

Case Report

Severe case of Mediterranean spotted fever in Greece with predominantly neurological features

Konstantina Tzavella,¹ Ioannis S. Hatzizisis,¹ Aikaterini Vakali,² Kalliopi Mandraveli,³ Dimitrios Zioutas⁴ and Stella Alexiou-Daniel³

Correspondence

Konstantina Tzavella
ktzavell@med.auth.grFirst Propedeutic Medical Department¹, Department of Radiology², First Department of Microbiology³ and Department of Cardiology⁴, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, GreeceReceived 19 September 2005
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Rickettsia conorii is endemic in Greece, though only a few cases of infection have been published to date. The case of a 58-year-old man from northern Greece with a severe form of Mediterranean spotted fever and rapid neurological deterioration is presented here. The patient received antibiotic treatment with doxycycline, showing immediate clinical and laboratory improvement. Diagnosis was confirmed later, during the second week after disease onset, by detection of elevated titres of IgM and IgG antibodies against *R. conorii* using an indirect immunofluorescence assay.

Case report

A 58-year-old retired and previously healthy man presented himself at a peripheral hospital in northern Greece with a sudden onset of chest pain at rest and headache. Clinical, laboratory and imaging investigation, including electrocardiogram, troponin T test, stress test and echocardiogram, showed no pathological findings; the chest pain receded spontaneously and the patient was released after 2 days. One day later, at home, the patient developed high fever (39 °C) with persisting headache and diffuse myalgia. He received amoxicillin-clavulanic acid orally, and showed only a slight improvement of his symptoms. Additionally, a facial and upper limb maculopapular rash occurred 2 days later, which was considered to be an allergic side effect of the antibiotic therapy. The antibiotics were discontinued and the patient received antihistamines. He still complained of headache, myalgia and subfebrile temperatures. The next day (6 days after disease onset) the patient suddenly developed confusion, for which reason he was transferred to our department immediately. Clinical examination at admission revealed an axillary body temperature of 37.8 °C and a fading diffuse maculopapular rash with no signs of lymphadenopathy. Neurological examination of the patient showed confusion, ataxia and dysarthria without neck stiffness or any focal neurological findings. Although a history of tick exposure was denied, a black necrotic scabbed lesion of 5 mm in diameter was found on the patient's left thumb.

Initial laboratory tests showed elevated levels of C-reactive protein, up to 8.5 mg dl⁻¹ (normal range <0.8 mg dl⁻¹), and procalcitonin, up to 1.6 ng dl⁻¹ (normal range <0.5 ng dl⁻¹), accelerated erythrocyte sedimentation rate

(70 mm h⁻¹), thrombocytopenia (70 000 platelets µl⁻¹) with normal white blood cell count and haemoglobin, impaired renal function (1.9 mg creatinine dl⁻¹, normal range 0.5–1.4 mg dl⁻¹; 101 mg serum urea dl⁻¹, normal range 10–50 mg dl⁻¹), elevated lactate dehydrogenase (1016 U l⁻¹, normal range 240–480 U l⁻¹), γ-glutamyl transpeptidase (183 U l⁻¹, normal range 8–65 U l⁻¹), alanine aminotransferase (172 U l⁻¹, normal range <38 U l⁻¹), aspartate aminotransferase (205 U l⁻¹, normal range <41 U l⁻¹) and alkaline phosphatase (509 U l⁻¹, normal range 40–129 U l⁻¹). Blood-gas analysis revealed hypoxaemia (pO₂ 60 mm Hg, pCO₂ 35 mm Hg, pH 7.4). The cerebrospinal fluid showed a slight pleocytosis (12 cells mm⁻³, 90% polymorphonuclear) and an increased level of protein (53 mg dl⁻¹). A CT (computed tomography) scan and ultrasound of the abdomen showed mild enlargement of liver and spleen without lymphadenopathy. Chest X-ray, CT scan and magnetic resonance imaging of the head, as well as an encephalogram, were normal.

The patient remained haemodynamically stable, but deteriorated neurologically within the first 24 h after admission, in spite of additional intravenous therapy with dexamethasone and mannitol. Due to clinical findings (diffuse maculopapular rash, fever, headache, myalgia, inoculation eschar) and laboratory findings (thrombocytopenia, elevated alanine and aspartate aminotransferase) a rickettsial infection was suggested, so antibiotic therapy with doxycycline (200 mg per day, orally) was started on the eighth day after disease onset. Only 24 h later a remarkable improvement was seen in the patient's neurological symptoms and the pathological laboratory findings. The rash temporarily worsened and became petechial, but disappeared approximately 7 days later.

Abbreviation: MSF, Mediterranean spotted fever.

At 12 days after disease onset an indirect immunofluorescent antibody test revealed elevated IgM and IgG titres to *Rickettsia conorii* (1:512 and 1:64, respectively) with rising titres, up to 1:2048 and 1:1024, respectively, 2 weeks later. No other source of infection was found. There was no growth on routine microbiological culture of blood, urine and cerebrospinal fluid; typhoid fever, endemic typhus and toxoplasmosis were ruled out.

The patient was discharged 14 days after admission, receiving doxycycline for a total of 15 days. He also remained asymptomatic without any pathological laboratory findings at control examinations 6 and 9 weeks later. There was a further increase of IgG titres against *R. conorii* (>1:2056), while the IgM titre declined continuously (final titre <1:64).

Discussion

Mediterranean spotted fever (MSF), also known as 'bouton-neuse' fever, is prevalent in Mediterranean countries, Africa, India, south-western and south central Asia, east Russia, and in areas around the Black Sea. It is caused by *R. conorii*, an obligate intracellular Gram-negative bacterium, and transmitted by the brown dog tick *Rhipicephalus sanguineus* in urban and suburban areas (Brouqui *et al.*, 2004; Martinez & Cossart, 2004; Raoult & Roux, 1997). Typical clinical features include fever, myalgia, headache, generalized maculopapular rash and an inoculation eschar ('tache noir') at the site of the tick bite (Raoult & Roux, 1997). MSF typically follows a benign course, but in about 6% of the cases it may cause severe illness involving multiple organs, with a mortality of 2.5–5% (Raoult *et al.*, 1986; Yagupsky & Wolach, 1993). Neurological involvement has been reported in 28% of patients and constitutes a negative prognostic factor for the outcome of the disease (Alioua *et al.*, 2003).

MSF is significantly seasonal, with most cases appearing during spring and summer months (Raoult & Roux, 1997; Alexiou-Daniel *et al.*, 2003). Seroepidemiological investigations showed a high seroprevalence of *R. conorii* among the healthy Greek population (Daniel *et al.*, 2002); however, only few cases of MSF have recently been reported (Alexiou-Daniel *et al.*, 2003; Spengos *et al.*, 2005).

In this report we presented a severe case of MSF with predominantly neurological features. The infection developed in July and the patient was living in an urban area of northern Greece without contact with domestic dogs. The severity of the illness was probably due to the delayed initiation of the appropriate antibiotic therapy with doxycycline. Our patient developed the symptoms gradually during the first week of the disease, so that he was treated for each one (e.g. chest pain, a possible initial symptom of myalgia, fever, rash) separately, while the underlying disease remained unrecognized. The initial flu-like symptoms of MSF may confuse physicians, and the common practice of prescribing β -lactams as empirical therapy may contribute to a delay in the diagnosis of bouton-neuse fever and result in

life-threatening complications or permanent disabilities in some infected individuals (Jensenius *et al.*, 2004). Early recognition of the disease and immediate administration of the appropriate antibiotic therapy is essential for rapid recovery and prevention of complications, but confirmation of diagnosis during the acute phase is difficult. For this reason, diagnosis of the disease should initially be based on epidemiologic criteria as well as on clinical findings and laboratory findings (e.g. thrombocytopenia, elevated alanine and aspartate aminotransferase), according to the diagnostic criteria described by Brouqui *et al.* (2004).

The diagnosis of bouton-neuse fever is usually confirmed by serological testing using an immunofluorescence assay, the reference technique in most laboratories, to detect IgM and IgG antibodies against *R. conorii* in acute and convalescent sera (La Scola & Raoult, 1997; Brouqui *et al.*, 2004). Detection of both antibodies can usually be made 7–15 days after disease onset, and therefore provides a retrospective diagnosis. In our case IgM and IgG antibodies against *R. conorii* were detected during the second week of the illness, showing a titre increase in excess of fourfold 2 weeks later.

Despite the delayed beginning, our patient recovered promptly after administration of doxycycline, currently the standard therapeutic regimen for MSF (Jensenius *et al.*, 2004).

In conclusion, due to the high seroprevalence of *R. conorii* in Greece we believe that MSF has been underrecognized and underreported so far, and may occur as a severe illness in our country. Not only domestic, but also foreign, physicians should be aware and remember the possibility of the disease for all febrile patients living in or recently travelling from a tick-infected area in Greece, even in the absence of an inoculation eschar and skin rash.

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