

## Case Report

## Severe Mediterranean spotted fever complicated by acute renal failure and herpetic oesophagitis

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Mediterranean spotted fever (MSF) is a tick-borne disease caused by *Rickettsia conorii*. Recently, complicated cases have been more frequently reported, even in previously healthy patients. We describe a case of severe MSF complicated by acute renal failure and associated with herpetic oesophagitis. Acyclovir therapy resulted in remission of oesophageal symptoms within 48 h.

## Introduction

Mediterranean spotted fever (MSF) is a tick-borne disease caused by *Rickettsia conorii*. In Italy about 400 cases are reported every year. Nearly half occur in Sicily, which is one of the most endemic regions. MSF is typically characterized by fever, skin rash and a black eschar at the site of the tick bite ('tache noire'). At present, severe forms are more frequently described and the current fatality rate for MSF is increasing (Brouqui *et al.*, 2007; Rovey *et al.*, 2008). Complications are described mainly in adult patients, and include hepatic, renal, cardiac and neurological impairment. Severe complications can be prevented by a prompt and efficacious antibiotic treatment. Diagnosis is based on epidemiological, clinical and laboratory criteria (Brouqui *et al.*, 2007). We describe a case of severe MSF complicated by acute renal failure and associated with herpetic oesophagitis.

## Case report

In August 2008 a 50-year-old Italian man was admitted to the Infectious Diseases Unit of the University Hospital of Palermo, Italy, because of continuous-remittent fever and malaise of 6 days duration. A diffuse rash had appeared the day before admission. An antibacterial therapy with amoxicillin/clavulanate had been started at home without an improvement of the symptoms.

In the patient's medical history there was no evidence of cardiac illness, diabetes mellitus, or hepatic, gastric or renal dysfunctions. On admission, the patient appeared acutely ill, with a maculo-papular rash with some petechial elements involving the trunk and the extremities, including palms and soles. Herpetiform skin lesions of 5 × 5 cm were

present on the upper lip and the nose. A single lesion of 20 mm in diameter surrounded by an inflammatory halo with a small central crust was observed on the right leg.

Physical examination showed a diffusely tender abdomen with significant splenomegaly and lower extremities oedema. Results of cardiovascular, respiratory and neurological examinations were unremarkable. The patient's blood pressure was 120/70 mmHg and his body temperature was 39.5 °C.

Laboratory examination demonstrated normal white and red blood cell counts and a normal haemoglobin value, with a low platelet count (51 000 cells  $\mu\text{l}^{-1}$ ), and increased serum urea (191 mg  $\text{dl}^{-1}$ ), creatinine (6.1 mg  $\text{dl}^{-1}$ ), aspartate aminotransferase (469 IU  $\text{l}^{-1}$ ), alanine aminotransferase (229 IU  $\text{l}^{-1}$ ) and C-reactive protein (26.77 mg  $\text{dl}^{-1}$ ). Coagulation parameters were within normal limits. Creatinine clearance was 12.8 ml  $\text{min}^{-1}$ .

Chest X-ray showed a bilateral pleural effusion. An abdominal ultrasound scan showed splenomegaly (transverse diameter 17 cm) and a normal aspect of both kidneys.

Because of a rash that was evocative of MSF, *R. conorii* serological testing was performed and two blood samples were collected for testing rickettsial DNA by real-time PCR using primers for the citrate synthase-encoding gene, *gltA* (Stenos *et al.*, 2005). Treatment with 100 mg doxycycline twice daily was started. Intravenous furosemide was administered (20 mg, three times daily, for 5 days) to reduce the oedema of the lower extremities and the bilateral pleural effusion.

The day after admission the patient complained of severe retrosternal pain and odynophagia and presented with melena. Oesophagogastroduodenoscopy (OGD) evidenced severe ulcerative lesions with raised edges and exudative bottoms throughout the entire oesophagus. There was

Abbreviations: HSV, herpes simplex virus; MSF, Mediterranean spotted fever; OGD, oesophagogastroduodenoscopy.

redness and punctiform bleeding of the antral mucosa. Lesions were consistent with herpetic oesophagitis and erosive gastritis. Oral acyclovir (800 mg daily for 10 days) and omeprazole (20 mg twice daily for 7 days) were prescribed, and remission of the oesophageal symptoms was obtained after 48 h treatment.

Specific anti-rickettsia IgM and IgG determinations were performed by an indirect immunofluorescence assay with antigens obtained from a clinical isolate of *R. conorii* subsp. *conorii* freshly prepared as described by Vitale *et al.* (1989). An immunofluorescent antibody test for *R. conorii* showed an increase of titres in two sera obtained after a 2 week interval (first sample IgM 1:40 and IgG negative; second sample IgM 1:1280 and IgG 1:640). Rickettsial DNA was detected from both full blood and buffy coat samples with a highly sensitive and specific real-time PCR assay for the detection of spotted fever and typhus group *Rickettsiae* using primers to the citrate synthase-encoding gene, *gltA* (Stenos *et al.*, 2005).

The ETI-HSVK-G enzyme immunoassay kit (Diasorin/Sorin Diagnostics), a qualitative ELISA for the detection of IgG antibodies to herpes simplex virus type 1 (HSV1) and/or type 2 (HSV2) gB-1 antigens in human serum, demonstrated a high titre of anti-HSV1 IgG.

Blood cultures were negative for aerobic/anaerobic bacteria, mycobacteria and fungi. Results of serological tests were negative for hepatitis viruses A, B and C, cytomegalovirus, Epstein-Barr virus, *Brucella* spp., *Leptospira* spp., *Salmonella* spp. and human immunodeficiency virus infections. Immunological work-up showed normal CD4 levels.

Monitoring laboratory tests were strictly performed and showed a progressive reduction in haemoglobin values ( $7.5 \text{ g dl}^{-1}$ ) and diuresis (200 ml per day) for 1 week, while a progressive defervescence and rash disappearance were also observed.

At discharge, haematochemical values were within normal ranges. The follow-up OGD 1 month after discharge showed no oesophageal lesions.

## Discussion

During the last few years rickettsial diseases have emerged in several Mediterranean countries (Rovero *et al.*, 2008; Schmulewitz *et al.*, 2008; Boillat *et al.*, 2008; Weinberger *et al.*, 2008). Until the 1980s, MSF was thought to be a benign illness with few complications and the proportion of deaths was  $<1\%$ . In recent times, complicated MSF cases have been reported, even in the absence of predisposing conditions (Colomba *et al.*, 2008; Leone *et al.*, 2008; Tsiachris *et al.*, 2008; Tzavella *et al.*, 2006). The pathogenesis of MSF complications results from vascular injury, which may be responsible for the dysfunction of different organs (Brouqui *et al.*, 2007; Rovero *et al.*, 2008; Schmulewitz *et al.*, 2008). Our patient was previously healthy. In particular, he denied any history of renal or

gastro-oesophageal disease. The only recognizable risk factor for a severe form of MSF could be the inappropriate antibacterial therapy that had been started at home and that could have delayed the correct treatment.

Renal impairment has been frequently described as a consequence of severe MSF. It has been observed that acute renal failure was most strongly associated with a fatal outcome (Sousa *et al.*, 2008).

To the best of our knowledge, an association between MSF and oesophagitis has never been reported. Oesophagitis due to HSV1 is a well-recognized entity in immunocompromised patients but it has rarely been described in immunocompetent hosts. It can represent either primary infection or reactivation. In our patient the diagnosis of HSV1 oesophagitis due to a reactivation of a primary infection was based on the concomitant presence of herpes labialis, characteristic endoscopic findings and HSV1 serological results. In our patient ulcerative lesions were present throughout the entire oesophagus, and the follow-up OGD 1 month after discharge showed no oesophageal lesions.

Severe complications of herpetic oesophagitis, including bleeding and oesophageal perforation, have rarely been reported in immunocompetent hosts (Chien *et al.*, 1992; Cronstedt *et al.*, 1992). Antiviral treatment of herpetic oesophagitis in immunocompetent hosts is controversial (Kurahara *et al.*, 1998; Ramanathan *et al.*, 2000). Early initiation of acyclovir therapy was beneficial for our patient, who had a striking response to the treatment within 48 h.

Our patient was affected by a severe MSF, complicated by acute renal failure and associated with a rare clinical picture of HSV1 reactivation. It can be supposed that a more virulent *R. conorii* strain affected our patient, causing the severe MSF. Acute renal failure could represent a cofactor for a transient decline of immunological status so that a latent herpetic infection could reactivate.

In conclusion, complicated MSF has to be taken into account even in individuals without any underlying risk factor. Severe MSF can be accompanied by clinical features that are more frequently observed in immunocompromised patients.

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