Short communication

Severe Israeli spotted fever with multiorgan failure in a child

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ABSTRACT

An increased risk of severe and fatal Israeli spotted fever (ISF) has been observed in adults, mostly associated with ISF strain. Here, we report a case of severe ISF with multiorgan failure in a Portuguese child.

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1. Background

Israeli spotted fever (ISF) is an acute, febrile tick-borne rickettsiosis caused by *Rickettsia conorii* Israeli spotted fever strain (Bacellar et al., 1999). The ISF strain is genetically very close to the *R. conorii* Malish strain, which causes Mediterranean spotted fever (MSF). They are both transmitted by the brown dog tick, *Rhipicephalus sanguineus sensu lato* (s.l.). *R. conorii* ISF strain was described for the first time in Israel in 1974 and later in ticks and patients from Portugal, Italy, Tunisia and Libya (Bacellar et al., 1999; Boillat et al., 2008; Znazen et al., 2011). Comparative studies in Portuguese patients infected either with *R. conorii* ISF or Malish strain showed that, although clinical manifestations are similar, the characteristic eschar at the tick bite site is less frequently reported in ISF (Sousa et al., 2003, 2008). Furthermore, there seems to be an increased risk of severe and fatal disease with the ISF strain (Sousa et al., 2003, 2008), mainly in adults, and rarely in children (Gross and Yagupsky, 1987; Sousa et al., 2008). Here, we report a severe ISF case with multiorgan failure in a Portuguese child.

2. Case report

On July 2013, a previously healthy 12-year-old girl presented to the emergency department with fever, mild headache, vomiting

and a three day-history of intense myalgia. The patient lived in a rural area in the south of Portugal (Beja district), and reported contact with dogs but could not recall any previous history of tick bites. Physical examination revealed a macular rash on both the palms and soles, a tender hepatomegaly but there was no sign of eschar. A blood sample was collected to perform serologic and molecular diagnosis for rickettsial infection and oral doxycycline was initiated. Twelve hours after hospital admission, her clinical status deteriorated with progressive obtundation, hypotension, hypoxemia and oliguria. She was referred to Dona Estefânia Hospital in Lisbon. Laboratory investigations showed: leukopenia of $2.200 \times 10^9/L$; thrombocytopenia of $59 \times 10^9/L$; prolonged prothrombin time and activated partial thromboplastin time; elevated D-dimer of 28,852 ng/ml with slightly raised fibrinogen level of 458 mg/dl; acute renal failure (serum creatinine 1.61 mg/dl), hepatic injury (aspartate aminotransferase 172 U/L; alanine aminotransferase 120 U/L), hyperbilirubinemia (2.2 mg/dl); and a C-reactive protein of 19 mg/dl. A lumbar puncture revealed clear cerebrospinal fluid, no pleocytosis, elevated protein concentration (71 mg/dl) and a normal glucose content (61 mg/dl). Imaging exams showed bilateral pleural effusion, mild pericardial effusion and ascites. The patient was admitted to the intensive care unit and treated with intravenous ceftriaxone and clindamycin, plus oral doxycycline. Fluid resuscitation, vasopressor drugs and non-invasive ventilation were also needed.

Differential diagnosis included common causes of bacterial sepsis and also HIV, Epstein–Barr virus, Cytomegalovirus, Enteroviruses, *Mycoplasma pneumoniae*, *Borrelia*, *Coxiella burnetii* and leptospira infections.

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The clinical suspicion of rickettsial infection was confirmed by molecular detection of rickettsial DNA on an acute sera sample (collected on the third day of disease). Sequencing targeting the *ompA* and *gltA* genes allowed identification of *R. conorii* ISF strain. Furthermore, detection of antibodies in acute and convalescent sera was performed by “in-house” immunofluorescence assay (IFA) using a *R. conorii* antigen as previously described (Sousa et al., 2008).

Seroconversion was demonstrated in convalescent sera collected after a four-week interval from the first negative serum sample, showing increased levels of IgM > 1024 and IgG > 4096 antibodies.

The clinical course was favorable, remaining afebrile and in spontaneous ventilation from the sixth day of illness. She was discharged eighteen days after admission with no sequelae.

3. Discussion

We describe a multiorgan failure caused by *R. conorii* infection in a 12-year-old girl. This severity of disease is uncommon in children. In fact, even in countries such as Portugal and Italy, where both strains of *R. conorii* circulate, more severe cases have been reported to be associated with ISF strain infection but, in general, no life threatening conditions have been described in children (Colomba et al., 2006; Gross and Yagupsky, 1987; Sousa et al., 2008). Nevertheless, complications in children with *R. conorii* infection including meningitis, meningoencephalitis, encephalitis, coronary involvement and fatal cases have been described (Bougteba et al., 2011; Cascio et al., 2011; Salva et al., 2014; Sousa et al., 2008). The delay in prompt and specific treatment for *R. conorii* infections is a strong factor that has been implicated in severe cases. In fact, this was one of the arguments for the three Israeli pediatric cases which presented with multi-system organ failure and fatal outcome reported by Yagupsky and Wolach (1993). The worsened outcome due to delay in treatment was also highlighted in Portuguese patients with MSF. The article, which includes six children aged 6–12 years, reports that a 12-year-old who developed encephalitis was infected with *R. conorii* Malish strain and did not receive specific treatment until the tenth day of illness (Sousa et al., 2008). In our case, doxycycline treatment was initiated for the child on the third day of disease onset. Moreover, although the child did not have a history of tick exposure or present an eschar, the clinician suspected of rickettsiosis and promptly initiated the anti-rickettsial treatment.

Excluding the delay in treatment, it is not known if the severity of this case was related to host immune response or to ISF strain.

In accordance with Walker et al. (2007) suggested rickettsiosis pathophysiology, our patient coagulation findings indicate a pro-coagulant state associated with endothelial injury, which results in elevated D-dimer with mildly increased plasma fibrinogen, as a result of the acute-phase response.

PCR detection of rickettsial DNA was very important for diagnosis confirmation since antibodies are not detectable earlier in the course of the disease. However, the prompt administration of empirical doxycycline in rickettsiosis suspicious cases is crucial for a favorable patient outcome, since *R. conorii* infection can progress very rapidly and the process can be difficult to reverse. Advances in the knowledge of pathogenic mechanisms of rickettsiosis require further attention.

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