Secondary haemophagocytic syndrome (sHS) revisited: A 6-years real-life study on presentation, aetiology and treatment

A. Stefos, P. Lalou, M. Boulbou, S. Georgiadou, N. Gatselis, K. Makaritsis, G.N. Dalekos, E.I. Rigopoulou

Department of Medicine and Research Lab of Internal Medicine; Department of Pathology, Medical School, University of Thessaly, Larissa, Greece
Haemophagocytic Syndrome
Introduction

- Immuno-mediated, hyperinflammatory, life-threatening disease
  1939 – Scott & Robb Smith

- Primary HS (Familial Haemophagocytic Lymphohistiocytosis) – genetic

  Secondary HS - reactive

- Estimated incidence
  - Childhood – 1 to 10 /10^6
  - Adults – 1/800000

Manuel Ramos-Casals et al Lancet 2014
Activation of immune system due to a triggering factor (infection, neoplasm, autoimmune diseases, other)

The underlying mechanism is a defect in granule-mediated cytotoxicity, resulting in deregulation of cytolytic activity

Persistent activation of lymphocytes and histiocytes

Enhanced antigen presentation and repeated interferon $\gamma$-dependent stimulation of Toll-like receptors

Uncontrolled proliferation and phagocytic activity
- Exaggerated inflammatory response caused by hypersecretion of proinflammatory cytokines such as IFN-γ, TNF-α, IL-1, IL-4, IL-6, IL-8, IL-10, and IL-18.

- This cytokine storm could be pathogenically related to the development of the main clinical and laboratory features of haemophagocytic lymphohistiocytosis and contributes to tissue damage and progressive systemic organ failure.
Five of the following criteria

- Fever ≥38.5°C or more
- Splenomegaly
- Cytopenias (affecting at least two of three lineages in the peripheral blood) Hb<10 g/dl, PLT<100x10^6/µl, ANC<1.0x10^6/µl
- Hypertriglyceridaemia >265mg/dL (fasting) and hypofibrinogenaemia <150 mg/dL (or both)
- Haemophagocytosis in bone marrow, spleen, lymph, nodes, or liver
- Low or absent natural killer-cell activity
- Ferritin greater than 500 ng/ml
- Increased soluble CD25 concentration (alpha chain of soluble interleukin 2 receptor)

Henter JI et al Pediatr Blood Cancer 2007
sHS- Results

32 patients

Retrospective analysis over the past 6 years

Clinical manifestations

Laboratory findings

Causes of HS

Management

Outcome
sHS- Results

32 patients
56.25% ♂
Age (median (range)): 57 (17-82) ys
sHS - Clinical manifestations

Symptoms

Median time to admission: 15 days

Median time to diagnosis: 5 days

- Fever >38,5: 100%
- Lungs: 37,5%
- CNS: 15,6%
- GIS: 3,1%
- Kidneys: 28,1%
- Skin: 25%
sHS - Clinical manifestations

- Lymphadenopathy: 50%
- Splenomegaly: 68.75%
- Hepatomegaly: 68.75%
sHS- Laboratory findings

- Anaemia: 81.2%
- Leukopenia-low WBC: 59.3%
- Thrombopenia: 84.3%
- Pancytopenia: 37.5%
- Ferritin: 100%

Special note: 15% > 10,000ng/ml

Laboratory findings:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertriglyceridaemia</td>
<td>81.3%</td>
</tr>
<tr>
<td>Hypofibrinogaemia</td>
<td>15.6%</td>
</tr>
<tr>
<td>Increased LFT’s</td>
<td>87.5%</td>
</tr>
<tr>
<td>DIC</td>
<td>12.5%</td>
</tr>
</tbody>
</table>
sHS- Laboratory findings

- NK-cells activity available in 1/32
- Histology (bone marrow, lymph node, spleen, subcutaneous node) available in 23/32 (71.8%)

Haemophagocytosis
# sHS- Causes

<table>
<thead>
<tr>
<th>Infections (n=26)</th>
<th>Neoplastic Disease (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Bacterial</td>
<td>• Tumor 20% (1/5)</td>
</tr>
<tr>
<td>30.7% (8/26)</td>
<td>• NHL 80% (4/5)</td>
</tr>
<tr>
<td>▪ Viral</td>
<td></td>
</tr>
<tr>
<td>23.1% (6/26)</td>
<td></td>
</tr>
<tr>
<td>▪ Leishmaniasis</td>
<td></td>
</tr>
<tr>
<td>46.2% (12/26)</td>
<td></td>
</tr>
</tbody>
</table>
sHS- Treatment

32 patients

(28) 87.5% Causative treatment + immunomodifying treatment

8% steroids

92% steroids + IVIG

(4) 12.5% causative treatment (L-AMB)

Antibiotics Antiviral chemotherapy
sHS - Outcome

6/7 underlying cause
1/7 nosocomial infection

cure 78%

death (7) 22%
sHS- Conclusions

• sHS carries a remarkable morbidity and mortality
• Underlying infections are the major cause of sHS (86.5%) and therefore, they should be thoroughly investigated in an index patient with sHS
• Early recognition and treatment with intravenous γ-immunoglobulin in association with corticosteroids proved to be an efficient treatment option for successful outcome in this life-threatening condition
Thank you