

Case Report

Atrial fibrillation in Mediterranean spotted fever

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Mediterranean spotted fever (MSF) is a tick-borne acute febrile disease caused by *Rickettsia conorii* and characterized by fever, maculo-papular rash and a black eschar at the site of the tick bite ('tache noir'). We describe the case of a 58-year-old man affected by MSF who developed atrial fibrillation. The patient presented himself to the hospital after 7 days of fever, malaise and severe headache. Cardiac auscultation revealed a chaotic heart rhythm and an electrocardiogram confirmed atrial fibrillation with a fast ventricular response. Diagnosis of MSF was made after the appearance of a maculo-papular skin rash, and treatment with oral doxycycline was started. An immunofluorescence antibody test confirmed *R. conorii* infection. The patient recovered after 7 days of treatment. Cardiac arrhythmia is a rare complication of MSF. Inflammation may play a role in the pathogenesis of atrial fibrillation. *R. conorii* is an intracellular bacterium which could trigger atrial fibrillation. Our patient was previously healthy and had no reported history of cardiac disease. This suggests that heart function should be monitored in MSF patients even in the absence of underlying risk factors.

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Introduction

Mediterranean spotted fever (MSF) is a tick-borne acute febrile disease caused by *Rickettsia conorii*. The vector of the infection is the brown dog tick *Rhipicephalus sanguineus*, which is widespread in the Mediterranean area. In Italy, there are approximately 400 cases of MSF every year. Nearly half of these cases occur in Sicily, which is one of the most endemic regions. MSF is typically characterized by fever, maculo-papular rash and a black eschar at the site of the tick bite ('tache noir'). Most cases follow a benign course. However, severe forms of the disease with major morbidity and higher mortality risk have been described. Complications are described mainly in adult patients and include hepatic, renal and cardiac impairment. Among heart complications, arrhythmia has been reported rarely. We describe the case of a 58-year-old man affected by MSF who developed atrial fibrillation.

Case report

In October 2007, a 58-year-old man was admitted to the emergency department of the University Hospital of Palermo (Italy) because of continuous remittent fever, malaise and a severe headache that had begun 7 days

before. An antibacterial and anti-inflammatory therapy had been started but no improvement of symptoms had been attained.

The patient lived in a rural area just outside Palermo city. In his medical history, there was no evidence of cardiac illness, diabetes mellitus, hepatic or renal dysfunctions. On examination, the patient appeared acutely ill. The cardiac auscultation revealed a chaotic heart rhythm with a heart rate of 115 beats min⁻¹. The blood pressure was 130/80 mmHg, and the body temperature was 39 °C. When an electrocardiogram (ECG) was performed, atrial fibrillation with a fast ventricular response was confirmed. Thus, the patient was admitted to the cardiology department where treatment with calciheparin and digoxin was started.

Laboratory examination demonstrated a low platelet (PLT) count (87 000 PLT mm⁻³), increased levels of urea (99 mg dl⁻¹) and creatinine (2.4 mg dl⁻¹) in serum, elevated C-reactive protein (4.39 mg dl⁻¹, normal value <1 mg dl⁻¹) and mildly elevated serum concentrations of aspartate aminotransferase (AST) (82 IU l⁻¹) and alanine aminotransferase (ALT) (90 IU l⁻¹). Red blood cell count, haemoglobin concentration, white blood cell count and coagulation parameters were within normal limits, as were serum creatine kinase and creatine kinase-MB concentrations. Due to the mild renal dysfunction, digoxin was substituted by bisoprolol and a good control of the fast ventricular tachycardia was obtained. On the second day, a

Abbreviations: ALT, alanine aminotransferase; AST, aminotransferase; ECG, electrocardiogram; MSF, Mediterranean spotted fever; PLT, platelet.



Fig. 1. Maculo-papular skin rash on the legs.

maculo-papular skin rash appeared on the trunk and legs (Fig. 1). We were consulted, as infectious disease specialists.

When we observed the patient at the Infectious Diseases unit, he complained of severe headache and photophobia, arthralgia and myalgia. The maculo-papular rash was also present on the palms and soles. A single lesion of 10 mm diameter with a small central crust was observed in the right mammary region (Fig. 2). No ticks were found attached to the patient. Clinical diagnosis of MSF was confirmed by the detection of *R. conorii*-specific antibodies by an immunofluorescence antibody test (IgM 1/320; IgG 1/640). *R. conorii* DNA was not detected in cutaneous tissue that was obtained by scraping the tache noir. Twice-daily treatment with oral doxycycline began on day 2 of admittance.



Fig. 2. Tache noir in the right mammary region.

On day 4 after admission, the patient was transferred to our Infectious Diseases unit. He was not febrile and his clinical conditions were improved. PLT count and renal function rapidly normalized. ECG readings were strictly monitored. For the development of a first-degree atrioventricular block, bisoprolol was stopped. On day 9, PLT count normalized ($417\,000\text{ PLT mm}^{-3}$) as did renal function parameters ($56\text{ mg urea dl}^{-1}$ and $0.93\text{ mg creatinine dl}^{-1}$). AST and ALT were still slightly altered (60 and 139 IU l^{-1} , respectively). Oral doxycycline was stopped after 7 days and the patient was discharged. Two weeks later, AST and ALT levels regularized and the patient was asymptomatic; ECG was normal.

Discussion

MSF is a common tick-borne disease during summer in the Mediterranean countries (Colomba *et al.*, 2006). In the last few years, the incidence of reported cases in Italy has slightly decreased. Nevertheless, severe complications of this infection continue to occur.

The seasonal peak of MSF occurs during the ticks' maximal activity period, from June to September. This patient became ill at the end of October because the very mild temperature of his home region allows the ticks to remain active in late autumn. For this reason, MSF had to be taken into consideration despite the season. Adults are more likely than children to undergo complications and severe forms of the disease, particularly if other conditions, such as diabetes, cardiovascular illness, chronic renal failure or alcoholism, are present. Recently, more complicated MSF cases have been reported in the absence of predisposing conditions (Tsiachris *et al.*, 2008; Tzavella *et al.*, 2006). Our patient was previously healthy and no history of risk factors was reported. In particular, he denied any cardiac disease, either arrhythmic or ischaemic.

The pathogenesis of MSF results from disseminated intraendothelial cell infection and vascular damage. Immune clearance of rickettsiae is associated with perivascular lymphohistiocytic infiltrates. Complete recovery follows the regeneration of endothelium and repair of the vascular lesions. MSF complications are associated with multifocal vascular injury which may be a result of renal, heart, central nervous system, pulmonary or gastrointestinal damage (Walker *et al.*, 1987, 1994).

Among MSF cardiac complications, arrhythmia has been rarely reported. To our knowledge, only one case of atrial fibrillation (Scaffidi *et al.*, 1981) and one of supraventricular tachycardia in a child (de Groot *et al.*, 1984) have been described.

It has been reported that inflammation may play a role in the pathogenesis of atrial fibrillation (Boos *et al.*, 2006). Inflammatory cells infiltrating the left atrial endocardium have been demonstrated in patients affected by this arrhythmia. Moreover, the pulmonary veins have a crucial role as one of the key trigger sites for the onset of atrial

fibrillation. We suggest that their endothelial injury could be the stimulus for this focal triggering. In particular, *R. conorii* is an intracellular bacterium that directly invades endothelial cells and provokes perivascular inflammation and activation of the acute phase response (Vitale *et al.*, 2001). On the basis of these observations, this agent should be considered among the pathogens that can trigger atrial fibrillation.

This patient showed a mild elevation of urea and creatinine sera levels. The alteration of renal function has been frequently described in patients affected by MSF. Different pathogenic mechanisms can impair the kidney during MSF including hypovolaemia and shock and a toxic effect of *R. conorii* on glomeruli (Skhiri *et al.*, 2004). The management of patients with renal and cardiac involvement should consider the toxicity of some drugs like digoxin.

Diagnosis of MSF is based on epidemiological, clinical and laboratory criteria (Brouqui *et al.*, 2004). Thrombocytopenia is one of the typical laboratory signs. Serological confirmation of infection is often delayed, thus adequate treatment has to be established independently. Promptly administered antibiotic treatment shortens the symptomatic period of MSF infection and prevents the appearance of severe complications.

In conclusion, MSF is an overall benign disease but underlying complications may cause difficulties for the treatment and may impair the outcome, especially in adults. Also, heart function should be monitored by ECG, even in patients without underlying diseases.

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