Clinical case of hemophagocytic lymphohistiocytosis: rare or undiagnosed syndrome?

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Hemophagocytic lymphohistiocytosis (hemophagocytic syndrome, HLH) is a life-threatening hyperinflammatory condition associated with a high mortality rate; it is characterized by hyperstimulation of histiocytes and cytotoxic T-cells, which leads to cytokine storm and multisystemic injury.

**Aim.** To present our own clinical case of the HLH development at the key aspects of pathogenic mechanisms, differential diagnosis, and therapeutic management of this syndrome.

**Materials and methods.** This article provides information on the HLH development in a 69-year-old man with the onset of this syndrome prior to a diagnosis of the underlying disease – splenic marginal zone lymphoma. The article summarizes the current literature data on clinical manifestations, diagnosis, and treatment of HLH.

**Results.** This article describes a case of secondary HLH from our clinical practice. The most common causes of HLH are malignant neoplasm, infectious factors and rheumatic diseases (when associated with the latest, HLH is called "macrophage activation syndrome"). The main clinical symptoms are prolonged high fever and hepatosplenomegaly; typical laboratory changes such as cytopenia, hyperferritinemia, hypertriglyceridemia, elevated liver enzymes and low fibrinogen levels.

**Conclusions.** Despite typical clinical features, HLH is a condition that often remains unrecognized and it is characterized by a poor prognosis. Prompt prescription of adequate treatment can improve patients’ prognoses and increase the survival rate.

**Key words:** hemophagocytic syndrome, macrophage activation syndrome, cytokine storm, hyperferritinemia, coagulopathy.

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Consideration of the differential diagnosis in HLH is an important step towards the successful treatment of this syndrome [5], because due to an insufficient specificity of its symptoms, this life-threatening condition is often left undiagnosed [32].

Aim

To present our own clinical case of the HLH development at the key aspects of pathogenic mechanisms, differential diagnosis, and therapeutic management of this syndrome.

Case report

A 69-year-old man was admitted to an inpatient department for adults of Medical Centre “Oberg” 13.02.2019 with complaints of periodical increased body temperature up to 40 °C, shortness of breath during usual physical activities, episodes of blood pressure drops to 60/30 mmHg, weight loss of 8 kg for the previous month, impaired sensation of the upper and lower extremities. The above complaints appeared 3 months before hospitalization, when a subfebrile temperature, cough and gradually increasing shortness of breath appeared without apparent reason. Over the previous month, the general status of the patient was significantly deteriorated: the shortness of breath and generalized weakness worsened, and episodes of hyperthermia reached 40 °C. The patient underwent repeated medical examinations in different healthcare facilities, where elevated ESR and C-reactive protein were noted. Repeated courses of antibacterial therapy did not show any significant improvement. During the treatment in the inpatient department, a systemic connective tissue disease was suspected, for which the patient received methylprednisolone 24 mg with a gradual decrease in dose (completely discontinued for the previous 10 days) without significant improvement of general status in the course of treatment. In 1.5 months after the disease onset, a sternal puncture was performed; a cytomorphological study showed a large number of histiocytes / macrophages in the bone marrow. PET/CT showed signs of fluorodeoxyglucose uptake in the skeletal bones (bone marrow) and in the enlarged spleen, associated with a metabolically active process. Ultrasound of bones (bone marrow) and in the enlarged spleen, associated with a metabolically active process. Ultrasound of bones (bone marrow) and in the enlarged spleen, asso...
picture of the presented specimens could correspond to a secondary bone marrow lesion against the background of splenic marginal zone lymphoma; reticular fibrosis was not pronounced (MF-1).

The journey towards establishing the final diagnosis seems short only on paper. In real life, it took 3 months of outpatient examination of the patient and long period of diagnostic and treatment phase in the hospital. Prolonged time needed for some laboratory tests, the relative rarity of both the underlying disease and its complications, the conflicting results of histopathological study to some extent delayed the start of the etiopathogenetic treatment. Upon establishing the final diagnosis, the patient was referred to a specialized hematological department for the further treatment. However, this case ended fatally in 5 months after ascertaining the HLH diagnosis.

In this clinical case we described diagnostic difficulties and the main phases of treatment of the patient with a protracted course of HLH against the background of an oncohematological disorder (splenic marginal zone lymphoma). The main diagnostic features in our case are persistent fever, cytopenia, elevated ferritin and sIL-2R. The rarity of this syndrome and the main hematological diagnosis delay the correct establishment of the diagnosis and the start of treatment. In our case, early diagnosis could have increased the patient’s life expectancy, but the overall prognosis would have remained poor.

Discussion

Primary HLH is a genetic with an autosomal recessive or X-linked type of inheritance. Gene mutations cause deficiency of perforin and other proteins involved in the formation of channels in target cell membranes and in the membrane fusion [28,34]. A common feature of the pathogenesis of various subtypes of HLH is loss of normal cytotoxic function of natural killers (NK cells) and cytotoxic T lymphocytes [9]. Due to some triggering factors (for example, infection), these cells produce abnormally high levels of gamma-interferon (IFN-γ) which causes the activation of macrophages [38]. Activated lymphocytes and macrophages secrete large amounts of pro-inflammatory and anti-inflammatory cytokines and chemokines [15]. As a result, the so-called “cytokine storm” arises: an uncontrolled increase in serum level of IFN-γ, tumor necrosis factor-α (TNF-α), interleukins (IL): IL-1β, IL-2, IL-6, IL-12, IL-16 and IL-18. Cytokine storm causes vascular endothelial damage and bone marrow suppression, which leads to the development of fatal bleeding, infectious complications and multiple organ failure [26].

Knowledge of the main chains of pathogenesis enables us to understand the causes of symptoms for each individual patient and to interpret the laboratory results correctly. For instance, such symptom as fever is caused by exposure to interleukins and TNF-α. An increase in ferritin occurs due to its hypersecretion by the activated macrophages. The latest also produce plasminogen activator which causes hyperfibrinolysis and reduced fibrinogen levels in the blood. Cytopenia is caused by the ability of cytokines to suppress hematopoiesis, as well as by hemophagocytosis in bone marrow. Hypertriglyceridemia occurs as a result of decrease in lipoprotein lipase activity due to elevated levels of TNF-α [6,15,27]. Infiltration of organs by activated lymphocytes and histocytes/macrophages leads to hepatosplenomegaly, elevated liver transaminase and bilirubin levels, and to the development of neurological disorders. Activated T lymphocytes also secrete sIL-2R (sCD25), the detection of which in serum is one of the diagnostic criteria for HLH [23].

Secondary HLH is classified according to triggering etiological factors:

1. Malignancy-associated HLH. Malignant neoplasms are the most common factor triggering HLH in adults (about 45–58 % of cases) [1,40]. The clinical course in this form of HLH is characterized by rapid progression and unfavorable prognosis [5]. Such patients, especially against the background of hemoblastoses, have primary immunodeficiency (secondary to malignancy), which is often aggravated by an antineoplastic therapy. That is why hemoblastoses trigger HLH much more often than solid tumors; in particular, the most common triggering factors are lymphomas, especially T-cell and NK-cell ones [1].

HLH can also develop in the context of immunotherapy of malignant tumors. Its emerging in such cases is associated with excessive release of cytokines caused by the use of drugs that activate T-cells (e.g., bispecific monoclonal antibodies, etc.) [5].
Table 2. Diagnostic criteria of HLH-2004 [13,16]

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<th>Case report</th>
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<tr>
<td><strong>Mutation characteristic of HLH confirmed by molecular diagnostics</strong> (pathologic mutations PRF1, UNC13D, STXBP2, Rab27a, STX11, SH2D1A, XIAP) or Presence of 5 out of the 8 diagnostic criteria listed below:</td>
</tr>
<tr>
<td>1. Fever ≥38.3 °C</td>
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<td>2. Splenomegaly</td>
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<td>3. Cytopenias affecting ≥2 of 3 lineages in the peripheral blood: Hemoglobin &lt;90 g/l (for infants up to 4 weeks old &lt;100 g/l); Platelets &lt;100 × 10^9/l; Neutrophils &lt;1.0 × 10^9/l</td>
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<tr>
<td>4. Hypertrophiectasia and/or hypofibrinogenemia: Triglycerides fasting ≥ 3.0 mmol/l; Fibrinogen ≤1.5 g/l</td>
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<tr>
<td>5. Hemophagocytosis in the bone marrow or lymph nodes or spleen</td>
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<td>6. Low or absent NK cell activity</td>
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<td>7. Ferritin ≥500 mg/l</td>
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<tr>
<td>8. Soluble CD25 (sIL-2R) ≥2,400 IU/ml</td>
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2. HLH triggered by infection. The most common infectious agents that provoke the development of HLH are viruses (41 %), mycobacteria (23 %), other bacteria (23 %) and fungi (13 %). Previously, Epstein–Barr virus is regarded as the most common viral pathogen due to its ability to cause clonal proliferation and hyperactivation of T-cells [3].

At present, the probable leader among the viral pathogens is SARS-CoV-2, the severe course of COVID-19 is associated with the development of the cytokine storm [36].

3. Macrophage activation syndrome is observed against the background of many rheumatic diseases both in children and in adults. It most frequently develops against the background of systemic juvenile idiopathic arthritis (sJIA) (overt HLH – approximately 10 % cases, subclinical – up to 40 %) and adult-onset Still’s disease (AOSD) [21,33]. This syndrome also occurs along with systemic lupus erythematosus (SLE), Kawasaki disease, juvenile dermatomyositis and mixed connective tissue disease [33].

One of the most frequent symptoms is high fever, usually unremitting, which occurs in approximately 96 % of patients and does not respond to antibiotic therapy. Splenomegaly is present in 84 % of pediatric patients and is slightly less common in adults (69 %). Its occurrence, as well as enlargement of the liver, is caused by the infiltration of tissues by histiocytes and lymphocytes [22,29]. Among the other characteristic features, weight loss, lymphadenopathy, skin rash can be noted [20]. Central nervous system failure also occurs, being manifested by seizures, encephalopathy, or asymptomatic with the appearance of characteristic radiographic changes, pleocytosis and increased protein in the cerebrospinal fluid [2]. Some patients develop diffuse peripheral neuropathy, manifested with pain and weakness in the limbs. Its occurrence is associated with the destruction of nerve myelin sheaths by macrophages [17].

The laboratory results display cytopenia (at least bili- neage in peripheral blood), hyperferritinemia, hypertriglyceri- idemia (especially in secondary HLH), hypofibrinogenemia, elevated transaminase level, hyperbilirubinemia, coagulation disorders, hyponatremia and hypoproteinemia [9]. Lactate dehydrogenase increases in almost 100 % of patients with secondary HLH and usually exceeds 500 U/l [10]. Ferritin level >500 ng/ml should cause suspicion of hemophagocytosis syndrome, while its increase >10 000 ng/ml has 90 % sensi- tivity and 96 % specificity in regards of establishing HLH diagnosis [9]. Leukocytosis is not a typical finding but may occur in patients with macrophage activation syndrome [16]. Coagulation disorders are observed in 60 % of patients; the laboratory results show prolongation of prothrombin time, elevated D-dimer (approximately in 50 % of patients) [38].

Determination of sCD25 (sIL-2R) level is one of the diagnostic criteria that characterizes the level of T cell activation and is used for diagnosing and monitoring of the syndrome. Recently, one more indicator was identified for use in evaluation of HLH activity – sCD163 [18].

An obligatory step in establishing the diagnosis is a bone marrow biopsy. It is used not only for verification of hemophagocytosis, but also for exclusion of such a factor of HLH development as leukemia [23]. However, it should be taken into account that in the early stages of the syndrome, bone marrow biopsy may show a normal picture or nonspecific changes [10].

Experts of the Histiocyte Society emphasize that such a known trigger of HLH as lymphoma may be hidden, and therefore difficult to diagnose. In such cases, computed tomography with the positron emission tomography is recommended followed by further biopsy of suspicious lesions (repeated if necessary). However, it should be kept in mind that reactive lymphocytes that infiltrate the organs may camouflage histopathological picture of lymphoma. Therefore, for establishing the diagnosis, a close cooperation between clinicians, pathologists (ideally – a pathologist specialized in lymphoma diagnostics) and immunologists is needed. For the patients with HLH of unknown etiology and splenomegaly, a possibility of splenectomy can be consi- dered, with the purpose to detect splenic lymphomas [19].

Other published studies also demonstrate the difficulty of diagnosing and the severity of the HLH prognosis on the background of lymphoma. According to a study by M. Verma et al., which included 9 patients with HLH and lymphoma, 3 patients did not receive chemotherapy and died within three weeks of the onset of symptoms, 6 patients who received chemotherapy achieved remission, but 2 patients had early relapse [39].

In case of our patient, the presence of immunosup- pressive status with Pneumocystis jirovecii infection in line with exclusion of probability of HIV and other viral (including herpes and hepatitis viruses) and bacterial infections, signifi- cantly enlarged spleen conditioned us to thoroughly search for oncohematological malignant neoplasms as a cause of HLH development. Given the results of the trephine biopsy, the next step in the management of this patient would have been splenectomy.

The HLH diagnostic criteria, which are currently in use, were proposed in 2004 and included updated recommendations of the Histiocyte Society (Table 2) [12]. However, they are often criticized for their insufficient specificity when used for severely ill patients [32].

Strict adherence to HLH criteria can sometimes be an obstacle in establishing this diagnosis [31]. Diagnostic criteria of HLH-2004 were developed for children and are not formally validated for adults. For this reason, to evaluate the probability of HLH, the HScore indicator is also applied, developed retrospectively for adult patients and available online as a calculator for general use: http://saintantoine. aphp.fr/score/ [19,35]. The patient, whose clinical case was described above, had 7 out of 5 required diagnostic
criteria. When checked on HScore, as mentioned above, the probability of HLH for his case made almost 100%.

The key determinants for the successful HLH therapy are timely diagnosis, elimination of the triggering factor and prompt initiation of treatment [12]. Since the development of HLH is associated with the hyperactivation of the immune system, the basis of therapy is immunosuppressive and myelosuppressive drugs. Primary HLH is almost always fatal without treatment; secondary (approximately) - in 50–75% cases [1]. Therefore, for most patients, an early aggressive treatment with dexamethasone and etoposide is justified [16].

Treatment protocol HLH-94, developed for pediatric patients, includes therapy with glucocorticoids (dexamethasone with an initial doze of 10 mg/m², halved every two weeks), etoposide (150 mg/m² per dose, twice weekly for 1–2 weeks with the further tapering of administration frequency), cyclosporin A and intraheathal methotrexate. It should be noted that strict adherence to the pediatric protocol in adults may lead to overtreatment with the development of toxicity. Therefore, an individualized approach should be considered with the tailoring of an adequate dose and duration of treatment, considering the presence of comorbidity. A reduced mode of etoposide administration can be applied: once per week with/without dose reduction to 50–100 mg/m² [19]. The presence of cytopenia and/or liver dysfunction are not contrindications to the prescription of etoposide, since these manifestations are secondary to the underlying disease. Etoposide is eliminated by kidneys; thus, the reduction of dosage should be performed when creatinine levels are increased [7].

Besides, an intravenous immunoglobulin therapy can be considered (up to 1.6 g/kg in divided doses over 2–3 days). The latest has an anti-inflammatory effect due to its ability to inhibit complement activation, neutralize cytokines and block Fc regions of antibodies and macrophages Fc receptors. However, in some cases, the use of this method of therapy is controversial (especially for AOSD) [19]. Potential new treatment strategies include the use of emapalumab (an interferon gamma blocking monoclonal antibody), ruxolitinib (a JAK inhibitor reducing production of proinflammatory cytokines and T-cell proliferation), alemtuzumab (monoclonal antibody targeting CD52 antigen, expressed on lymphocytes, macrophages, dendritic cells), rituximab (monoclonal antibody targeting CD20) [24,25]. For the patient described above, we implemented such components of treatment recommendations for HLH as the use of glucocorticoids and administration of intravenous immunoglobulin.

Macrophage activation syndrome has somewhat different treatment approaches. As initial treatment, it is recommended to prescribe methylprednisolone pulse therapy (1 g/day for 3–5 days) for such patients. In case of insufficient response to this therapy, it is recommended to add cyclosporine A (2–7 mg/kg per day) or anakinra (IL-1 inhibitor) [19].

In adult patients with refractory/recurrent HLH in the absence of treatment for the condition that caused HLH, as well as in patients with certain types of malignant neoplasms, the hematopoietic stem cell transplantation should be considered [7].

At the same time, a specific therapy of HLH is prescribed, targeted on elimination of the triggering factor of immunological hyperactivation: treatment of malignant neoplasms, acute infections or rheumatic diseases [40]. The next strategic step after establishing the diagnosis and prescription of treatment is evaluation of therapeutic response. Since etoposide is a myelosuppressive agent, monitoring solely of peripheral blood indicators does not allow to reliably determine the effectiveness of treatment. It is necessary to monitor immune activation by performing repeated measurements of the sCD25 level for evaluation of treatment effectiveness. The ferritin normalization is often slower than that of sCD25, for it can return to normal over many months after the resolution of HLH [16].

Conclusions

1. A rare case of HLH due to splenic marginal zone lymphoma has been described.
2. Non-specific nature of the clinical presentation of HLH in our case hampered its diagnostics and delayed the start of treatment. This syndrome should be suspected in patients with high and persistent fever, cytopenia (especially three-lineage), elevated transaminase levels, elevated ferritin and coagulopathy.
3. HLH in adults is a syndrome that emerges due to certain triggering factors (malignant neoplasm, infection or rheumatic disease). Therefore, it is always necessary to search actively for the processes which might provoke the evolving of HLH, particularly, for malignant neoplasms.
4. Treatment of this syndrome is focused on reduction of the cytokine storm and elimination of the triggering factor.

Conflicts of interest: authors have no conflict of interest to declare.

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