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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%

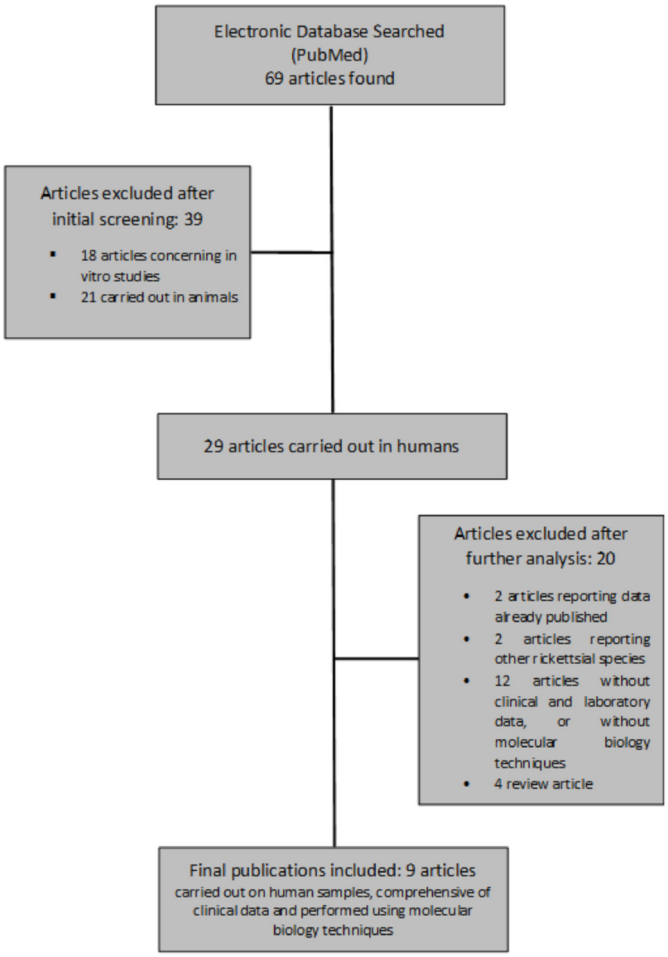

Figure 1. Study selection. Algorithm depicting literature search flow chart and why studies were included or excluded.

of patients died of multiorgan failure, acute renal and hepatic failure, purpura fulminans and acute encephalitis.

In all cases, molecular biology techniques allowed the detection of copies of rickettsial DNA with amplification of specific sequences of the genes encoding 16S rRNA, the 17-kDa protein, citrate synthase (gltA), and the outer membrane proteins OmpA and OmpB (Znazen et al., 2013) on blood (13 cases), eschar (3 cases) and autopsy samples (2 cases).

Serology, performed with immunofluorescence assay (IFA) or enzyme-linked immunosorbent assay (ELISA), was positive in only 11% of cases.

In all cases, therapeutic regimens included intravenous or oral doxycycline.

ISF does not appear to be limited to Israel, but is more widespread in the Mediterranean countries than first believed, and cases from Italy, Portugal, Libya and Tunisia have been reported.

The two cases of severe ISF we described had a favorable course. Case 1 experienced severe sepsis reaching new criteria for diagnosis of sepsis (Giamarellos-Bourboulis et al., 2016); he had a proven risk factor for developing a severe form of the disease; analysis of the relationship between comorbidities and a fatal MSF outcome demonstrated that alcoholism is a statistically significant host condition which is a risk factor for a fatal outcome and for severity of disease (De Sousa et al., 2008). Case 2 had encephalitic symptoms but did not have risk factors like the other cases examined. Nevertheless, most examined cases of ISF presented severe forms of the disease and a high fatality rate was found.

De Sousa et al. carried out a prospective study on 69 Portuguese patients with ISF and compared the clinical picture and severity of *R. conorii* subsp. *israelensis* and *R. conorii* subsp. *conorii* infection. They showed a statistically significantly greater severity of ISF compared to MSF infection caused by *R. conorii* subsp. *conorii*; case fatality rate for *R. conorii* subsp. *israelensis* was significantly greater than for *R. conorii* subsp. *conorii* infection (29% vs. 13%), and a greater percentage of patients with ISF strain infection required admission to ICU, compared to those with *R. conorii* subsp. *conorii* infection (36% vs 22%) (De Sousa et al., 2008). All cases reported in Israel have been fatal, as well as the two cases which occurred in the UK – a tourist traveling in Portugal and another subject probably infected in Libya (Weinberger et al., 2008; Znazen et al., 2011; Boillat et al., 2008). Among the cases of ISF described in Portugal, apart from the cases described by De Sousa, two of those reported by Bacellar died of shock and multiorgan failure (Bacellar et al., 1999). Of the 7 cases described in Italy, outcome was favorable in the two cases we have reported and in two out of five reported by Giammanco; the other 3 patients developed disseminated intravascular coagulation and progression toward coma and one of these patients died the day after admission (Giammanco et al., 2005a).

Therefore, *R. conorii* subsp. *israelensis* would appear to be more virulent than *R. conorii* subsp. *conorii* even if the microbial pathogenic mechanism by which it causes more severe illness remains to be determined.

Gastrointestinal symptoms such as nausea, vomiting, and diarrhea have been prominent manifestations reported in patients with fatal course of ISF and, overall, more frequent in patients with ISF compared with *R. conorii* subsp. *conorii*–infected patients (De Sousa et al., 2008).

Tache noire, the black eschar at the site of the tick bite, in our experience is present in more than 60% of cases of MSF (Cascio et al., 2001; Colomba et al., 2006; Cascio et al., 1998; Cascio et al., 2002); however, it is markedly less noted in ISF, where it was present in only 27% of patients. The absence of eschar may be an obstacle to correct diagnosis especially in cases of travelers coming from non-endemic areas (Znazen et al., 2011; Boillat et al., 2008). Therefore, rickettsiosis should always be suspected in febrile travelers, especially when they present with a rash, even in the absence of history of tick exposure and inoculation eschar; patients should start appropriate therapy without delay if suspicion of rickettsiosis arises in order to prevent a poor outcome due to aggressive rickettsial strains. Indeed, the supposed ability of the ISF rickettsia to cause life-threatening disease has been also ascribed to late diagnosis due to its uncharacteristic presentation (Yagupsky and Wolach, 1993).

Tetracyclines are considered standard treatment for MSF even thought they can cause significant adverse effects like staining of the teeth and bone toxicity, especially in children. For this reason the macrolides have emerged as a potential alternative therapy in children (Cascio et al., 2001; Cascio et al., 2002; Cascio and Colomba, 2002). In all reviewed cases, but one, doxycycline was promptly started; delayed medical consultation and late initiation of antimicrobial therapy (6 days after symptoms onset) may have contributed to the fatal course in the UK tourist traveling in Portugal (Chai et al., 2008). Haemophagocytic lymphohistiocytosis is a rare but potentially fatal disease that can be associated with Rickettsial infection and other zoonotic diseases (Cascio et al., 2012; Cascio et al., 2011).

Serology was positive in only 11%. Therefore, it would be advisable to use a PCR test that allows rapid diagnosis through the detection of copies of rickettsial DNA (Znazen et al., 2013). Skin biopsy specimens, particularly eschar biopsy specimens, can be used for detection of Rickettsia spp. by molecular tools, but this technique is invasive and painful for patients and is difficult to

Table 1
Clinical characteristics, therapy and outcome of 91 ISF cases.

Author/Year (ref) (n. patients)	Country	Age (years or average)	Sex	Medical history	Presenting symptoms and signs				Eschar, (n)	PCR (eschar/ blood/ autopsy)	Serology (IFA or ELISA)	Outcome	Therapy
					Fever (n)	Cutaneous (n)	CNS (n)	Gastrointestinal (n)					
Bacellar et al. (1999) (3 pts)	Portugal	71	3 F	unremarkable	Yes (3)	Rash (2)	Headache (2)	Nausea (1), Vomiting (2), Epigastric pain (1)	Absent	Blood (3 pts)	Positive (1pt)	1 Cured, 2 Died	Oral Doxycycline plus others not specified
Amaro et al. (2003) (8 pts)	Portugal	59.3	4 M, 4 F	unremarkable	Yes (8)	Rash (7)	Headache (5)	Abdominal cramps and pain (4), Diarrhea (2), Vomiting (1), Upper gastric hemorrhage (1), Oral ulcers (1)	Present (5 pts)	Blood (3 pts)	Positive (3 pts)	4 Cured, 4 Died	NA
Giammanco et al. (2005a) (5 pts)	Italy	49	3 M, 2 F	unremarkable	Yes (5)	Rash (5)	Headache (5)	No	Present (2 pts)	Blood (5 pts)	positive (4 pts)	4 Cured, 1 Died	Oral Doxycycline
Weinberger et al. (2008) (1 pt)	Israel	51	1 M	unremarkable	Yes	Rash	Headache	No	Absent	autopsy samples	Negative	Died	Oral doxycycline plus i.v. meropenem
Chai et al. (2008) (1 pt)	UK Traveler to South Portugal	63	1 F	unremarkable	Yes	Rash	Headache	Diarrhea	Absent	autopsy samples	Positive	Died	Oral doxycycline plus ciprofloxacin
De Sousa et al. (2008) (69 pts)	Portugal	NA	NA	unremarkable	Yes (65)	Rash (63)	Headache (28)	Vomiting (23), Diarrhea (17)	Present (23, 38%)	Blood and eschar (numbers NA)	NA	49 Cured, 20 (29%) Died	Doxycycline (46 pt) Doxycycline plus fluoroquinolone (7 pt) Fluoroquinolone (6 pt)
Boillat et al. (2008) (1 pt)	Libya	63	1 M	unremarkable	Yes	Rash	Headache	Epigastric pain	Absent	Eschar	Negative	Died	doxycycline plus ceftriaxone
Znazen et al. (2011) (2 pts)	Tunisia	45, 46	2 M	unremarkable	Yes (2)	Rash (2)	Headache (2)	No	Absent	Blood (1 pt) and eschar (2 pts)	Positive (1 pt)	2 Cured	NA
Bota et al. (2016) (1 pt)	Portugal	12	1 F	unremarkable	Yes	Rash	Headache	Vomiting	Absent	Blood	Positive	Cured	Ceftriaxone, clindamycin, plus oral doxycycline
Present cases (2 pts)	Italy	55	1 M, 1 F	Alcoholism (1)	Yes (2)	Rash (2)	Headache (2), mental confusion (1), dysarthria (1), signs of meningeal irritation (1)	Vomiting (1)	Absent	blood	Positive (2 pts)	2 Cured	Doxycycline plus piperacillin-tazobactam and vancomycin

perform on certain areas of the body (Parola et al., 2013). PCR detection followed by genetic characterization can determine the genotype of the organism to the level of genus, species, and strain, and allows an update of epidemiological knowledge. To date, the genomes of all R. conorii subspecies have been sequenced. The draft genome of R. conorii subsp. Israelensis yelded a total genome of 1,252,815 nucleotides in which no plasmid has been detected. Orthologous genes between R. conorii subsp. israelensis and the other three R. conorii subspecies were identified suggesting that the genomes of these bacteria were almost perfectly syntenic. However, some genes, like those for NADH dehydrogenase I chain B (NuoB), glycerol-3-phosphate cytidyltransferase (TagD), and MazG-like protein were not detected in the R. conorii subsp. israelensis genome, while they were present in those of the other three R. conorii subspecies. Whether this difference explains the differences in clinical expression observed among subspecies remains to be demonstrated (Cascio et al., 2011).

In conclusion, the geographic distribution of ISF is wider than previously thought and it is possible that severe cases of MSF described in literature and believed to be caused by *R.conori* subsp. *conorii* were instead caused by *R. conorii* subsp. *israelensis* (Colomba et al., 2014; Saporito et al., 2010).

Conflicts of interest

None.

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