INTRODUCTION

Hemophagocytic lymphohistiocytosis or hemophagocytic syndrome (HPS) is a uncommon hematologic disorder typically characterized by the activation of macrophages/histiocytes with notable hemophagocytosis in the bone marrow and other reticuloendothelial systems (1).

The predominant clinical and laboratory features of HPS are fever (often hectic and persistent), cytopenias, hepatitis (elevated liver enzymes), hepatosplenomegaly (organomeg-
The clinical and laboratory findings in patients with HPS are summarized in Table II.

The major findings in the microscopic examination of the bone marrow specimens obtained from the patients with HPS were megaloblastic anemia (n=2), chronic granulomatous disease (n=1), and bone marrow sea-blue histiocyte syndrome (n=1).

**Table I: Diagnostic criteria for hemophagocytic syndrome**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tr>
<td><strong>1. Familial disease/known genetic defect</strong></td>
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<td><strong>2. Clinical and laboratory criteria (5/8 criteria)</strong></td>
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<tr>
<td><em>Fever</em></td>
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<td><em>Splenomegaly</em></td>
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<td>*Cytopenia = &gt; 2 cell lines</td>
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<td>Hemoglobin &lt; 90 g/l (below 4 weeks &lt; 120 g/l)</td>
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<td>Platelets &lt; 100 · 109/l</td>
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<td>Neutrophils &lt; 1 · 109/l</td>
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<tr>
<td>*Hypertriglyceridemia and/or hypofibrinogenemia</td>
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<td>Fasting triglycerides = &gt; 3 mmol/l</td>
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<td>Fibrinogen &lt; 1.5 g/l</td>
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<td>*Ferritin &gt; 500 µg/l</td>
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<tr>
<td>*sCD25 = &gt; 2400 U/ml</td>
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<tr>
<td>*Decreased or absent NK-cell activity</td>
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<tr>
<td>*Hemophagocytosis in bone marrow, CSF or lymph nodes</td>
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</table>

From Schneider et al (10).

**RESULTS**

Fifteen patients out of 288 cases with unspecific cytopenia were reported to be effected with HPS (Figure 2).

Eight patients were male (53.3%) and 7 patients were female (46.7%) with a mean age of 39.7±20.7 (range: 14-72) years at the time of diagnosis (Figure 3).
In terms of bone marrow cellularity, there were 9 cases (60%) with normocellularity, 5 cases (33.3%) with hypercellularity and 1 case (6.7%) with hypocellularity.

Two patients (13.3%) died before the diagnosis of HPS was made. The remaining patients were discharged after appropriate management.

**DISCUSSION**

This series showed that almost 5% of the patients with otherwise unexplained progressive cytopenia suffer from HPS. Although the cytopenia is a key finding in patients with HPS, to our knowledge there is no report about the real frequency of this condition among patients with unexplained cytopenia.

In a series by Fukaya et al., 1014 inpatient patients with systemic autoimmune diseases were evaluated as to the presence of HPS. Finally, 30 patients (2.3%) fulfilled the HPS criteria (11).

The male to female ratio was 1.1 in our study. This finding is in line with the previous reports indicating that there is no obvious gender preponderance in cases with HPS (12,13).

The mean age of the patients was 39.7±20.7 (range: 14-72) years in the present study, with the most common age group 20-29 years. In another study by Ishii et al., the age distribution showed a peak of autoimmune disease- and infection-associated HPS in children, while familial type and lymphoma-associated HPS occurred almost exclusively in infants and the elderly, respectively (14). Thus, it seems that the age of the patients is a key determiner of the type of HPS.

It should be noted that the possible underlying causes of HPS were not investigated in our study, because it was not part of our objectives. However, the cases with primary HPS were apparently not included because there was another referral centre specialized in pediatric hematologic/oncolologic disorders in the region which did not participate in the present study. Further multicenter studies are possibly indicated in this regard to have more definite conclusions drawn.

The main clinical and laboratory findings of the studied patients with HPS were cytopenia, fever, hyperferritinemia, elevated erythrocyte sedimentation rate (ESR), hypertriglyceridemia, organomegaly, deranged (raised) liver enzymes, lymphadenopathy, neurological symptoms, and rash in a decreasing order of frequency. All these findings are in conformity with previous reports (12,15) except for elevated ESR, indicating a role of inflammatory
process in some of the patients. This needs to be clarified in further studies.

Before HPS was confirmed and an appropriate therapy started, two patients (13.3%) with HPS died in our series. On the other hand, all the remaining 13 patients were discharged after receiving sufficient treatment. Hence, it may be concluded that first, HPS carries a significant mortality rate if left untreated; and second, HPS is still a great challenge to be timely diagnosed (16,17).

In summary, although HPS is generally considered as a rare entity, the current study showed that this may not be quite accurate at least among patients with otherwise unexplained cytopenia. Likewise, the patients with HPS are possibly a high risk group for early mortality if left untreated (18). As a consequence, it seems wise for all patients with unexplained cytopenia to undergo a thorough examination for possible presence of HPS.

To the best of our knowledge, this is the first study that deals with the association between unexplained cytopenia and HPS. Due to the heterogeneity of the disease, particularly in terms of its characteristics (14), as well as the race and ethnicity of the patients (9), further controlled investigations may be warranted to have the issue elucidated.

REFERENCES


2. **Filipovich AH**: Hemophagocytic lymphohistiocytosis (HLH) and related disorders. Hematology Am Soc Hematol Educ Program 2009, 127-131


