

# The Hemophagocytic Syndrome/Macrophage Activation Syndrome: A Final Common Pathway of a Cytokine Storm

Martine Szyper-Kravitz MD

Center for Autoimmune Diseases and Department of Medicine B, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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The hemophagocytic syndrome, or hemophagocytic lymphohistiocytosis, is a clinical syndrome associated with a variety of underlying conditions leading to a severe inflammatory response. This inflammatory response is induced by a "cytokine storm" and is characterized by the proliferation and activation of macrophages in the reticuloendothelial system, causing lymphadenopathy, hepatosplenomegaly and pancytopenia. The hallmark of this syndrome is the impairment or absence of natural killer and cytotoxic T cell function. The uncontrolled and ineffective immune activation results in multiorgan dysfunction.

HPS is classified as primary or genetic, and secondary or reactive. Both types, which are associated with increased mortality, can occur at any age and be precipitated by infections. Genetic or primary HPS is an autosomal-recessive or x-linked disease and can be familial or associated with immune deficiencies. Secondary or reactive HPS occurs most commonly in the setting of infections, although most patients have no known immune defect. The most common triggers are viruses of the herpes group, especially Epstein-Barr virus, but bacteria, parasites and fungi have all been reported as inciting

agents. Malignancies and especially lymphomas can be associated with reactive HPS. The prevalence of HPS is difficult to estimate due to its rarity. A special form of HPS develops in association with autoimmune diseases and is termed macrophage-activation syndrome. MAS occurs most commonly in the setting of systemic juvenile rheumatoid arthritis, systemic lupus erythematosus, adult Still's disease and Sjogren syndrome, but occurrence with other autoimmune diseases such as systemic sclerosis and vasculitis has been reported [1]. The prevalence of MAS in one report was 3% [1]. Mortality due to MAS or HPS associated with autoimmune diseases is significantly high, 38.5%, according to a recent French multicenter study [2].

Clinically, HPS is characterized by persistent fever, lymphadenopathy, hepatosplenomegaly and pancytopenia. Typical laboratory abnormalities include elevated levels of liver transaminases, bilirubin, lactate dehydrogenase, ferritin and triglycerides, but low levels of fibrinogen. The active phase of the disease is characterized by increased levels of the  $\alpha$ -chain of the soluble interleukin-2R (sCD25), which makes it a valuable marker for diagnosis [3] as well as for prognosis since increased levels correlate with increased mortality [4]. Impairment or absence of NK and cytotoxic T cell activity has also been demonstrated [5].

The clinical picture and laboratory manifestations result from increased levels of inflammatory cytokines secreted

by activated T cells and macrophages, particularly Th1 cytokines such as interferon-gamma, IL-12 and IL-18, which correlate with disease activity [6]. The pro-inflammatory cytokines IL-1 $\beta$ , IL-6 and tumor necrosis factor-alpha are also elevated. This highly pro-inflammatory milieu is responsible for the clinical picture: elevated levels of IL-1 and IL-6 cause prolonged fever; TNF $\alpha$  and INF $\gamma$  lead to pancytopenia; TNF $\alpha$  inhibits lipoprotein lipase resulting in hypertriglyceridemia. Organ infiltration by activated lymphocytes and histiocytes results in lymphadenopathy, hepatosplenomegaly and liver dysfunction.

Several genetic mutations have been described in the primary form of HPS, all leading to defective immune activation and regulation. The known mutations in HPS interfere with several processes of cytotoxic activity, such as fusion and trafficking of cytolytic vesicles and release of perforin and granzyme. Less is known about the pathogenesis of secondary HPS. In patients with virus-associated HPS, the "cytokine storm" accompanying the infection, the regulation of complement activity, and the presence of Toll-like receptors have been suggested as possible mechanisms. Some investigators [7] have proposed that in patients with EBV-associated HPS the proliferation of EBV infected-T cells selectively up-regulates the expression of TNF $\alpha$ , INF $\gamma$  and other cytokines, which stimulate macrophages and histiocytes and result

HPA = hemophagocytic syndrome

MAS = macrophage-activation syndrome  
NK = natural killer

IL = interleukin  
TNF $\alpha$  = tumor necrosis factor-alpha  
INF $\gamma$  = interferon-gamma  
EBV = Epstein-Barr virus

in their uncontrolled accumulation in various organs.

The diagnostic criteria for HPS include fever, splenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, abnormal natural killer cell function, elevated soluble IL-2 receptor-alpha level and elevated ferritin level (> 500 µg/L). Five of the eight criteria are required for the diagnosis.

In 2004 the Histiocyte Society revised the treatment protocol for HPS, which includes dexamethasone, etoposide and cyclosporin A. Early administration of etoposide was shown to play a crucial role in the induction of remission and survival [8]. In familial cases of HPS chemotherapy can be followed by stem cell transplantation.

This issue of *IMAJ* features a case report illustrating the versatility of this serious and potentially fatal syndrome. Aikawa et al. [9] describe the development of MAS in a 10 year old patient with active juvenile rheumatoid arthritis who first presented with pneumonia. He later developed multiorgan involvement with pancytopenia, coagulopathy, increased liver enzymes, and extreme elevations in the levels of ferritin – all compatible with the clinical and laboratory features of HPS or MAS. The diagnosis was confirmed by a bone marrow aspirate showing activated macrophages with erythrophagocytosis. Treatment with methylprednisolone and cyclosporine A induced a sustained complete remission.

In 2007 a 20 year old man was admitted to our medical department with fever, lymphadenopathy, hepatosplenomegaly, mild pancytopenia, elevated liver enzymes and atypical lymphocytes on his blood smear. He was discharged with the working diagnosis of infectious mononucleosis-like disease. He was readmitted 2 weeks later with persistent fever, skin rash and marked splenomegaly. He had extreme levels of

ferritin (11,125 ng/ml N-18-323) and developed coagulopathy. A polymerase chain reaction test for EBV was highly positive, leading to the diagnosis of EBV reactivation. Serum levels of IL-2 receptor were extremely high (15,732 U/mL N-2000 U/mL) and NK cell activity extremely low, suggesting the diagnosis of HPS. Despite intensive care and aggressive treatment including antibiotics, cyclosporine A, intravenous immunoglobulin and anti-CD20 (rituximab), the patient developed multiorgan failure with acute respiratory distress syndrome and died on hospital day 25. Histological, phenotypical and molecular features of the bone marrow, lymph node, and liver biopsies disclosed infiltration by a T cell lymphoproliferative disease with a natural killer phenotype. Occasional histiocytes with signs highly suggestive of hemophagocytosis were found in the lymph node biopsy. We concluded that the patient had EBV-associated lymphoma with HPS.

The case presented in this issue, together with the personal experience of clinicians who encounter and treat the rare cases of HPS, illustrate the different facets of this syndrome. HPS or MAS is a clinical and potentially fatal syndrome that may result from a variety of triggers such as infections, autoimmune diseases, pregnancy, malignancies, and drugs. Interestingly, biological agents such as etanercept (for rheumatoid arthritis) have been associated with the induction of HPS as well as with cases of HPS remission [10]. HPS may mimic systemic diseases and may sometimes be associated with them. The association of HPS with infection heightens the role of a deranged immune response at the beginning of this syndrome, particularly EBV, even in cases of primary HPS. Molecular studies for mutations associated with HPS are costly and not routinely performed. The conversion of all these variables poses a tremendous

diagnostic challenge. As physicians are commonly confronted with patients presenting with persistent fever, organomegaly and pancytopenia, it should be remembered that this usually benign and frequently labeled "viral disease" may masquerade a more sinister and fatal syndrome.

#### Correspondence:

**Dr. M. Szyper-Kravitz**

Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel

**Phone:** (972-3) 530-2652

**email:** martine@post.tau.ac.il

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