Haemophagocytic syndrome and rickettsial diseases

Antonio Cascio,1,2 Salvatore Giordano,3 Piera Dones,3 Silvia Venezia,4 Chiara Iaria2,5 and Ottavio Ziino4

1Dipartimento di Patologia Umana, Università di Messina, Messina, Italy
2AILMI (Associazione Italiana per la Lotta contro le Malattie Infettive) Università di Messina, Messina, Italy
3Unità Operativa Complessa Malattie Infettive, ARNAS ‘Civico, Di Cristina, Benfratelli’, Palermo, Italy
4Unità Operativa Complessa Oncoematologia Pediatrica, ARNAS ‘Civico, Di Cristina, Benfratelli’, Palermo, Italy
5Dipartimento di Malattie Infettive e Tropicali, Università ‘La Sapienza’, Roma, Italy

Haemophagocytic lymphohistiocytosis is a rare but potentially fatal disease resulting from dysregulated activation and proliferation of lymphocytes. We present a case of haemophagocytic syndrome occurring in a 5-year-old Italian boy as a complication of Mediterranean spotted fever. The characteristics of this case have been analysed and contextualized among those of another 15 cases of haemophagocytic syndrome associated with rickettsial diseases found through a systematic review of the international literature.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) (haemophagocytic syndrome) is a potentially fatal hyperinflammatory syndrome that is characterized by histiocyte proliferation and haemophagocytosis. HLH may be inherited (primary, familial) and occurs generally in infants or may be secondary to any severe infection, malignancy or rheumatological condition and occurring at any age. HLH is diagnosed using clinical criteria developed by the HLH Study Group of the Histiocyte Society (Gupta & Weitzman, 2010; Henter et al., 2007). The diagnosis is established by fulfilling one of the following criteria. (i) A molecular diagnosis consistent with haemophagocytic syndrome (e.g. PRF mutations, SAP mutations, MUNC13-4 mutations). (ii) Having five out of eight of the following: fever; splenomegaly; cytopenia (affecting more than two cell lineages, ≤9 g haemoglobin dl⁻¹, <100 000 platelets μl⁻¹, <1000 neutrophils μl⁻¹); hypertriglyceridaemia (≥265 mg triglycerides dl⁻¹) and/or hypofibrinogenaemia (≤150 mg fibrinogen dl⁻¹); haemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy; low or absent natural killer (NK) cell cytotoxicity; hyperferritinemia (≥500 ng ferritin ml⁻¹); elevated soluble CD25 (≥2400 IU interleukin-2Rα chain ml⁻¹) (Henter et al., 2007).

We describe a case of HLH that occurred in an Italian child as a complication of Mediterranean spotted fever (MSF). The characteristics of this case have been analysed and contextualized among those of another 15 cases of HLH associated with rickettsial diseases found through a systematic review of the international literature.

Case report

A 5-year-old boy presented to the emergency department of ‘G. Di Cristina’ Children’s Hospital, Palermo, Italy, with a 3 day history of remittent fever non-responsive to antipyretics and with upper abdominal pain. On admission, physical examination showed a seriously ill patient; his temperature was 39.0 °C, pulse rate 140 beats min⁻¹, respiratory rate 36 breaths min⁻¹ and blood pressure 110/85 mmHg. He was alert and oriented to time and place, but apathetic. He presented a generalized maculopapular rash that included the palms and soles. Abdominal examination revealed an enlarged and distended abdomen with normally active bowel sounds. The liver and spleen were palpable 2 cm under the costal margins. He had a palpable lymphadenopathy in the neck and in inguinal regions. The rest of the physical examination was unremarkable.

Haemochromatometric analysis revealed a total leucocyte count of 3500 cells μl⁻¹ with 25 % neutrophils, 70 % lymphocytes and 4 % monocytes, anaemia (9 g haemoglobin dl⁻¹) and thrombocytopenia (a count of 61 000...
platelets µl⁻¹). Blood biochemical tests showed the following abnormal results: C-reactive protein, 10.7 mg l⁻¹ [reference range (RR) 0–5 mg l⁻¹]; aspartate aminotransferase, 70 IU l⁻¹ (RR 5–45 IU l⁻¹); alanine aminotransferase, 58 IU l⁻¹ (RR 5–45 IU l⁻¹); total protein, 5.9 g dl⁻¹; albumin, 2.7 g dl⁻¹; lactate dehydrogenase, 1455 U l⁻¹; gamma glutamyl transpeptidase, 131 U l⁻¹; triglyceride, 165 mg dl⁻¹; and ferritin, 1310 ng ml⁻¹. Other biochemical studies including glucose, cholesterol, BUN (blood urea nitrogen), creatinine, uric acid, inorganic phosphorus, alkaline phosphatase, and total bilirubin and coagulation profiles, were all within normal limits. Multiple cultures of blood and urine were negative for bacteria, mycobacteria and fungi. Serological studies for human immunodeficiency virus 1 and 2, hepatitis B and C, cytomegalovirus, parvovirus, *Mycoplasma, Brucella, Leishmania* and *Toxoplasma* were negative. Tests for Epstein–Barr virus capsid IgG and IgM antibodies were negative. Tests of IgM against *Rickettsia conorii* by indirect immunofluorescent antibody test were positive at a 1:40 dilution (moderately positive), while IgG were negative.

Peripheral blood flow cytometry did not reveal a clonal population suggestive of leukaemia, lymphoma or aberrant NK cells. Bone marrow aspiration was performed on hospital day 2 and demonstrated severe hypocellularity and haemophagocytosis. Ultrasound evaluation of the abdomen showed splenomegaly (spleen diameter 94 mm). Genetic testing for HLH did not demonstrate perforin 1, MUNC 13-4 or SYNTAXIN 11 gene abnormalities.

Considering the clinical manifestations, the seasonality and the moderately positive serology for *R. conorii*, a diagnosis of MSF was considered and the patient was started on intravenous 50 mg chloramphenicol kg⁻¹ per day divided in four doses. His condition ameliorated and on the third day the fever disappeared and the chloramphenicol was replaced by 15 mg clarithromycin kg⁻¹ per day in two divided doses and continued for another 7 days. All of the symptoms and abnormal laboratory findings were relieved by day 10. However, the clinical features of the patient (fever, hepatosplenomegaly) and his laboratory evaluation (pancytopenia, hypertriglyceridaemia, elevated ferritin and bone marrow haemophagocytosis without any obvious evidence of malignancy) fulfilled the revised diagnostic criteria for HLH. The patient was followed up 1 week after hospital discharge and continued to do well. Repeat bone marrow aspiration was performed 21 days after the original bone marrow examination and showed complete resolution of the haemophagocytic process and re-establishment of normal tri-lineage haematopoiesis. A follow-up at 6 months was unremarkable and the patient remained asymptomatic 1 year after the initial presentation. The clinical suspicion of MSF was confirmed by a 16-fold increase in antibody titres against *R. conorii* determined by indirect immunofluorescent antibody test.

**Discussion**

Rickettsioses are diseases caused by small Gram-negative obligate intracellular bacteria belonging to the family *Rickettsiaceae* (genera *Rickettsia, Orientia, Ehrlichia* and *Anaplasma*) transmitted to humans by arthropod bite (Raoult, 2009). Major findings in rickettsioses and ehrlichioses include fever in a patient with exposure to a potential vector that may be associated with rash, inoculation eschar or localized lymphadenopathy. Biologically, neutropenia, thrombocytopenia and moderate increases in transaminases are common (Cascio et al., 1998; Dumler et al., 2007; Gouriet et al., 2006; Mouffok et al., 2009). *Rickettsiae* are classified into the typhus group and spotted fever group, with *Orientia* comprising the classic scrub typhus group (Dumler et al., 2001; Fournier & Raoult, 2009). *Rickettsiae* target vascular endothelial cells lining the small- and medium-sized blood vessels during human infections, but can invade underlying tissue such as smooth muscle cells, perivascular macrophages and monocytes (Sahni & Rydkina, 2009). The main target cells of *Ehrlichiae* are macrophages, including Kupffer cells, hepatocytes and endothelial cells (Sotomayor et al., 2001). Ehrlichial infection is controlled by a combination of NK T, CD4 and CD8 T lymphocytes, antibodies, gamma interferon, interleukin-10 and tumour necrosis factor alpha. *Ehrlichia chaffeensis* circumvents host defences by inhibiting the fusion of infected phagosomes with lysosomes and inhibiting the signal transduction pathway of gamma interferon-mediated anti-ehrlichial activity (Lee & Rikihisa, 1998). Human cells are capable of controlling rickettsial infections intracellularly, the most relevant location in these infections, by one or a combination of three mechanisms involving nitric oxide synthesis, hydrogen peroxide production and tryptophan degradation (Feng & Walker, 2000). These mechanisms involve complex interactions of CD4⁺ and CD8⁺ T lymphocytes, macrophages, NK cells, B lymphocytes, antibodies, cytokines and chemokines. Inflammatory responses of humans (serum levels of endothelial activation markers and cytokines) appear to coincide with the disease severity and inflammatory potential of pathogenic *Rickettsia* (Sahni & Rydkina, 2009). Proliferation of cytotoxic T cells could drive excessive macrophage activation and induce haemophagocytosis (Dierberg & Dumler, 2006).

The pathophysiology of acquired HLH is not fully understood. However, an uncontrolled immune response can lead to hypersecretion of cytokines, an upregulation of adhesion molecules and MHC I and II molecules on mono-macrophages, and an expansion of inflammatory monocytes (i.e. an increase in CD14⁺/CD16⁺ expression) (Emminger et al., 2001; Kerévé et al., 1999). And this exaggerated inflammatory response could result in uncontrolled proliferation and phagocytic activity of histiocytes (Rouphael et al., 2007). HLH is a life-threatening clinicopathological entity characterized by an impaired or absent function of NK cells and cytotoxic T cells. This dysregulation results in uncontrolled and ineffective immune activation leading to cellular damage and multiorgan dysfunction as well as proliferation and activation of...
benign macrophages with haemophagocytosis throughout the reticuloendothelial system causing pancytopenia, hepatosplenomegaly and lymphadenopathy (Rouphael et al., 2007; Verbsky & Grossman, 2006). HLH has been documented in patients with severe cases of intracellular microbial infection, including avian influenza, leishmaniasis, tuberculosis and typhoid fever, etc. (Silva-Herzog & Detweiler, 2008).

A PubMed search of cases of HLH that occurred during rickettsial disease was performed combining the terms (rickettsia OR orientia OR ehrlichia OR rickettsiosis OR rickettsioses OR tsutsugamushi OR scrub typhus OR spotted fever OR boutonneuse) AND (haemophagocytic OR haemophagocytosis OR haemophagocytosis OR haemophagocytic OR erythrophagocytosis) for the period January 1950 to August 2010; the references were also checked for relevant articles, including review papers. A study was considered eligible for inclusion in the systematic review if it reported data on patients with rickettsial diseases who had microscopic signs of haemophagocytosis. The PubMed search identified 495 papers. After a scrupulous analysis of these papers we considered 13 articles; 1 other article not found in PubMed, but cited in other papers was also considered (Wada et al., 2001). One paper reporting a case of scrub typhus complicated by HLH and parvovirus infection was excluded because it was published in Japanese and lacked an English abstract (Miyakawa et al., 2006). Three other papers reporting pathological findings in patients (now deceased) with Rocky Mountain spotted fever (RMSF) or with human monocytic ehrlichiosis (HME) were excluded because no clinical data about the patients were available (Dierberg & Dumler, 2006; Jackson et al., 1986; Woodard et al., 1981). Overall, 13 articles describing 15 cases of rickettsial disease complicated by HLH, published between the years 1990 and 2010, were further evaluated together with our patient data. Data regarding the clinical characteristics, therapy and outcome of all these patients are shown in Table 1.

In five cases HLH complicated the course of MSF, a disease caused by R. conorii and endemic principally in the Mediterranean area (Berner et al., 1989; Premaratna et al., 2009; Sotto et al., 1994). In seven cases HLH complicated the course of scrub typhus, a disease caused by Orientia tsutsugamushi endemic in the Far East (Chen et al., 2000; Iwasaki et al., 1994; Kobayashi et al., 1992; Takami et al., 2002; Wada et al., 2001). In four cases HLH complicated the course of HME, a disease caused by E. chaffeensis endemic in North America (Abbott et al., 1991; Burns et al., 2010; Doran et al., 1989; Marty et al., 1995) and in one of these was probably the cause of death (Marty et al., 1995). Strangely enough, there are no reports of HLH in patients with RMSF, a disease caused by Rickettsia rickettsii endemic in the Americas, with the exception of two papers. In these two studies reporting the post-mortem findings for RMSF patients, HLH was found in eight children and five adults, respectively (Dierberg & Dumler, 2006; Woodard et al., 1981).

In almost all the cases, the diagnosis of rickettsial diseases was confirmed serologically. Serological techniques cannot easily distinguish between different Rickettsia species of the spotted fever group. In the past, all cases of rickettsioses with spotted fever group antibodies were considered to have MSF in countries where this disease was endemic. In recent years, the rickettsial field has undergone a substantial evolution, particularly because of the technologic advances in molecular genetics (Roverey et al., 2008). Thus, it cannot be excluded that the case of MSF occurring in Israel could be caused by R. conorii subsp. israelensis or the case occurring in Sri Lanka could be caused by R. conorii subsp. indica (Berner et al., 1989; Premaratna et al., 2009); or that the cases of HME with serology positive for Ehrlichia canis were caused by E. chaffeensis rather than E. canis (Abbott et al., 1991; Doran et al., 1989).

Apart from our case, HLH occurred in children less than 15 years old in only 2 other cases (Burns et al., 2010; Doran et al., 1989), while the remaining 13 patients were adult (age range 21–75). Cytopenia (≤9 g haemoglobin dl⁻¹, <100 000 platelets μl⁻¹, <1000 neutrophils μl⁻¹) affecting more than two cell lineages, apart from the present case, was reported only in four other cases (Burns et al., 2010; Doran et al., 1989; Pérez-de Pedro et al., 2008; Premaratna et al., 2009). A fibrinogen level lower than 150 mg dl⁻¹ was reported only in one case (Burns et al., 2010). Triglyceride levels ≥265 mg dl⁻¹ were reported only in three cases (Burns et al., 2010; Pérez-de Pedro et al., 2008; Sotto et al., 1994). Ferritin levels ≥500 ng ml⁻¹ were reported only in three cases, apart from our case (Burns et al., 2010; Chen et al., 2000; Pérez-de Pedro et al., 2008). A study of NK cells and molecular tests excluding a familial form of HLH were performed only in one other case (Burns et al., 2010) apart from in our case. Determination of soluble CD25 antigen was not performed in any of the cases. Of the cases reviewed, except for our own, only one fulfilled the updated diagnostic criteria of HLH (as described earlier; Burns et al., 2010); however, only four of the cases were published after 2007 (Burns et al., 2010; Pérez-de Pedro et al., 2008; Premaratna et al., 2009).

Doxycycline was used in seven cases, minocycline in four cases, tetracycline hydrochloride in one case and chloramphenicol in two cases. Steroids were used in three cases (Burns et al., 2010; Marty et al., 1995; Pérez-de Pedro et al., 2008) and in one case were associated with ciclosporin (Pérez-de Pedro et al., 2008).

The severity of rickettsial diseases varies with the causative agent and the host. Some Rickettsia species, such as R. rickettsii and Rickettsia prowazekii, and O. tsutsugamushi often cause more severe diseases. Some variations in the same disease are seen between regions for scrub typhus and RMSF. Currently, the RMSF fatality rate reported by the Centers for Disease Control and Prevention is very low, possibly suggesting misdiagnosis. Host factors also play a role in severity. Old age, alcoholism and a deficit in glucose-6-phosphate dehydrogenase have been associated
### Table 1. Clinical characteristics, therapy and outcome of 16 cases of rickettsioses complicated by haemophagocytic syndrome

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (sex, country)</th>
<th>Disease</th>
<th>Duration of illness prior to admission (days)</th>
<th>Symptoms</th>
<th>Fibrinogen (cells mm(^{-3}))</th>
<th>Triglyceride (g dl(^{-1}))</th>
<th>Ferritin (kDa)</th>
<th>Splenomegaly</th>
<th>Lowest no. of WBC (platelets mm(^{-3}))</th>
<th>Lowest HB level (g dl(^{-1}))</th>
<th>Lowest no. of platelets</th>
<th>CID</th>
<th>Highest AST/ALT level</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berton et al. (1989)</td>
<td>30/M, Israel</td>
<td>MSF</td>
<td>NA</td>
<td>Fever, myalgia, arthralgia, nausea, vomiting, maculopapular rash on palms and soles</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>65/75</td>
<td>Tetracycline HCl</td>
<td>Cured</td>
</tr>
<tr>
<td>Doura et al. (1989)</td>
<td>4/F, USA</td>
<td>HME</td>
<td>30</td>
<td>Fever, lethargy, vomitting, irritability, photophobia</td>
<td>130</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>900 [52 %]</td>
<td>8.7</td>
<td>63/000</td>
<td>Yes</td>
<td>68/182</td>
<td>Chloramphenicol</td>
<td>Cured</td>
</tr>
<tr>
<td>Abbott et al. (1990)</td>
<td>67/M, USA</td>
<td>HME</td>
<td>10</td>
<td>Fever, chills, myalgia, diathrosis, hypotension, septic shock</td>
<td>210.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2700 [kDa]</td>
<td>10.0</td>
<td>90/000</td>
<td>Yes</td>
<td>124/NA</td>
<td>Cured</td>
<td></td>
</tr>
<tr>
<td>Kobayashi et al. (1992)</td>
<td>47/F, Japan</td>
<td>Scrub typhus</td>
<td>NA</td>
<td>Respiratory failure</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Decreased</td>
<td>Yes</td>
<td>NA (increased)</td>
<td>Minocycline</td>
<td>Cured</td>
</tr>
<tr>
<td>Sotto et al. (1994)</td>
<td>42/M, France</td>
<td>MSF</td>
<td>NA</td>
<td>Fever, headache, maculopapular and purpuric rash, myalgia, arthralgia</td>
<td>420</td>
<td>342</td>
<td>NA</td>
<td>NA</td>
<td>5400 [85 %]</td>
<td>15</td>
<td>17/000</td>
<td>No</td>
<td>90/110</td>
<td>Doxycycline</td>
<td>Cured</td>
</tr>
<tr>
<td>Iwasaki et al. (1994)</td>
<td>58/F, Japan</td>
<td>Scrub typhus</td>
<td>NA</td>
<td>High fever, dry cough, headache, polyarthritis, eschar</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>1800 [kDa]</td>
<td>63/000</td>
<td>NA</td>
<td>128/NA</td>
<td>Minocycline</td>
<td>Cured</td>
</tr>
<tr>
<td>Marty et al. (1995)</td>
<td>67/F, USA</td>
<td>HME</td>
<td>4</td>
<td>Intermittent fever, malaise, confusion, cough, stiff neck, nausea, myalgia</td>
<td>343.8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>29000</td>
<td>NA</td>
<td>1641/232</td>
<td>No</td>
<td>34 %</td>
<td>Vancomycin, ceftriaxone, steroids, dexamethasone</td>
<td>Cured</td>
</tr>
<tr>
<td>Wada et al. (2001)</td>
<td>53/F, Japan</td>
<td>Scrub typhus</td>
<td>NA</td>
<td>Fever, rash, lymphadenopathy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>191</td>
<td>Yes</td>
<td>NA (increased)</td>
<td>Minocycline</td>
<td>Cured</td>
</tr>
<tr>
<td>Chen et al. (2000)</td>
<td>21/M, Taiwan</td>
<td>Scrub typhus</td>
<td>14</td>
<td>Spiking fever, general malaise, epigastric pain, cervical lymphadenopathy</td>
<td>NA</td>
<td>176</td>
<td>1415</td>
<td>Yes</td>
<td>9000 [kDa]</td>
<td>9.3</td>
<td>209</td>
<td>No</td>
<td>140/166</td>
<td>Doxycycline</td>
<td>Cured</td>
</tr>
<tr>
<td>Takami et al. (2002)</td>
<td>75/F, Japan</td>
<td>Scrub typhus</td>
<td>NA</td>
<td>Fever, headache, maculopapular rash, lymphadenopathy and eschar</td>
<td>NA</td>
<td>NA</td>
<td>183</td>
<td>NA</td>
<td>5600 [kDa]</td>
<td>12.8</td>
<td>14/000</td>
<td>No</td>
<td>44/32</td>
<td>Doxycycline, prednisolone</td>
<td>Cured</td>
</tr>
<tr>
<td>Takeda et al. (2002)</td>
<td>69/F, Japan</td>
<td>Scrub typhus</td>
<td>7</td>
<td>High fever, anorexia, diathrosis, maculopapular rash and eschar</td>
<td>NA</td>
<td>NA</td>
<td>282</td>
<td>NA</td>
<td>1300 [kDa]</td>
<td>11.3</td>
<td>75/000</td>
<td>No</td>
<td>35/17</td>
<td>Minocycline</td>
<td>Cured</td>
</tr>
<tr>
<td>Pérez-de Pedro et al. (2008)</td>
<td>38/F, Spain</td>
<td>MSF</td>
<td>NA</td>
<td>High fever, myalgia, headache, nausea, vomiting, maculopapular rash on palms and soles</td>
<td>221</td>
<td>316</td>
<td>5509</td>
<td>Yes</td>
<td>1500 [85 %]</td>
<td>10.7</td>
<td>20/000</td>
<td>No</td>
<td>86/115</td>
<td>Doxycycline, levofloxacin, ceftriaxone, dexamethasone</td>
<td>Cured</td>
</tr>
<tr>
<td>Premaratna et al. (2009)</td>
<td>58/F, Sri Lanka</td>
<td>Scrub typhus</td>
<td>10</td>
<td>Fever, eschar</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>2300 [34 %]</td>
<td>56/000</td>
<td>No</td>
<td>NA/NA</td>
<td>Doxycycline</td>
<td>Cured</td>
</tr>
<tr>
<td></td>
<td>37/F, Sri Lanka</td>
<td></td>
<td>12</td>
<td>Fever, pallor, lymphadenopathy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3300 [38 %]</td>
<td>9.6</td>
<td>106/000</td>
<td>No</td>
<td>NA/NA</td>
<td>Doxycycline</td>
<td>Cured</td>
</tr>
<tr>
<td>Buern et al. (2010)</td>
<td>10/M, USA</td>
<td>HME</td>
<td>5</td>
<td>High fever, hypotension, altered mental status and seizure</td>
<td>93</td>
<td>287</td>
<td>&gt;10000</td>
<td>Yes</td>
<td>520 [kDa]</td>
<td>10.2</td>
<td>50</td>
<td>No</td>
<td>2430/582</td>
<td>Doxycycline, dexamethasone, Chloramphenicol</td>
<td>Cured</td>
</tr>
<tr>
<td>Present case</td>
<td>5/M, Italy</td>
<td>MSF</td>
<td>3</td>
<td>Fever, maculopapular rash on palms and soles</td>
<td>200</td>
<td>165</td>
<td>1310</td>
<td>Yes</td>
<td>3500 [25 %]</td>
<td>9</td>
<td>61/000</td>
<td>No</td>
<td>70/58</td>
<td>Doxycycline</td>
<td>Cured</td>
</tr>
</tbody>
</table>

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; DIC, disseminated intravascular coagulation; F, female; Hb, haemoglobin; M, male; NA, not available; WBC, white blood cell.
with more severe disease. In such patients, a multipleorgan dysfunction syndrome can be observed that usually leads to a fatal outcome. Gangrene of the extremities can also be observed in severe cases.

Without treatment, familial HLH is often rapidly fatal, and the reported mortality for secondary HLH can exceed 50% (Freeman & Ramanan, 2011). Although, in addition to the treatment of any existing triggers, HLH treatment focuses on the suppression of the hyperinflammatory state, steroids were used in three cases only.

The prognosis of rickettsial diseases associated with HLH is unknown. It may depend on a number of factors, including the Rickettsia sp. involved, various host factors, the degree of inflammation, the delay in antibiotic therapy and the association of immunosuppressive drugs (Raoult, 2006). There are relatively few studies in the literature describing post-mortem examination findings in fatal RMSF or HME cases, such as the ones by Woodard et al. (1981) or Dierberg & Dumler (2006). Furthermore, in none of the reported fatal cases of MSF found in the literature was a diagnosis of HLH excluded. However, a diagnosis of primary HLH should always be excluded. In fact, with improved molecular diagnostics it is recognized that cases of adult onset HLH that had previously been considered secondary may represent a primary HLH with underlying mutation in the PFR1 gene (Freeman & Ramanan, 2011; Nagafuji et al., 2007).

Conclusions

We think that HLH should be considered in severe cases of rickettsial disease especially if associated with pancytopenia. Further studies are needed to understand whether (as we think) an immunosuppressive treatment such as treatment with steroids could be beneficial in those cases that do not respond promptly to antibiotic therapy.

Acknowledgements

Written consent was obtained from the patient’s parents for publication of the study.

References


