# Hemophagocytic Syndrome with Hyperferritinemia: a Stormy Immunological Response

Gisele Zandman-Goddard MD[1,3] and Yehuda Shoenfeld MD[2,3]

[1]Department of Medicine C, Wolfson Medical Center, Holon, Israel
[2]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

**KEY WORDS:** hemophagocytic syndrome, hyperferritinemia, cytokine storm, catastrophic antiphospholipid syndrome (cAPS), disseminated intravascular coagulopathy (DIC)

*IMAJ* 2013; 15: 253–254

Hemophagocytic syndrome (also known as hemophagocytic lymphohistiocytosis or macrophagic activating syndrome) is an excessive immunological response leading to a cytokine storm. Clinically, HPS mimics other diseases such as sepsis and hence is often undetected if not sought. The clinical diagnosis is based on five of eight findings: fever, splenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hyperferritinemia (above 500 ng/ml), low or absent natural killer cell activity, and elevated soluble interleukin-2 receptor alpha levels. Molecular mutations (PRF1, UNC, Munc18-2, Rab27a, STX11, SH2D1A, BIRC4) or hemopagocytic cells within the bone marrow biopsy are diagnostic. Early treatment includes steroids and/or cyclosporine. HPS secondary to Epstein-Barr virus infection is treated successfully with etoposide. In one study, the median time from suspicion to diagnosis was 5 days (range 1–27 days). Corticosteroids and/or cyclosporine was the most frequently used treatment regimen. Other agents used were etoposide, intravenous immunoglublin, cyclophosphamide, and chemotherapy. The mortality rate was 72%, with multi-system organ failure being the most common cause of death. Median survival time from diagnosis was 35 days [1].

HPS and related diseases – including sepsis, systemic inflammation response syndrome, multi-organ dysfunction syndrome, and adult-onset Still's disease – share a cytokine storm and hyperferritinemia as a common pathogenesis. In HPS, natural killer cell and cytotoxic T cell activity secondary to an impairment of the granzyme system leads to uncontrolled perforin release. The perforin and granzyme proteins are physiologically usually released in response to a virally active or tumor-derived target cell, leading to controlled apoptosis. In HPS the result is a cytokine storm and the release of high levels of interferon-gamma and IL-10, whereas elevated levels of IL-6 are seen in sepsis and not HPS [2].

A genetic familial type of HPS exists, where the mutations recognized to date affect granule-dependent cytotoxicity. This form of HPS appearing in childhood will not be discussed here. Acquired forms of adult HPS can be secondary to infections, hematologic malignancies, autoimmune diseases such as systemic lupus erythematosus, or following biologic drug exposure [3]. In one observational study, 15 episodes of HPS occurred in SLE patients with active disease. The patients appeared febrile, showed no sign of infection, had evidence of active lupus, and did not respond to intravenous immunoglobulin. Some had elevated titers of anticardiolin antibodies. All had excessive hyperferritinemia. Hemophagocytosis was diagnosed on bone marrow biopsy and the patients responded to steroids, while an additional immunosuppressive agent was necessary for others. Worse prognoses in HPS include anemia, thrombocytopenia, disseminated intravascular coagulopathy, jaundice, and hyperferritinemia [4]. Blockade of tumor necrosis factor-alpha may be a therapeutic option in SLE patients who develop a cytokine storm manifesting as HPS [5].

In autoimmune diseases, hyperferritinemia is a marker for Still's disease, which is also characterized by cytokine hyperactivity. Abnormal levels of ferritin are also encountered in SLE, rheumatoid arthritis, multiple sclerosis, and thyroiditis [6].

In this issue of *IMAJ*, Sacks and co-authors [7] present the complicated case of a patient with adult Still's disease who developed Klebsiella urosepsis and hyperferritinemia (39,727 ng/ml), DIC, limb ischemia and gangrene. Quadruple limb amputation was performed due to a life-threatening situation from which the patient recovered. She fulfilled the criteria for catastrophic antiphospholipid syndrome and HPS (the cells were identified in the bone marrow). Catastrophic APS is a severe form of APS characterized by multiple organ demise following specific triggers such as infection and surgery. cAPS has an increased mortality rate when compared to classical APS. Treatment entails the addition of immunosuppressants to anticoagulants. Hyperferritinemia in cAPS is yet to be investigated.

HPS = hemophagocytic syndrome

IL = interleukin
SLE = systemic lupus erythematosus

DIC = disseminated intravascular coagulopathy
APS = antiphospholipid syndrome
cAPS = catastrophic antiphospholipid syndrome

Are there common mechanisms for cAPS and HPS? Firstly, both cAPS and HPS may be induced by infections. In HPS, the commonly associated viral infections include Epstein-Barr virus and herpes simplex. In cAPS, the infections may be bacterial, viral, or other. The common infections include pneumonia or urinary tract infection. The common viral associated pathogens leading to cAPS include herpes simplex, among others.

What is the mechanism for hyperferritinemia in the immune response? Elevated ferritin levels are not only acute-phase reactants. Ferritin has a direct effect on the immune system. Macrophage ferritin accumulates during inflammation, when serum iron decreases and iron in specific cells increase. Pathogen ferritins are miniferritins that confer resistance to oxidative damage. During infection and inflammation, it is the relative "iron deficiency" created by the host redistribution of iron, with a deficit in serum that leads to an increase in macrophages, synthesized in response to environmental iron deficiency and associated with virulence.

Ferritin is released during cellular damage in the liver and spleen. There is increased secretion of ferritin by macrophages and hepatocytes. In addition, there is decreased clearance due to reduced glycosylation or down-regulation of ferritin receptors. Ferritin may act directly by influencing oxidative stress [6].

It is not yet clear whether similar mechanisms lead to pronounced inflammatory states as seen in Still's disease, DIC, HPS and cAPS. Are these syndromes part of a spectrum? Is the patient susceptible to these states once an inflammatory state begins? Do these patients have a related genetic background? Infections in autoimmune patients (HPS, cAPS) trigger the development of these diseases. Microthrombi ensue (DIC, CAPS) following the infection, leading to a life-threatening disease. All are characterized by a cytokine storm. Hyperferritinemia is present in this spectrum, but is yet to be determined in cAPS and DIC.

**Address for correspondence:**
**Dr. G. Zandman-Goddard**
Dept. of Medicine C, Wolfson Medical Center, P.O. Box 63, Holon 58100 Israel
**Phone:** (972-3) 502-8674
**Fax:** (972-3) 502-8810
**email:** goddard@wolfson.health.gov.il

### References

1. Shabbir M, Lucas J, Lazarchick J, Shirai K. Secondary hemophagocytic syndrome in adults: a case series of 18 patients in a single institution and a review of literature. *Hematol Oncol* 2011; 29: 100-6.
2. Castillo L, Carcillo J. Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation. *Pediatr Crit Care Med* 2009; 10: 387-92.
3. Amaral MC, Alves JD. Pathogenesis of multiorganic failure in autoimmune diseases. *Autoimmun Rev* 2009; 8: 525-8.
4. Lambotte O, Khellaf M, Harmouche H, et al. Characteristics and long-term outcome of 15 episodes of systemic lupus erythematosus-associated hemophagocytic syndrome. *Medicine* 2006; 85: 169-82.
5. Aringer M, Smolen JS. Therapeutic blockade of TNF in patients with SLE – promising or crazy? *Autoimmun Rev* 2012; 11: 321-5.
6. Zandman-Goddard G, Shoenfeld Y. Ferritin in autoimmune diseases. *Autoimmun Rev* 2007; 6: 457-63.
7. Sacks S. Adult onset Still's disease complicated by hemophagocytic syndrome and catastrophic antiphospholipid syndrome resulting in four limb amputation. *IMAJ Isr Med Assoc J* 2013; 15: 192-4.

## Capsule

### Crystal structure of the entire respiratory complex I

Complex I is the first and largest enzyme of the respiratory chain and has a central role in cellular energy production through the coupling of NADH:ubiquinone electron transfer to proton translocation. It is also implicated in many common human neurodegenerative diseases. Baradaran and team report the first crystal structure of the entire, intact complex I (from Thermus thermophilus) at 3.3Å resolution. The structure of the 536 kDa complex comprises 16 different subunits, with a total of 64 transmembrane helices and 9 iron-sulphur clusters. The core fold of subunit Nqo8 (ND1 in humans) is, unexpectedly, similar to a half-channel of the antiporter-like subunits. Small subunits nearby form a linked second half-channel, which completes the fourth proton-translocation pathway (present in addition to the channels in three antiporter-like subunits). The quinone-binding site is unusually long, narrow and enclosed. The quinone headgroup binds at the deep end of this chamber, near iron-sulphur cluster N2. Notably, the chamber is linked to the fourth channel by a 'funnel' of charged residues. The link continues over the entire membrane domain as a flexible central axis of charged and polar residues, and probably has a leading role in the propagation of conformational changes, aided by coupling elements. The structure suggests that a unique, out-of-the-membrane quinone-reaction chamber enables the redox energy to drive concerted long-range conformational changes in the four antiporter-like domains, resulting in translocation of four protons per cycle.

*Nature* 2013; 494: 443

Eitan Israeli

**"Art is the elimination of the unnecessary"**

Pablo Picasso (1881-1973), Spanish painter, sculptor, printmaker, ceramicist and stage designer. As one of the greatest and most influential artists of the 20th century, he is widely known for co-founding the Cubist movement and for the wide variety of styles that he helped develop and explore