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REVIEW ARTICLE

Hemophagocytic lymphohistiocytosis — what's new in old diagnostic and clinical criteria?

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a condition of overexpressed inflammatory response resulting in hypercytokinemia, macrophages infiltration and subsequent multiple organ failure. Without treatment, it leads to death. The main etiological factors include: viral, bacterial and parasitic infections, malignancies and autoinflammatory diseases. The main clinical manifestations are: high fever ≥38°C, lymphadenopathy, splenomegaly, hepatomegaly. Central nervous system involvement occurs in 30–70% of cases. Less common symptoms include: dyspnea, cough, arrhythmias, jaundice, peripheral edema, rashes, albinism and diarrhea. The picture of the disease seen in laboratory tests consists of: duopenia, hypofibrinogenemia (<150 mg/dL) high D-dimers level, hyperferritinemia. Other abnormalities include hypertiglyceridemia, elevated liver enzymes, hyperbilirubinemia, hypoalbuminemia and hyponatremia. Diagnostics include: laboratory tests, histopathological examination, lumbar puncture, radiological imaging, functional test and genetic checking. It is important to rule out factors mimicking HLH. Some of the old, well known criteria are no more relevant nowadays. The aim of the therapy is immunosuppressive, immunomodulatory and anti-cytokine treatment, using HLH-2004 protocol. In secondary HLH, elimination of the causative agent is critical. In case of primary HLH, or relapse of secondary forms allogenic transplantation is the only curative treatment. The prognosis is uncertain.

Key words: hemophagocytic syndrome, hypercytokinemia, macrophage activation syndrome

Introduction

Definition

Hemophagocytic lymphohistiocytosis (HLH) is a condition of specific hyperinflammation that directly leads to death without prompt treatment. It should not be classified as a disease, but rather as a certain set of clinical conditions that lead to an overexpressed inflammatory response resulting in infiltration of internal organs by macrophages and subsequent multiorgan failure [1].

Pathophysiology

In congenital syndromes, there is a defect in the production of certain proteins responsible for the correct course of the granule-dependent cytotoxicity mechanism. These cytotoxic granules contain granzymes and protein-perforin, which are released at the immunological synapse between infected cells and cytotoxic lymphocytes and NK cells. As a result of the defect described above, a paralysis of the killing cells occurs and, consequently, a vicious circle is set in motion — the helper lymphocytes, stimulated by the trigger, instead of stimulating the NK cells and cytotoxic lymphocytes, cause their inhibition and dysfunction. However, they stimulate production of IFN-γ and stimulate macrophages, which together with INF-γ fuel the so-called “cytokine storm” leading to even greater paralysis of cytotoxic lymphocytes and NK cells, which cannot cope with elimination of infectious agents. Under the influence of INF-γ and macrophages, infiltration of organs occurs, leading to organ dysfunction. The cytokines that play a key role in hyperinflammation include IL-6, IL-10, INF-γ, as well as IL-1, IL-8, IL-12, IL-18, and TNF-α [1, 2].

For acquired forms of HLH, the exact pathogenesis is not fully understood. It seems that viruses and other infectious agents block the function of NK and cytotoxic lymphocytes. It has been observed, e.g. in the case of EBV-acquired HLH, that NK and cytotoxic lymphocytes are directly infected (instead of B lymphocytes) and destroyed by the virus. This infection stimulates helper lymphocytes and results in the production of INF-γ, proinflammatory cytokines, which in turn activate macrophages and stimulate the secretion of TNF-α, IL-6, plasminogen activator, and ferritin.

A cascade of these reactions leads to the defined metabolic abnormalities and clinical manifestations of HLH [2].

Clinical picture

Usually, the first symptoms of HLH occur in the form of full-blown syndrome, resembling sepsis, but there are hemophagocytic syndromes with an initially sparse symptomatic course. The primary forms usually occur at a young age, while the acquired form affects children older than 2 years of age. There are rare exceptions, however, and congenital forms of HLH are sometimes revealed even in teenagers [3, 4].

Most patients present with high, non-remitting fever, ≥38°C, poorly responsive to medication as a result of proinflammatory cytokines. Exceptions are premature infants, in whom the temperature may be even lower than 36.6°C. Other clinical features include splenomegaly (97% of patients) and hepatomegaly (>50% of patients) with or without laboratory signs of liver dysfunction. Very often, generalized or local lymphadenopathy (effect of hemophagocytosis in lymph nodes) is observed in patients. Kidney involvement (edemas, dysuria, anuria) and pulmonary infiltration (dyspnea, cough, decreased saturation), or skin rash can be seen in HLH-MAS (macrofage activation syndrome). 30–73% of patients develop central nervous system (CNS) involvement. This usually accompanies the generalized form of the disease, but sometimes it is the only symptom of HLH. Clinical symptoms include seizures (mainly in young children), positive meningeal signs, ataxia (in older children), opisthotonos and cranial nerve palsy. It happens that patients without neurological symptoms have changes in imaging studies and vice versa — patients with multiple neurological changes do not always have visible abnormalities in radiological imaging. Less frequent clinical manifestations of hemophagocytic syndrome include: arrhythmia (mainly in the course secondary to Kawasaki disease) or chronic bloody diarrhea (XLP-2), albinism or pseudoalbinism — typical for primary HLH such as Hermansky-Pudlak Syndrome (HPS), Griscelli syndrome (GS II), and Chediak-Higashi syndrome (CHS) [3, 4–6].

The disease presentation seen in laboratory tests includes:

1) Duopenia (decreased morphology values affecting 2 cell lines e.g. thrombocytopenia and anemia, or granulocytopenia and thrombocytopenia *etc*.) resulting from bone marrow immunosuppression under the influence of proinflammatory cytokines (TNF-α, INF-ɣ). It occurs in 80% of patients. The exceptions are patients with MAS, in whom in the early stages of the disease morphological parameters may be normal. It is now considered that a decreasing platelet count is a very sensitive marker of HLH and its recurrence [2, 7];

2) Hyperferritinemia — is another fairly important marker of the syndrome. Values above 500 μg/L may suggest hemophagocytic syndrome. However, it should be remembered that ferritin, which is an acute phase protein as well as a marker of iron deficiency and iron overload marker, will not be very sensitive in the context of patients after transplantation, multiple transfusions or liver disease. Although in the international HLH criteria a ferritin value >500 μg/L is given, it is currently accepted that a value >2000 μg/L is relevant for the diagnosis of HLH;
3) Hypofibrinogenemia (<150 mg/dL) resulting mainly from hepatic dysfunction and INF-γ-induced increase in plasminogen activator is a quite sensitive parameter of the syndrome activity. While monitoring the coagulation system, it is also important to pay attention to rising D-dimers, which are often significantly elevated in active HLH;
4) Hyperglyceridemia (>3 mmol/L or 265 mg/dL) resulting from inhibition of lipoprotein lipase by TNF-α, is another component of the diagnostic criteria. In the context of recent guidelines, its diagnostic value is no more relevant.

Less common laboratory criteria include elevated liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST)], hyperbilirubinemia, hypoalbuminemia, hyponatremia (may be a marker of CNS involvement or apparent as a result of hypertriglyceridemia) [8, 9].

The diagnostic criteria for HLH are presented in Table I.

Table I. Diagnostic criteria for HLH (based on HLH-2004 protocol)

The diagnosis can be confirmed by:
A. Detection of mutations (*PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A or BIRC4*)
or
B. Meet 5 of the following 8 criteria
1. Fever >38.3°C
2.Splenomegaly
3. Duopenia: • **Hb <9 g/L (in neonates Hb < 10 g/L)** • **PLT <100 ×10^3/mL** • **GR < 1 ×10^3/mL**
4. Hypertriglyceridemia >265 mg/dL (>3 mmol/L) and/or hypofibrinogenemia <150 mg/dL
5. Hemophagocytosis in bone marrow/lymph nodes/liver*

6. Low/no NK cell activity
7. Ferritin >500 µg/L
8. Elevated sCD25 levels

*Liver biopsy for material collection is not currently recommended

Cytological and histopathological confirmation

One of the important diagnostic criteria for HLH is hemophagocytosis. It can be found in bone marrow, liver, spleen, lymph nodes and cerebrospinal fluid (CSF). It usually checked in bone marrow and CSF. In the past, biopsies of lymph nodes, liver and even spleen were also performed. Due to safety concerns, the latter two tests are not performed nowadays. It should be remembered that in the early stages of the disease, hemophagocytosis may not be present in BM, and in about 40% of patients it is not present at all in bone marrow examination. BM biopsy should therefore be performed several times, as changes may appear over time. In addition to hemophagocytosis, normal cellularity is observed in the bone marrow of patients with primary HLH, sometimes with an elevated red cell line. In contrast, in HLH-MAS, there is an increased percentage of granulocytic lineage in the marrow. In addition, a follow-up bone marrow examination can rule out proliferative disease as well as Leishmaniasis infection (amastigotes present in microscopic examination). In case of Leishmania suspicion, a bone marrow sample should be taken for polymerase chain reaction (PCR) testing as test from peripheral blood often gives false negative results. Until now it was thought that diagnosis should only be made if there was a positive history of travel to the Mediterranean region. Nowadays, due to the widespread distribution of the parasite (Germany, the Netherlands), this test is considered mandatory for diagnostic screening [10].

Another very important diagnostic test is lumbar puncture with collection of cerebrospinal fluid (CSF). It is mandatory to examine the fluid for pleocytosis, protein, glucose, lactates and microbiological examination. In most cases, a predominance of lymphocytes is observed in the CSF smear, while hemophagocytosis alone is described in only 39% of cases. Lumbar punctures should be repeated in the absence of baseline fluid changes, as in the case of bone marrow examination. During disease monitoring it is important to perform follow-up lumbar punctures, in which signs of disease retreatment are usually seen earlier than on imaging studies. In primary forms of HLH, CSF lesions are more commonly present, with no abnormalities on CNS MR imaging [6, 11].

Infrequently performed tests include microscopic examination of the hair performed when congenital immunodeficiency running with albinism is suspected.

Imaging studies

Radiological imaging is very important part of diagnostic. Magnetic resonance imaging (MRI) is gold standard imaging to exclude central nervous system involvement. Lesions, typical of HLH are: symmetric periventricular infiltrates, sometimes cerebellar lesions, usually not involving the thalamus or brainstem, not enhancing in T-1 dependent sequence. As previously mentioned, there are patients with symptoms without MRI changes, as well as patients without neurologic symptoms with lesions on imaging studies. It is important that diagnostic imaging and lumbar puncture should be performed before start of therapy. When monitoring the disease, if the neurological symptoms disappear, it is not necessary to repeat the imaging examinations, but it is necessary to control the cerebrospinal fluid by lumbar puncture. It should also be kept in mind that abnormalities seen on imaging studies may be a result of chemotherapy. Examples include changes consistent with posterior reversible encephalopathy (PRES), associated with steroid therapy and CSA [6, 11].

In addition abdominal and lymph node ultrasound, cardiac ultrasound and chest radiography are performed in every patient. In justified cases (strong suspicion of HLH secondary to malignancy) the diagnostics should be extended.

Functional tests

Functional tests provide great support in the diagnosis of hemophagocytic syndrome. It should be emphasized that they are performed only in a few highly specialized laboratories.

The primary test is the degranulation assay. It evaluates the process of exocytosis that occurs in cytotoxic cells by assessing the expression of CD170a and CD170b antigens on activated cells. Abnormalities of the degranulation process are an indication to look for some congenital forms of HLH. For example, degranulation defect and decreased cytotoxicity test results may indicate defects of *MUNC, STX11 and STXPB2* genes (FHL-3, FHL-4, FHL-5) responsible for production of proteins involved in maturation and fusion of exocytic granules with the cell membrane. Impaired degranulation is also observed in Griscelli syndrome and Chediak-Higashi syndrome.

The cytotoxic assay allows examing the cytotoxic capacity of NK cells. It defines cytotoxicity as the number of leukemic cell line K562 cells killed by cytotoxic cells. The test is performed using radioactive chromium or fluorescent dye and propidium iodide. It is performed by flow cytometry. Its reduced values suggest a congenital defect. The test result

distinguishes patients with a reduced number of NK cells without loss of cytotoxicity from patients with normal or reduced numbers of NK cells and reduced cytotoxic function.

Another important test is the evaluation of NK cell activity. Transiently reduced NK cell counts may accompany acquired forms of HLH due to overuse. In patients who enter remission of the disease, NK counts return to normal. In the congenital forms, usually NK counts and activity are permanently reduced. However, it should be remembered that there are forms of HLH with normal numbers and activity of NK cells. [12, 13].

Intracellular expression of perforin (a glycoprotein that has the ability to incorporate and form channels in the cytoplasmic membrane of target cells, inducing of apoptosis in the target cell) is assessed by flow cytometry. This test that can be very helpful when congenital forms are suspected. Abnormal expression of perforin, with reduced cytotoxicity test values and normal degranulation values may suggest a genetic form of FHL2 (*PRF1*).

An important test that should be performed in males is expression of XIAP and SAP. In case of abnormal result may primary HLH (XLP-1, XLP-2) can be suspected.
The concentration of soluble receptor for IL-2 (sCD25) shows the activation level of T lymphocytes.
It is a sensitive marker of hemophagocytic syndrome and is one of the diagnostic criteria (sCD25 level >2400 U/mL). Apart from time of diagnosis, a follow-up test can be performed after about 2 weeks — the marker should decrease within treatment [5, 7, 12].

Genetic testing

A genetic test is not always needed to make the diagnosis of hemophagocytic syndrome. Sometimes it is sufficient that the patient only meets the diagnostic criteria (Table I) for the disease. Immunologic and genetic tests are necessary to rule out congenital HLH. The commonly used Sanger test is a quick and easy way to rule out basic mutations that are already known. The disadvantage of this method is that it only targets previously known genetic alterations. In contrast to traditional methods, NGS sequencing allows for inspection of almost the entire genome, and detection of new mutations responsible for HLH. This method, of course, has its limitations like very high costs, but in the future, it will certainly become a more common tool, useful in patients suspected of having HLH or other immunodeficiencies [13, 14].

Secondary hemophagocytic syndromes — diagnostic tips

This group includes acquired HLH, which develops due to other factors such as infection, drugs, neoplasms, or connective tissue disease.

EBV-HLH

The most common causes in this group of acquired HLH are viral infections and among them Epstein-Bárr virus (EBV). It infects mainly B-lymphocytes, controlled by NK-lymphocytes and cytotoxic lymphocytes. The development of EBV-HLH depends on age, stage of disease, and number and function of NK and cytotoxic lymphocytes. EBV-HLH during primary infection tends to occur in younger children, in contrast to lymphoproliferative disease or chronic EBV infection, which is typical in older children and adolescents and tends to occur during the reactivation phase of infection. Typical features on physical examination include jaundice, skin rashes, breathing difficulties, neurological disturbances (seizures). In laboratory tests high levels of lactate dehydrogenase, hyponatremia and high values of liver enzymes can be observed. Most patients have bone marrow and/or lymph node involvement, and CSF examination reveals elevated pleocytosis and protein levels. CNS may also be involved. In contrast to other forms of HLH, there is an increased soluble IL-2 receptor (sCD25) with normal or slightly decreased NK cell activity. Presence of EBV-HLH does not exclude lymphoma [15, 16].

HLH secondary to severe acute respiratory syndrome coronavirus *2* (SARS‑CoV-2) infection

HLH may be triggered also by other infectious factors including coronary disease 2019 (COVID-19). Recent reports suggest that the hypercytokinemia caused by the novel Coronavirus infection, COVID-19, has significant similarities with the laboratory and clinical findings of HLH. Due to the rapid deterioration of patients' general status, sHLH needs a timely diagnosis for the initiation of life-saving treatment [17]. Similarly to the clinical symptoms of sHLH the majority of patients with COVID-19 present with high fever, cough, dyspnea, myalgia or fatigue [18]. Likewise HLH patients, COVID-19 patients present with several laboratory abnormalities [i.e., thrombocytopenia, lymphocytopenia, elevated D-dimer, serum ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP) and IL-6 levels] [19, 20].

Multisystem inflammatory syndrome in children (MISC-C)

Recent reports suggest a new COVID-19 related clinical syndrome, with significant hyperinflammation and similarities to Kawasaki disease (KD), which can be found in children [21].

MIS-C can appear at any time, although most commonly occurs 1–6 weeks following infection, and may overlap with an acute respiratory COVID-19 presentation [22, 23]. Clinical symptoms can be similar to KD with coronary artery aneurysms and extracardiac manifestations. Apart from typical symptoms associated with KD (hand and foot inflammation/swelling, rash, mucous membrane changes/strawberry tongue, conjunctivitis, lymphadenopathy) [24], MIS-C can present with significant gastrointestinal manifestations (vomiting, diarrhea and severe abdominal pain), neurologic involvement, hyperferritinemia, cardiogenic shock leading to multiorgan failure. It is very important to differentiate between MISC-C and sHLH because treatment of Multisystem Inflammatory Syndrome is partially different involving mainly: remdesivir, immunoglobulin (IVIG), corticosteroids, anakinra and tocilizumab [21].

Secondary hemophagocytic syndrome associated with malignancies

HLH associated with malignant neoplasms is more common in adults, however pediatric cases are also described. It is important to distinguish between HLH occurring during tumor onset or relapse and hemophagocytic syndrome occurring in remission of the disease and associated with chemotherapy. In the first case HLH is caused by the tumor itself. Presumably, tumor cells (e.g., lymphoma) secrete interleukins: INF-γ, IL-6, which are involved in the development of HLH. The soluble receptor for IL-2 (sCD25) is a marker of both HLH and certain lymphomas. It is also important to remember that EBV is both a "trigger" for HLH and a cause of some lymphoid proliferations. In the pediatric population, T-cell lymphomas are the most common cause of secondary HLH.

In case of HLH on the background of chemotherapy, immunosuppressive therapy and infections [especially bacterial, cytomegalovirus (CMV), EBV and fungal infections] are triggering factors. The greatest difficulty in the diagnosis of patients is the fact that most symptoms of HLH (fever, pancytopenia, coagulation abnormalities, high inflammatory markers) are also present in malignancy. Genetic testing may be helpful in diagnosis. For example, certain defects resulting in the development of XLP1 should be associated with a higher predisposition to B-cell lymphoma in boys, especially after EBV exposure, as opposite to XLP-2 which is not associated with lymphoma [16, 25].

Macrophage activation syndrome (MAS)

Definition of macrophage activation syndrome (MAS) refers to hemophagocytic syndromes complicating connective tissue diseases. Excessive activation of T lymphocytes and macrophages leads to a condition of hyperinflammation, wits symptoms of: cytopenias, hepatic dysfunction, coagulation disorders and hyperferritinemia. Typically, MAS does not occur at the time of diagnosis, but rather at a later stage, only in 25% is it concurrent. Approximately 7–17% of patients develop a full-blown macrophage activation syndrome, while a mild, subclinical syndrome is seen in more than 60% of cases. A very characteristic feature is the improvement of rheumatologic symptoms at the onset of HLH. The clinical picture of the disease includes: high fever, generalized lymphadenopathy, edema, hepatosplenomegaly. It resembles sepsis. In addition, a hemorrhagic rash can be found on physical examination, and in the more advanced stage of the disease, nose and gastrointestinal bleeding is possible. In addition, CNS symptoms such as seizures, behavioral disturbances, and even coma are quite common. Cerebrospinal fluid examination reveals high pleocytosis with moderately elevated protein level. Renal infiltration is quite common and is associated with high mortality rate. Approximately 25% of patients present with pulmonary infiltration and thus respiratory distress, dyspnea, cough and even features of respiratory failure. In laboratory tests a very characteristic feature of MAS is a rapid decrease of sedimentation rate (OB) value with still high CRP. Additionally, In biochemical parameters there is a significant increase in transaminases with a very slight increase in bilirubin and slight hypoalbuminemia. In coagulogram, massive abnormalities including intravascular coagulation are described. Another very typical marker of MAS is very high ferritin level (>5000 ng/L). Apart from that, hypertriglyceridemia, high LDH levels, low sodium levels are observed in laboratory tests. Diagnosis of MAS poses many problems due to overlapping symptoms of rheumatic diseases and the hemophagocytic syndrome itself. There are numerous diagnostic criteria dedicated to the diagnosis of MAS. Some of the most recent are shown in Table II [26–31].

Table II. Classification criteria for macrophage activation syndrome (MAS) [18]

Patient with fever, suspected of having idiopathic juvenile arthritis (SJIA)
Meets criteria for macrophage-MAS activation syndrome when:
• ferritin >684 ng/mL

And 2 of the following:
• PLT <181 $\times 10^9$/L
• AspAT >48 U/L • Tg >156 mg/dL
• Fibrinogen ≤360 mg/dL

Authors' contributions

All authors contributed to design of study, writing of manuscript, critical review, and final approval.

Conflict of interest

All authors have nothing to disclose with respect to this paper.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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32.