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REVIEW

Hemophagocytic syndromes

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Review

Summary Hemophagocytic syndromes (hemophagocytic lymphohistiocytosis, HLH) represent a severe hyperinflammatory condition with the cardinal symptoms prolonged fever, cytopenias, hepatosplenomegaly, and hemophagocytosis by activated, morphologically benign macrophages. Biochemical markers include elevated ferritin and triglycerides, and low fibrinogen. Whereas in children several inherited immune deficiencies may lead to this syndrome, most adults with HLH have no known underlying immune defect. Nevertheless, impaired function of natural killer (NK) cells and cytotoxic *T*-cells (CTL) is characteristic for both genetic and acquired forms of HLH. Frequent triggers are infectious agents, mostly viruses of the herpes group. Malignant lymphomas, especially in adults, may be associated with HLH. A special form of HLH in rheumatic diseases is called macrophage-activation syndrome.

Initially HLH may masquerade as a normal infection since all symptoms, even though less pronounced, may also be found in immune competent patients. Patients with HLH, however, cannot control the hyperinflammatory response which, if untreated, is fatal in genetic cases and in a high percentage of acquired cases. Awareness of the clinical symptoms and of the diagnostic criteria of HLH is important to start life-saving therapy with immunosuppressive/ immunomodulatory agents in time.

Hemophagocytosis by macrophages as an isolated phenomenon can be found in many situations such as hemolytic anemia, metabolic diseases or malignancies. In hemophagocytic lymphohistiocytosis (HLH), hemophagocytosis is part of a sepsis-like clinical syndrome caused by severe hypercytokinemia as the consequence of a highly stimulated but ineffective immune response.

Classification and terminology of HLH

HLH occurs in all age groups. It is not a single disease but a clinical syndrome that can be encountered in association with a variety of underlying

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conditions leading to the same characteristic inflammatory phenotype (Fig. 1).

Genetic forms of HLH

Genetic (primary) HLH is inherited in an autosomal recessive or *x*-linked manner and can be divided into two subgroups: familial HLH (FHLH) in which the clinical syndrome of HLH is the only manifestation, and the immune deficiencies Chédiak-Higashi syndrome (CHS 1), Griscelli syndrome (GS 2) and *x*-linked proliferative syndrome (XLP) which have distinctive clinical features besides the sporadic, though frequent development of HLH.

In FHLH the onset of the disease is below one year of age in 70-80% of the cases,[1,2] however, several late-onset cases in adolescence and even adulthood have been published.[3,4]

Acquired forms of HLH

Acquired (secondary) HLH can occur in all age groups. It was first described by Risdall and colleagues in adults with a viral infection following organ transplantation.[5] Subsequently it became clear that most patients had no known underlying immune defect and that also nonviral agents such as bacteriae, protozoae and fungi could trigger HLH .[6,7] Consequently the term virus-associated hemophagocytic syndrome (VAHS) was replaced by infection-associated hemophagocytic syndrome (IAHS), in many cases also without the proof of an infectious agent as long as the classical symptoms were present. Leading triggering agents in IAHS are viruses of the herpes group, especially Epstein-Barr virus (EBV) and cytomegalovirus (CMV); a frequent nonviral agent associated with HLH in children is leishmania.[8,9]

The identification of an infectious organism does not help to discriminate between genetic and acquired forms of HLH, since also most episodes in genetic HLH are triggered by infections.[10,11]

Acquired HLH in association with malignant diseases, especially lymphomas (lymphoma-associated hemophagocytic syndrome; LAHS), has been reported mostly in adults.[12,13] HLH can develop before or during treatment, associated with an infection or without a known triggering factor. Interestingly, in patients with LAHS from Japan, the EBV genome was detected only rarely in patients with *B*-cell lymphoma but was present in more than 80% of patients with T/NK cell lymphoma.[14] EBV-infected T/NK cells appear to play a major role in the development of LAHS as well as EBV-associated HLH without lymphoma.[15]

Macrophage-activation syndrome (MAS), a special form of HLH which occurs in children and adults with autoimmune diseases will be described below separately.

Clinical symptoms and laboratory findings

Prolonged fever, hepatosplenomegaly and cytopenias are the cardinal symptoms of HLH. Lymphadenopathy, rash, icterus or neurological symptoms

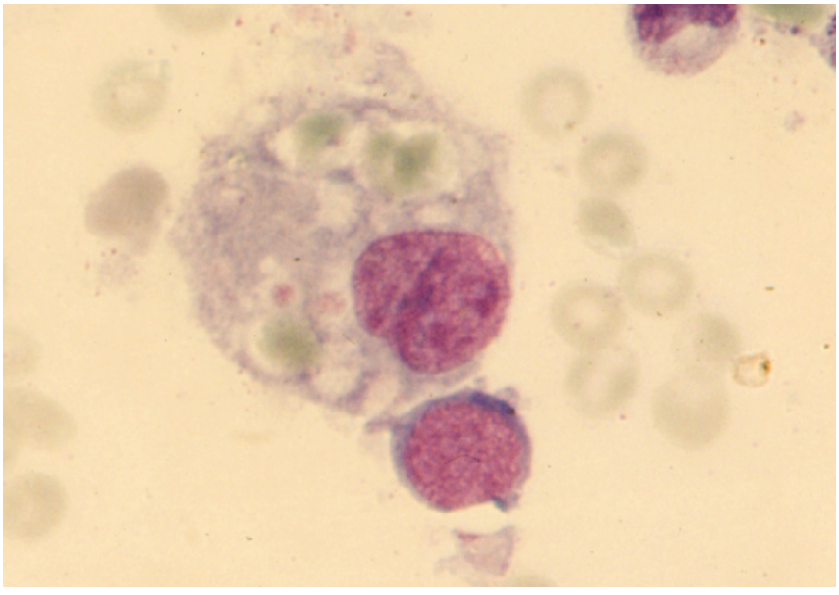

Figure 1 Histiocyte with phagocytosis of erythrocytes and platelets.