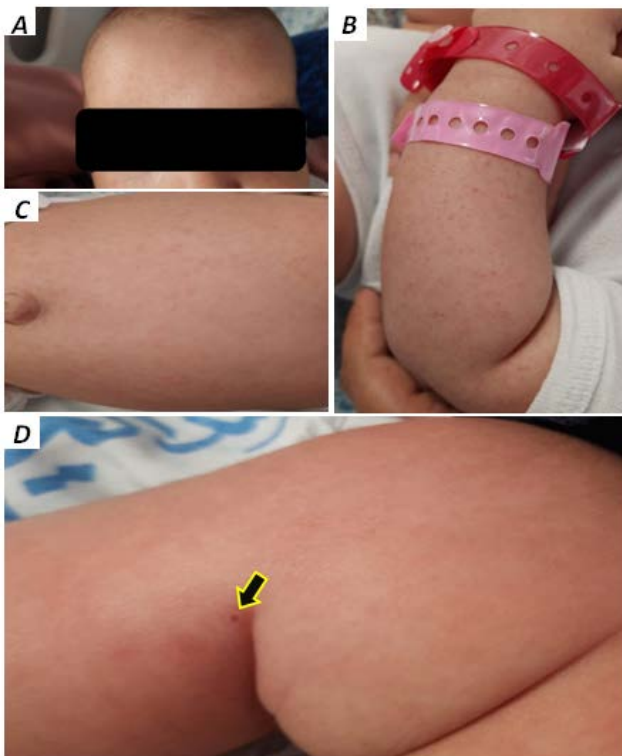
## 1. Introduction

Mediterranean spotted fever (MSF) is an acute tick-borne febrile disease, also termed as Boutonneuse fever, Israeli spotted fever, Indian tick typhus, Kenya tick typhus, mainly occurring in the Mediterranean region and its surrounding areas. MSF is caused by a rickettsial pathogen known as *Rickettsia conorii* [1,2,3]. This vector-borne pathogen is usually transmitted to humans through canine tick bites (*Rhipicephalus sanguineus* also called “brown dog tick”) [4]. MSF was first identified in 1910 in Tunisia by Connor and Bruch [5]. The incidence of MSF tends to demonstrate a cyclical variation and seasonal pattern, because the vast majority of reported cases seem to spring up in warm weather, especially from May to October when the tick is highly active [6,7,8]. Clinical manifestations of MSF are non-specific and similar to that of Rocky Mountain spotted fever [9]. MSF patients usually present with a classical triad of fever, maculopapular rash, and an inoculation eschar (also known as “tache noire”) at the bite site [1]. Patients also may complain of headache, joint pain, muscle ache, local lymph node enlargement, hepatosplenomegaly and/or Gastrointestinal manifestations [10,11,12]. Cardiovascular,

neurological and/or renal dysfunctions are seen in severe forms of the disease [1]. Given the non-specific features of MSF, a high suspicion index is required along with confirmatory laboratory testing to make the diagnosis early [13]. Serology and polymerase chain reaction (PCR) are the diagnostic modalities of choice, while culture has a limited role in establishing the diagnosis of MSF [1]. MSF is generally a mild and self-resolving disease. Nevertheless, lethal forms have been reported that seem to resemble viral hemorrhagic fevers, for instance Crimean-Congo Hemorrhagic Fever (CCHF) and should be considered in the differential diagnosis of thrombocytopenic fever syndromes [14]. Although tetracyclines are generally contraindicated in children before age of nine, Doxycycline is the favored antibiotic for the treatment of MSF in all age groups including children, which should be initiated empirically before the diagnosis is confirmed to prevent the development of serious complications [15]. We herein report a 3-month-old male child patient who presented with fever, generalized rash, and a black dot in the knee region. Diagnosis of MSF was suggested based on the clinical presentation and confirmed by the PCR with successful treatment and complete recovery as the first documented case of *Rickettsia conorii* infection in Palestine with early prompt recognition and effective therapeutic intervention.

## 2. Clinical Report

M.J., a 3-month-old Palestinian male infant, a product of cesarean section delivery due to large gestational age pregnancy, which was complicated by gestational diabetes mellitus controlled with appropriate diet. The patient's birth weight was 4500 grams; he did not require admission to the neonatal intensive care unit and was discharged home in good condition. He was in good health state and gaining weight consistent with his age until 22 July 2022, when the mother noticed a tick on her infant's left leg and removed it. Three days later, the infant received Penta-valent vaccine and started to have an undocumented fever. On 27 July 2022, the infant was admitted to our hospital (Al-Makassed Islamic Charitable Hospital in Jerusalem) due to fever, generalized skin spots associated with irritability and decreased oral intake. Upon admission, physical assessment revealed fever with temperature of 39.3 °C, diffuse maculopapular rash involving the face, abdomen, and forearms, along with eschar in the medial aspect of left knee (Figure 1: a, b, c & d). Cardiac and respiratory examination were unremarkable. Significant findings of laboratory evaluation are presented in Table 1. Urinalysis, cerebrospinal fluid analysis and their cultures were normal. Spotted fever was initially suspected and a combined treatment of doxycycline (4.4 mg/kg in 2 separate doses) and cefotaxime have been administered empirically. Molecular testing was performed and disclosed the presence of *Rickettsia Conorii* and diagnosis of Mediterranean spotted fever (MSF) was confirmed. The Patient achieved complete recovery and discharged home.



**Figure 1.** (a): maculopapular rash on the forehead, (b): maculopapular rash on the forearm, (c): maculopapular rash on the abdomen, (d): inoculation eschar “tache noire” at the site of tick bite on the medial aspect of left knee (arrow)

**Table 1. Laboratory data**

Laboratory parameter	The value	Reference range
<b>Complete blood count (CBC)</b>		
Hb (g/dl)	14	13.5-17.5
PLT (*10 <sup>3</sup> )/μl	60 ↓	142-450
<b>Inflammatory markers</b>		
CRP (mg/dl)	256 ↑	0-6
ESR (mm/hour)	18 ↑	0-15
LDH (IU/L)	543 ↑	135-225
<b>Liver studies</b>		
AST (U/L)	73 ↑	10-40
ALT (U/L)	55 ↑	8-42
Albumin (g/dl)	2.8 ↓	3.8-4.4
<b>Kidney function</b>		
CRE (mg/dl)	0.8	0.6-1.1
BUN (mg/dl)	7.4	6-20

Hb: hemoglobin, PLT: platelet, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRE: creatinine, BUN: blood urea nitrogen.

## 3. Discussion

Rickettsiae is a group of gram-negative strict intracellular coccobacilli of eukaryotes that depend on the cytosol of the host for growth and multiplying. They are considered zoonotic pathogens as they cause different human illnesses by the bite of infected arthropods. These illnesses are classified into three main bio-groups including spotted fever bio-group, typhus group, and scrub typhus bio-group [16].

Spotted fever bio-groups include Rocky Mountain spotted fever, rickettsialpox and Mediterranean spotted fever (MSF). MSF is a tick-borne infection caused specifically by *rickettsia conorii*. Dogs that carry the infected ticks (brown dog ticks) are the most important risk factors for human transmission. After the portal entry of *rickettsia conorii* through the skin, which is made by the tick bite, it affects endothelial cells of the arterioles and capillaries, mainly in the dermis but other various organs can be also affected as the organism disseminates through the blood stream [17].

*Rickettsia conorii* exerts its pathologic effect on its target cell by adhering to a cell membrane protein which facilitates its entrance to the cell. Then it secretes phospholipase D and hemolysin C, which destroy the phagosomal membrane and prevent intracellular phagocytosis, enabling it to grow and multiply in a large number resulting in the destruction of the cell membrane and release of the organism into the blood stream. The site of infected vascular endothelial cells, which contain the multiplying organisms, it becomes infiltrated by mononuclear cells accompanied by increased vascular permeability leading to leakage of intravascular fluid into the tissue space resulting in edema. During this vasculitis process, platelets are consumed causing thrombocytopenia [15].

*Rickettsia conorii* needs 1 to 16 days as an incubation period, and then the disease usually appears as an acute febrile illness with malaise, headache and maculopapular rash that develops 3-5 days following fever. The rash usually starts on the extremities, then spreads to the trunk,

neck, palms, and soles; it usually spares the face (in our case it is not spared). Moreover, only in 14-40% of cases there is cutaneous necrosis at the site of tick bite because of rickettsial vasculitis known as tache noire [1].

Diagnosis of MSF is confirmed by either serology or PCR; while it's difficult to culture rickettsia because it does not stain well with gram stain. Serological assays that detect antibodies to rickettsial antigen include indirect immunofluorescence, complement fixation, latex fixation, indirect hemagglutination, enzyme immunoassay, and microcoagulation [13].

MSF is usually a mild self-resolving disease, but late and/or misdiagnosis can lead to fatal complications including cardiac dysfunction, neurological abnormalities, and/or renal impairment. Early empiric antibiotic treatment should be administered in any patient presenting with clinical features suggesting MSF prior diagnosis confirmation. Doxycycline (200 mg/day) is the best first therapeutic option for MSF. However, in children younger than nine years, doxycycline is given as 4.4 mg/kg and according to American academy of Pediatrics (AAP) it is the drug of choice for any age group as far as its used for short duration. Chloramphenicol mainly and macrolides (Clarithromycin, and Azithromycin) can be used as alternate antibiotics. Josamycin is also effective, especially in pregnant women. [15,18,19].

Our reported case is a typical presentation of MSF disease; there is a history of tick contact as the mother mentioned -while the absence does not exclude it-. In addition, there is an eschar where the mother noticed the tick (Figure 1D), after which the infant started to suffer from high grade fever associated with irritability and decreased oral intake. Two days later, MSF typical rash appeared on the extremities and then spread to the trunk with involvement of the face (Figure 1 A, B & C). All of these features helped us in early recognition of the condition with the initiation of an appropriate antibiotic intervention, thus avoiding complications.

Laboratory studies showed -as shown in Table 1- elevated inflammatory markers, thrombocytopenia, elevated liver enzymes, and low albumin. Rickettsiae conorii can cause hypoalbuminemia by different pathological mechanisms; for example; illness-related decrease intake, renal involvement with resultant proteinuria, and/or hepatic vasculitis. Our diagnosis was confirmed by detection of rickettsiae conorii by PCR from the tache noire. But the treatment started from the first day with doxycycline and the patient responded and improved well.

According to the Center for Disease Control and Prevention recommendations 2016; doxycycline is the drug of choice for all age groups with tick-borne rickettsial disease and should be started as soon as possible even before confirming the diagnosis. Patients should improve with initiating the treatment and if the fever does not improve after 48 hours, other diagnoses should be considered including coinfection. Moreover, prevention of tick-borne disease is facilitated with avoidance of tick attachment [20].

## 4. Conclusion

We present the first case of Mediterranean spotted fever (MSF) in Palestine in a 3-month-old infant. MSF is caused

by gram-negative, obligate intracellular bacilli, namely, rickettsiae conorii transmitted by a tick bite; it targets the endothelial cell causing vasculitis, usually in the dermis but other different organs can be also involved. Classically, it presents as an acute febrile illness with tache noire, maculopapular rash, headache, and other nonspecific symptoms. High clinical suspicion is required for early diagnosis and treatment.

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