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Review

Israeli Spotted Fever in Sicily. Description of two cases and minireview

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ABSTRACT

Mediterranean spotted fever (MSF) is endemic in Italy, where *Rickettsia conorii* subsp. *conorii* was thought to be the only pathogenic rickettsia and *Rhipicephalus sanguineus* the vector and main reservoir. *R. conorii* subsp. *israelensis*, which belongs to the *R. conorii* complex, is the agent of Israeli spotted fever (ISF); apart from Israel, it has also been found in Italy (Sicily and Sardinia) and in different regions of Portugal. We describe here two severe cases of ISF which occurred in otherwise healthy Italian adults. Their characteristics are analyzed and discussed in the light of other 91 cases found through a systematic review of international literature.

Contents

Introduction

Rickettsia conorii subsp. *israelensis*, which belongs to the *R. conorii* complex, is the agent of Israeli spotted fever (ISF). It was first reported in 1974 in Israel and distribution appeared to be restricted only to that country (Goldwasser et al., 1974; Mumcuoglu et al., 2002).

Several cases of postmortem diagnosis of ISF have been described in children and adults in Israel using cell culture methods, animal inoculation and immunohistochemical detection of rickettsial antigen in paraffin-embedded tissue obtained at autopsy (Yagupsky and Wolach, 1993; Aharonowitz et al., 1999 Aharonowitz et al., 1999). Only later was nested PCR applied to sera and tissue in several fatal cases of rickettsial infections and shown to be effective in establishing the correct diagnosis (Schattner et al., 1992; Keysary et al., 2007; Weinberger et al., 2008).

Rickettsia conorii subsp. *conorii* was thought to be the only pathogenic rickettsia of the spotted fever group in Europe where it is endemic in southern Europe, with sporadic cases reported in northern and central Europe. *Rhipicephalus sanguineus* is the vector and a potential reservoir of *R. conorii* subsp. *conorii* in the

Abbreviations: MSF, Mediterranean spotted fever; ISF, Israeli spotted fever; PCR, Polymerase chain reaction; MRI, Magnetic resonance imaging; ICU, intensive care unit; IFA, Immunofluorescence assay; ELISA, enzyme-linked immunosorbent assay; n.v., normal value; NA, not available.

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Mediterranean area. However, in the last few decades, newly recognized tick-borne rickettsioses have been shown to be present in Europe (Parola et al., 2013), and *R. conorii* subsp. *israelensis* has also been detected in *Rhipicephalus sanguineus* and in human cases in Sicily and Sardinia, Italy and in different regions of Portugal (Giammanco et al., 2003; Chisu et al., 2014; Giammanco et al., 2005a; Bacellar et al., 1999; Bacellar et al., 1995; Amaro et al., 2003; De Sousa et al., 2003a; De Sousa et al., 2008; De Sousa et al., 2005).

Every year, about 300 cases of Mediterranean spotted fever (MSF) are notified (mainly from June through September) in the Italian island of Sicily.

MSF is typically characterized by fever, skin rash and a black eschar at the site of the tick bite ("tache noire") (Cascio et al., 2001; Colomba et al., 2006 Colomba et al., 2006).

We report here two cases of ISF in otherwise healthy Sicilian adults and review all articles describing cases of ISF in which the diagnosis was made using molecular biology techniques.

Case 1

A 45-year-old Romanian man, in Italy for five years, previously healthy, except for a treated pulmonary tuberculosis ten years before, was admitted to Palermo University Hospital, Italy, in July 2016 for an history of fever (39 °C), headache, mialgia and weakness for 5 days. One day before admission a generalized rash developed. The patient was an alcoholic and lived in a rural environment in Sicily and owned a dog.

On admission, he was febrile (38.9 °C), tachycardic (120/min), tachypnoeic (40/min), oliguric and complained of severe muscle pain. A physical examination showed diffuse macular rash on the trunk and extremities, including palms and soles. The day after admission, a few petechial lesions appeared on his legs. Laboratory investigations yielded the following results: C-reactive protein level 253 mg/L (n.v. <5 mg/L); leukocyte count, 5.9×10^9/L; platelet counts, 13×10^9/L; creatinine 1.08 mg/dL; aspartate aminotransferase, 464 U/L; alanine aminotransferase, 126 U/L; γ-glutamyltranspeptidase, 45 U/L; pH 7.45; lactate, 2.5 mmol/L; D-dimer, 19.000 ng/mL (n.v. 10–250 ng/mL). Routine blood and urine cultures, serologic tests for HIV, *Leptospira* spp. and *Rickettsia* spp. were performed but the results were not diagnostic. Treatment with intravenous piperacillin-tazobactam (4.5 gr three times a day) plus vancomicin (1 gr twice a day) and oral doxycycline (100 mg twice a day) was immediately started.

On the second day of hospitalization, the patient's condition worsened: the skin rash became overtly petechial, and the picture of severe sepsis with multiorgan system failure worsened. Laboratory results were not diagnostic except real-time PCR assay for *R. conorii* subsp. *Israelensis*.

Rickettsial DNA was detected from full blood specimens with a highly sensitive real-time PCR assay for the detection of spotted fever and typhus group rickettsiae using previously published primers and probe to the Rickettsia rickettsii citrate synthase gene, gltA (Stenos et al., 2005). The CSisr-P probe (5′-FAM-TGT AAT AGC AAG AAT CGT AGG CTG GAT G-TAMRA-3′) was specifically designed from a highly conserved region of the citrate synthase gene to detect *R. conorii* subsp. israelensis in addition to SFG rickettsiae.

The patient was treated with doxycycline for seven days, and fever subsided completely after three days of treatment. The patient was discharged from hospital 10 days after admission, without any sequel.

Case 2

A 65-year-old otherwise healthy Italian woman was hospitalized with a 6-day history of high fever (40 °C), headache, vomiting and, four days later, a maculopapular rash involving the trunk, limbs, palms, and soles. On admission, the patient was agitated, confused, dysarthric and exhibited bilateral dysdiadochokinesis. Mild neck stiffness and positive Kernig's sign were present. She was febrile (39 °C), tachycardic (100 bpm), and tachypnoeic (respiratory rate 28 breaths per minute). A maculopapular rash covered the entire body surface, and petechial lesions were also present on the ankles. A brain CT scan was negative for acute ischemic-hemorrhagic events. MRI, performed with the suspect of encephalitis, showed gliotic outcomes based on hypoxic-ischemic lesions. Laboratory investigations yielded the following results: C-reactive protein level 67 mg/L, leukocyte count 52×10^9/L, platelet count 73×10^9/L, aspartate aminotransferase 172 U/L; alanine aminotransferase 289 U/L, d-dimer 2264 ng/mL. Routine blood and urine cultures, serologic tests and PCR for Rickettsia spp. were performed. (see above). The patient did not give consent for the execution of a lumbar puncture. Treatment with intravenous ceftriaxone (2 g twice a day) plus vancomicin (1 g twice a day) and oral doxycycline (100 mg twice a day) was immediately started. Laboratory results were not diagnostic except real-time PCR assay for *R. conorii* subsp. *israelensis*. The patient was treated with doxycycline for seven days and was discharged from hospital 20 days after admission. Fever subsided completely after four days of hospitalization.

Literature review and discussion

For the review of published cases, a PubMed search was performed combining the terms (israelensis OR israeli) AND (Rickettsia OR Rickettsioses OR Conorii) without limits; references were also checked for relevant articles, including review papers.

A study was considered eligible for inclusion in the review if it reported cases of ISF documented by molecular biology methods. Our search retrieved 69 articles; of them, 30 described human cases of probable ISF (Yagupsky and Wolach, 1993; Weinberger et al., 2008; Giammanco et al., 2005a; Bacellar et al., 1999; Amaro et al., 2003; De Sousa et al., 2003a; De Sousa et al., 2008; De Sousa et al., 2005; Bota et al., 2016; Znazen et al., 2011; Boillat et al., 2008; Chai et al., 2008; Znazen et al., 2013; Mokrani et al., 2012; Oteo and Portillo, 2012; Atias et al., 2010; Harrus et al., 2007; Brouqui et al., 2007; De Sousa et al., 2006; Giammanco et al., 2005b; De Sousa et al., 2003b; Leitner et al., 2002; Klein et al., 1995; Eremeeva et al., 1994; Kelly et al., 1994; Manor et al., 1992; Hanuka et al., 1992; Rehácek and Tarasevich, 1991; Wolach et al., 1989; Yagupsky and Gross, 1985) but only the 9 describing 91 patients with ISF confirmed by molecular biology techniques (Weinberger et al., 2008; Giammanco et al., 2005a; Bacellar et al., 1999; Amaro et al., 2003; De Sousa et al., 2008; Bota et al., 2016; Znazen et al., 2011; Boillat et al., 2008; Chai et al., 2008) were further considered (Figure 1).

Most of the articles were single case reports, but there was one large case series by De Sousa et al. (De Sousa et al., 2003a; De Sousa et al., 2008).

Data regarding the clinical characteristics, therapy, diagnosis and outcome of the above 91 patients with ISF and our two new cases are shown in Table 1.

All but two cases were contracted in three countries: Israel, Portugal and Italy. One case was reported in a patient returning from a trip to Libya and one case in Tunisia (Znazen et al., 2011; Boillat et al., 2008). Mean age was 56.2 (min. max 12-76; sd 15.29).

Medical history was unremarkable in all reviewed cases reported except in the first of our two cases that had a history of chronic alcohol abuse.

The illness had a sudden onset with fever (81%), rash (77%), headache (44%); tache noire was present in 27% of the cases, and gastrointestinal symptoms were present in 50% of the cases. 27.3%