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Abstract

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Reference


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Q fever and Mediterranean spotted fever associated with hemophagocytic syndrome: case study and literature review

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SUMMARY

Background: Hemophagocytosis during Q fever (QF) and Mediterranean spotted fever (MSF) is rare and only a few cases have been reported. We aimed to investigate the characteristics, outcome, and treatment of QF/MSF-associated hemophagocytosis.

Methods: We retrospectively reviewed all patients with a diagnosis of QF or MSF and suspected hemophagocytic syndrome (HS), according to Henter’s criteria, between 2002 and 2011, and compared the latter to patients without HS or with lymphoma-associated HS.

Results: Seventeen patients with HS (median age 42 years, range 5–68 years; five females (29%)) with QF (n = 8) and MSF (n = 9) were included in this study. When comparing patients with QF- and MSF-associated HS with patients without HS (n = 11), HS-associated signs (splenomegaly, ferritinemia, hypertriglyceridemia, and cytopenia) were significantly more frequent in patients with histological HS (p < 0.05), along with a greater number of Henter’s criteria. Despite the presence of HS-associated signs, treatment was similar in these two subgroups, including the time to recovery and the outcome. When compared to lymphoma-associated HS (n = 10), the outcome in QF/MSF-associated HS was significantly different, with mortality in 70% of lymphoma patients versus none in QF- and MSF-associated HS (p < 0.05).

Conclusion: Hemophagocytosis is a rare occurrence during the course of QF and MSF. The presence of profound cytopenia is quite unusual in QF and MSF and should bring to mind the presence of associated HS. Nevertheless, hemophagocytic syndrome is associated with a good outcome in this condition.

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1. Introduction

Hemophagocytic syndrome (HS) is a rare life-threatening condition characterized by fever, organomegaly, cytopenia, and the presence of histological hemophagocytosis.1,2 HS is due to uncontrolled macrophage activation leading to phagocytosis of different hematopoietic cells and an overproduction of proinflammatory cytokines. HS may be categorized into primary genetic and secondary HS, which is associated with malignancy, autoimmune disease, drug hypersensitivity reactions, and/or infections. The diagnosis of HS remains controversial; the Henter criteria and Imashuku criteria have been elaborated for primary HS, and while widely used, have yet to be evaluated in secondary HS.3

HS has been associated with a large variety of viral, bacterial, and parasitic pathogens, with Epstein–Barr virus (EBV) and mycobacteria being the main infectious causative agents.4 Among infections causing HS, Q fever (QF) and Mediterranean spotted fever (MSF), caused by Coxiella burnetii and Rickettsia conorii, respectively, have rarely been described. QF manifestations are highly aspecific, mostly acute hepatitis or pneumonia for the acute form and endocarditis for chronic QF. MSF, transmitted by the brown dog tick Rhipicephalus sanguineus, causes a febrile rash predominantly on the palms and soles, with the occasional presence of a black spot, which corresponds to the eschar of tick inoculation. The outcome and treatment of HS in these two infections remain undetermined (Table 1).5–13 We targeted MSF and QF because they are among the most frequent infections caused by intracellular pathogens associated to HS. The aim of the present study was to describe HS associated with QF and MSF and to analyze the outcome and treatment of HS in

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E-mail address: arsene.mekinian@jvr.aphp.fr (A. Mekinian).
Table 1

| Pt Ref. | Age/sex | Fever | Cytolysis | TG | Diagonos
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<tr>
<td>C</td>
<td>Pb</td>
<td>Ec</td>
<td>SMG</td>
<td>Neutrophils</td>
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<tr>
<td>1</td>
<td>65/M</td>
<td>+</td>
<td>No Dyspnea, cough</td>
<td>+</td>
<td>4.460</td>
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<td>338</td>
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<td>N</td>
<td>2.3</td>
<td>592</td>
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<td>2</td>
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<tr>
<td>8</td>
<td>17/F</td>
<td>+</td>
<td>Maculo-papular</td>
<td>No</td>
<td>NA</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>26/M</td>
<td>+</td>
<td>No Cough</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.0</td>
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<tr>
<td>10</td>
<td>N</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
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<td></td>
<td>2</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; F, female; Hb, hemoglobin; HS, histological hemophagocytic syndrome; SMG, splenomegaly; LDH, lactate dehydrogenase; M, male; MSF, Mediterranean spotted fever; NA, not available; NP, not performed.

These patients. Patients with QF- or MSF-associated HS were compared to patients with lymphoma-associated HS, as well as patients with QF or MSF but without HS. An exhaustive literature review of HS associated with QS and MSF was also performed.

2. Patients and methods

2.1. Study patients

We retrospectively reviewed all patients with a diagnosis of QF or MSF and suspected HS between 2002 and 2011 at four university hospitals (Bondy, Avicenne, Pontoise, and Marseille). HS was determined according to the presence of six of the eight Henter’s criteria: (1) fever >38.5 °C for more than 7 days; (2) splenomegaly; (3) bicytopenia (hemoglobin (Hb) <9 g/dl, platelets <100 x 10^9/L, neutrophils <1 x 10^9/l); (4) ferritinemia >500 μg/l or fibrinogen >1.5 g/l; (5) triglyceridemia >3 mmol/l; and (6) histological evidence of hemophagocytosis. Since natural killer (NK) cell activity and soluble interleukin (IL)-2R levels are not routinely performed, at least five of eight Henter’s criteria were required to retain a diagnosis of HS. HS was also analyzed according to the Imashuku score: (1) fever >7 days; (2) bicytopenia (Hb <9 g/dl, platelets <100 x 10^9/l), white blood cell count <2 x 10^9/l; (3) ferritinemia >1000 μg/l; (4) lactate dehydrogenase >1000 IU/l; and (5) histological evidence of hemophagocytosis.

QF and MSF were diagnosed using serological data with paired sera: two different standardized indirect immunofluorescence antibody tests (bioMérieux and Eurobio commercial kits) were used, and cut-off titers were anti-phase II IgG ≥1:200 and anti-phase II IgM ≥1:50 for the diagnosis of acute QF, and IgG ≥1:80 for MSF. Anti-phase I IgG and IgM for the diagnosis of chronic QF were negative in all QF patients. Two patients with QF had positive PCR on paraffin-embedded hepatic biopsy.

The diagnosis of HS was ascertained by histological examination when available, while the presence of fibrin ring granuloma was analyzed from liver biopsy (Figure 1).

For each patient, data pertaining to medical history, laboratory and histological data, and treatments were collected. The data for each patient were systematically reviewed by two investigators (ML and VP). HIV, cytomegalovirus, EBV, herpes simplex virus, and parvovirus B19 virus serologies were also recorded when available. None of the patients had a family history of HS, autoimmune diseases, or neoplasia.

2.2. Control cases

Eleven patients with a diagnosis of QF and MSF without HS from our hospitals between 2002 and 2011 were also retrospectively analyzed. Ten patients with B lymphoma and associated HS were also analyzed in order to compare the outcome of QF- and MSF-associated HS.

2.3. Literature review

A bibliographic search was performed (1984 to January 2012), by two investigators (ML and VP) using the MEDLINE database (National Library of Medicine, Bethesda, MD, USA) with the following keywords Q fever, Coxiella burnetii, Mediterranean spotted fever, fibrin ring granuloma, Rickettsia conorii, hemophagocytic syndrome, histiocytic hemophagocytosis. All articles with sufficient data were included in the literature review. The literature search yielded 13 citations; all were analyzed and nine were included in the review (four cases were excluded because of insufficient data).

...
2.4. Statistical analysis

Data are expressed as medians with ranges for continuous variables, and as frequencies with percentages for qualitative variables. The Fisher’s exact test was used to compare qualitative variables, while the non-parametric Mann–Whitney U-test or Wilcoxon test was used for continuous variables, as appropriate. Statistical analyses were carried out using GraphPad Prism version 5.1 (GraphPad Software, San Diego, 2007).

3. Results

3.1. All patients with QF/MSF and HS

Seventeen patients (median age 42 years, range 5–68 years; five females (29%)) with QF (n = 8) and MSF (n = 9) were included in the study. The general characteristics and laboratory data of these patients are summarized in Table 1. Underlying immunodepression was present in two cases (diabetes mellitus and alcoholic hepatopathy). An exposure factor was present in all cases (travel in an epidemic area, contact with infected animals). At least one cytopenia was present in 15 of 17 cases (88%), with anemia in 14 cases (82%), thrombocytopenia in 13 cases (76%), and neutropenia in seven cases (41%) (Table 1). Hyperferritinemia was noted in 10 of 11 cases (91%), hypertriglycerideremia in eight of 13 cases (65%), and hepatic cytolysis in 12 of 17 cases (71%).

QF was confirmed in eight cases and MSF in eight cases, with serological median titers of phase II IgG 1:590 for QF and IgG 1:1920 for MSF. HS was confirmed with more than five of eight Henter criteria in three of 17 cases (18%), with three or four criteria in 13 cases (82%), and with four or five Imashuku criteria in eight of 17 cases (47%). Histological hemophagocytosis was present in 15 of 17 cases (88%), while histological analysis was not performed in the two remaining cases. Histological hemophagocytosis was confirmed in all cases of patients with QF and in seven of nine cases (78%) with MSF. Fibrin ring granulomas were present in three of five cases of patients with QF on liver histology.20

Patient treatment consisted of doxycycline in all cases, in association with ceftriaxone (n = 2; 13%), levofloxacin (n = 3; 13%), intravenous immunoglobulins (n = 2; 13%), hydroxychloroquine

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Table 2

Comparison of patients with QF fever/Mediterranean spotted fever–associated hemophagocytic syndrome with patients without hemophagocytic syndrome and with patients with lymphoma–associated hemophagocytic syndrome

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>QF/MSF without HS n = 11</th>
<th>QF/MSF with HS n = 17</th>
<th>Lymphoma n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 (23–85)</td>
<td>42 (11–68)</td>
<td>60 (33–89)</td>
</tr>
<tr>
<td>Females</td>
<td>4 (35%)</td>
<td>5 (29%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Fever</td>
<td>10 (90%)</td>
<td>17 (100%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Splenomegaly, clinical</td>
<td>0</td>
<td>8 (47%)</td>
<td>5 (55%)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13 (10.7–14)</td>
<td>10.3 (7–15)</td>
<td>8.5 (6–12.7)</td>
</tr>
<tr>
<td>Platelets (×10⁹/l)</td>
<td>253 (260–560)</td>
<td>87 (3–830)</td>
<td>30 (8–45)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/l)</td>
<td>50 (20–300)</td>
<td>173 (35–700)</td>
<td>90 (31–388)</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/l)</td>
<td>50 (20–512)</td>
<td>123 (30–585)</td>
<td>29 (11–109)</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>55 (12–170)</td>
<td>200 (30–310)</td>
<td>164 (56–425)</td>
</tr>
<tr>
<td>Ferritinemia (μg/l)</td>
<td>430 (200–780)</td>
<td>4406 (275–15 000)</td>
<td>7400 (900–20 800)</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/l)</td>
<td>410 (250–630)</td>
<td>1074 (348–2301)</td>
<td>1178 (430–5334)</td>
</tr>
<tr>
<td>Triglycerides (g/l)</td>
<td>1.5 (1–2)</td>
<td>3 (1.1–3)</td>
<td>3.9 (1.3–6)</td>
</tr>
<tr>
<td>Henter’s criteria</td>
<td>1 (0–2)</td>
<td>4 (2–6)</td>
<td>4 (3–5)</td>
</tr>
<tr>
<td>Serology cut-off</td>
<td>416 (160–1200)</td>
<td>1024 (160–5120)</td>
<td></td>
</tr>
<tr>
<td>Intravenous immunoglobulins</td>
<td>0</td>
<td>2 (12%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0</td>
<td>1 (6%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Recovery (days)</td>
<td>7 (2–30)</td>
<td>10 (2–15)</td>
<td>36 (12–64)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>7 (70%)</td>
</tr>
</tbody>
</table>

All values are medians with ranges, or numbers with frequencies. QF, Q fever; MSF, Mediterranean spotted fever; HS, hemophagocytic syndrome.

a p < 0.05 QF/MSF–HS vs. QF/MSF without HS.
b p < 0.05 QF/MSF–HS vs. lymphoma–HS.
c p < 0.05 QF/MSF without HS vs. lymphoma–HS.
nausea/vomiting \( n = 1 \); 6\%), and corticosteroids \( n = 1 \); 6\%). The median duration of antibiotic treatment was 15 days (range 10–21 days). No deaths were recorded and all patients recovered with a median delay of 10 days (range 2–15 days).

3.2. Comparison of QF- and MSF-associated HS patients with those without HS and with those with lymphoma-associated HS

Eleven patients (median age 60 years, range 23–85 years; four females (35\%)) with QF \(( n = 6 \) ) and MSF \(( n = 5 \) ) without HS were included (Table 2). In these patients, complaints were fever \(( n = 10 / 11 \) ), cough \(( n = 3 \) ), headache \(( n = 4 \) ), arthralgias \(( n = 6 \) ), nausea/vomiting \(( n = 1 \) ), and skin lesions \(( n = 5 \) ), however none had splenomegaly. Acute-phase reactants (erythrocyte sedimentation rate >40 mm/1\(^{\text{th}}\) h and C-reactive protein (CRP) >10 mg/l) were present in all cases, although none had cytopenia. Hyperferritinaemia was noted in three of 10 cases (30\%), triglyceridaemia was normal in all cases, and hepatic cytosis was present in four of 10 cases (40\%). Patient treatment consisted of doxycycline in all cases, in association with quinolones \(( n = 2 \); 18\%) and hydroxychloroquine \(( n = 2 \); 18\%). The median duration of antibiotic treatment was 21 days (range 14–90 days). No deaths were reported and all patients recovered with a median delay of 7 days (range 4–30 days).

A second control group with a diagnosis of B lymphoma included 10 patients (median age 59.5 years, range 33–89 years; two females (20\%)) (Table 2). Eighty percent of patients had severe cytopenia, with anaemia in eight cases (81\%), thrombocytopenia in all cases, and neutropenia in three of 10 cases (30\%). Hyperferritinemia was noted in all cases, hypertriglyceridaemia in four of eight cases (50\%), and hepatic cytosis in six of 10 cases (60\%). Patient treatment consisted of intravenous immunoglobulins \(( n = 10 \); 100\%), with corticosteroids \(( n = 9 \); 90\%) and chemotherapy \(( n = 7 \) cases; 70\%). The median duration of hospitalization was 36 days (range 12–64 days) and seven of 10 (70\%) patients died.

When comparing patients with QF- and MSF-associated HS with patients without HS, HS-associated signs were significantly more frequent in patients with histological HS \(( p < 0.05 \) ), along with an increased number of Henter’s criteria (Table 2). In particular, whereas hemoglobin and platelet levels remained normal in patients without HS, median levels were significantly lower in patients with associated HS. Conversely, despite the more frequent presence of HS-associated signs, treatment was similar in these two subgroups, as were time to recovery and outcome. Similarly, HS-associated signs were significantly more frequent in patients with lymphoma than in patients without HS, although associated immunosuppressive agents and deaths were significantly more important in lymphoma patients (Table 2).

When comparing patients with QF- and MSF-associated HS with patients with lymphoma-associated HS, hemoglobin and platelet levels were significantly less important than in lymphoma patients, whereas other HS-associated signs and Henter’s criteria were similar (Table 2). In contrast, despite more frequent associated corticosteroid and immunoglobulin treatment in lymphoma patients, the outcome in these patients was dramatic in comparison to patients with QF- and MSF-associated HS, with deaths in 70\% of cases versus none in QF- and MSF-associated HS \(( p < 0.05 \) ).

4. Discussion

In the present study, we describe the association of HS with QF and MSF, and demonstrate the good outcome of HS in these patients. Even mild cytopenia (especially thrombocytopenia) can be seen in these infections; in our study in patients with associated HS, median levels of cytopenia were much lower and could increase the association of secondary HS. In contrast to malignancy- and HIV-associated HS, no immunosuppressive treatment was usually necessary in QF- or MSF-associated HS and a complete recovery could be attained with antibiotic treatment in almost all patients.

The diagnosis of HS can be challenging, and the presence of five of eight Henter’s criteria, as well as all histological hemophagocytosis is usually required. Even though these criteria were assessed only in children in primary HS, they remain widely used, although studies in both secondary HS and in adult HS are still lacking.\(^{15\%}\) Moreover, these criteria include NK cell activity and soluble IL-2R levels, which are rarely determined in routine practice. Similar to the cases reported in the literature, only a few of our patients fulfilled the Henter criteria, although NK cell activity and soluble IL-2R levels were not performed in our clinical study. Nevertheless, the presence of HS is highly probable in our patients, since HS signs were significantly more frequent in patients with suspected HS, and most of the patients also presented histological hemophagocytosis. However, HS remains otherwise largely underdiagnosed, and the use of Henter’s criteria, which combine certain criteria not routinely performed in daily practice, could make this diagnosis still more difficult.

Mild cytopenia could occur in QF or MSF without HS. In our patients with suspected HS, the number of cytopenias and their median levels significantly differed from patients without HS, since their frequency and median levels were similar to lymphoma-associated HS. Nevertheless, other diagnoses could explain the presence of cytopenia in QF and MSF. Bone marrow necrosis could also account for pancytopenia, and cases of autoimmune cytopenia have been described. Spleen rupture, although rare, could also complicate the outcome of these infections. Nevertheless, all of these situations remain rare, and the presence of other HS signs in our patients along with histological hemophagocytosis argues for HS-associated cytopenia in these patients. Hence, compared to patients without HS, the presence of cytopenia in patients with QF and MSF should warn of the presence of underlying HS and therefore prompt the investigation of other signs of HS.

The pathophysiology of acquired HS is not fully understood. An inappropriate Th-1 response to intracellular pathogens and deficiency in cytotoxicity of NK and T CD8 cells could result in persistent activation of lymphocytes and histiocytes, leading to the production of high levels of pro-inflammatory cytokines, upregulation of adhesion molecules, and expansion of inflammatory monocytes. Proliferation of cytotoxic cells associated with an uncontrolled immune response could drive excessive macrophage activation and induce HS, but data are lacking to definitely conclude on the HS pathways in these infections.

The prognosis of HS is variable and depends on the underlying disease, but generally remains poor.\(^{21\%}\) In patients with hematological disease and EBV-associated lymphoma, the prognosis is even more dramatic, as illustrated here in patients with lymphoma-associated HS. Moreover, recovery generally requires the use of specific treatments, such as corticosteroids or other immunosuppressive drugs.\(^{22\%}\) In the present study, even though HS-associated signs and Henter’s criteria were similar in patients with lymphoma HS and infectious HS, the outcome was nonetheless excellent in QF- and MSF-associated HS, in most cases without additional treatment other than antibiotics. Furthermore, while organomegaly, cytopenia, CRP levels, and other HS signs were more important in patients with HS in comparison to QF and MSF patients without HS, treatment, outcome, and recovery delays were similar in these patients, and thus argue against the need for any HS-specific treatment in patients with QF- and MSF-associated HS. In our study, additional treatment was used in two patients (immunoglobulins in two cases, with associated steroids in one of
them), and the need for treatment other than antibiotics in some selected patients could not be excluded.

Limitations of the present study include the small number of patients as well as its retrospective design. Most of the patients did not fulfill Henter’s HS criteria, although the comparison with a control group without HS highlighted the high frequency of HS-associated signs, thus justifying the diagnosis of HS. The absence of NK cell activity and soluble IL-2R levels could largely explain the absence of Henter’s criteria in these patients, and is counter-balanced by the presence of histological HS in most of these individuals.

In conclusion, hemophagocytosis is a rare occurrence during the course of Q fever and Mediterranean spotted fever. The presence of profound cytopenia should bring to mind the possible presence of associated HS, but HS seems to be associated with a good outcome in this condition.

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Conflict of interest: No conflict of interest to declare.

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