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Clinical case of hemophagocytic lymphohistiocytosis: rare or undiagnosed syndrome?

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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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Клінічний випадок гемофагоцитарного лімфогістіоцитозу: рідкісний чи нерозпізнаний синдром?

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Гемофагоцитарний лімфогістіоцитоз (гемофагоцитарний синдром, ГЛГ) – небезпечний для життя гіперзапальний стан, що супроводжується високою смертністю та характеризується підвищеною стимуляцією гістіоцитів, цитотоксичних Т-клітин, призводить до цитокінового шторму та мультисистемного ураження.

Мета роботи – навести власний клінічний випадок виникнення ГЛГ, розкрити ключові моменти патогенетичних механізмів, диференційної діагностики та лікувальної тактики ГЛГ.

Матеріали та методи. Наведено інформацію про виникнення ГЛГ у чоловіка віком 69 років, яке передувало встановленню діагнозу основного захворювання – лімфоми маргінальної зони селезінки. Узагальнено відомості сучасної фахової літератури щодо його клінічних проявів, діагностики та лікування.

Результати. У статті наведено власне спостереження з практики випадку вторинного ГЛГ. Найпоширеніші причини виникнення ГЛГ – злоякісні новоутворення, інфекційні чинники та ревматичні захворювання (в останньому випадку його називають синдромом активації макрофагів). Головні клінічні симптоми – тривала лихоманка та гепатоспленомегалія; характерні лабораторні зміни – цитопенія, гіперферитинемія, гіпертригліцеридемія, підвищення рівня печінкових ферментів і низький рівень фібриногену.

Висновки. ГЛГ – стан, який, незважаючи на типову клінічну картину, часто залишається нерозпізнаним, характеризується несприятливим прогнозом. Раннє призначення адекватного лікування дає змогу поліпшити прогноз пацієнта та підвищити виживаність.

Ключові слова: гемофагоцитарний лімфогістіоцитоз, синдром активації макрофагів, цитокіновий шторм, гіперферитинемія, коагулопатія.

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Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome is a condition characterized by uncontrolled severe systemic hyperinflammation which arises in the context of a genetic disorder of the immune system (primary HLH) or is a complication of malignancy, infection or a rheumatic disease (secondary HLH) [14,37]. When associated with rheumatic disease, HLH is termed macrophage activation syndrome (MAS) [4]. The symptoms of primary HLH usually appear in the first years of life, while secondary HLH can develop at any age [8].

Considering a relative rarity of this syndrome (primary HLH occurs in approximately 1 per 50,000 live births, the exact prevalence of secondary one is unknown), the diagnostic phase is especially important. Reduction of its duration allows to determine the appropriate treatment tactics promptly and to improve a possible patient's prognosis [13,30,37]. It is emphasized that timely diagnosis is critical, as patients with HLH often experience rapid decompensation leading to multiple organ failure and death [11]. According to the retrospective analysis of 62 HLH cases, the median of overall survival in patients is 2.1 months (1.4 months – for malignancy-associated HLH and 22.8 months – for non-malignancy associated HLH) [30].

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 "Oberig" 13.02.2019 with complaints of periodic 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 the lower extremities showed thrombosis of the sural vein of the lower third of his left leg, due to which the patient received rivaroxaban 20 mg.

Upon admission (13.02.2019): general pallor, vesicular breathing, O_2 saturation level when breathing room air – 90 %, respiratory rate – 22/min, blood pressure – 90/60 mmHg, peripheral edema. In neurological status: signs of sensorimotor polyneuropathy of the upper and lower (to a greater extent) extremities with a mild paraparesis, gait disturbance, decreased vibratory sensation.

The results of laboratory tests at the moment of admission and over time are presented in *Table 1*. Upon admission, the dissociation between ESR level (15 mm/hour) and significant increase in C-reactive protein up to 177.0 mg/l was noted. In the urinalysis, protein was absent, leukocyturia was up to 45 in the visual field. Blood test: hyponatremia 125 mmol/l (normal range 136–146 mmol/l); levels of urea – 20.13 mmol/l (normal range 2.76–8.07 mmol/l), uric acid – 643.60 μmol/l (normal range 149–458 μmol/l), albumin – 25.47 g/l (normal range 32–52 g/l), fibrinogen was within normal range.

Intravenous contrast-enhanced computed tomography (*Fig. 1*) showed splenomegaly (17.7 × 6.5 cm), increased vascular marking of lungs, slight liver enlargement. Fibrobronchoscopy: pale bronchial mucosa, contact bleeding, a small amount of purulent content. A cytologic examination of tracheobronchial contents detected the presence of a substantial number of leukocytes, histiocytes, mucous and fibrous detritus. During bacterial culture test, a growth of aerobic and facultative anaerobic bacteria was not detected, PCR test for *Mycobacterium tuberculosis* was negative. Absence of adequate increase in saturation relevant to the increase in the level of oxygen supply, the dissociation between the severity of clinical manifestations and changes in computed tomography prompted to suggest the presence of pneumocystis pneumonia. A bronchoalveolar lavage was evaluated by the PCR method for *Pneumocystis jirovecii* with a positive result. Due to this, the HIV test was repeated; antibodies were not detected.

Before the results of specific additional laboratory tests were known, the therapy with dexamethasone, sulfomethoxazole / trimethoprim, red blood cell transfusion, intravenous administration of albumin, anticoagulants, antibacterial agents and CPAP was prescribed.

In the course of treatment performed, an increase in hemoglobin was observed from 76 g/l (the minimum level within the initial observation period) to 89 g/l and lowering of creatinine. However, a progressive reduction in the number of leukocytes up to 2.71 G/l (neutrophils up to 0.99 G/l) claimed the attention. Due to the presence of fever, hemophagocytosis in bone marrow, bilineage cytopenia, splenomegaly, hyperferritinemia, hypertriglyceridemia, the most substantiated diagnosis was hemophagocytic lymphohistiocytosis, though its etiology remained unclear. To confirm this diagnosis, the sIL-2r test was performed, with the level that reached >7500 units/ml (above the upper threshold of the diagnostic capability of an analyzer). The probability of HLH according to HScore was 99.97 %.

After confirmation of life-threatening complication, a more aggressive treatment was initiated: the therapy was supplemented with intravenous immunoglobulin of 0.8 g/kg twice two days in a row (24–25.02.2019), methylprednisolone pulse therapy 250 mg three days in a row (25–27.02.2019) with subsequent switch to oral therapy and doses were gradually tapered over time. In the course of treatment performed, improvements in the clinical and laboratory condition of the patient were observed, such as a decrease in body temperature to subfebrile level, an increase in the number of leukocytes up to 6.2 G/l (29.02.2019). However, the severity of dyspnea did not significantly decrease, O_2 saturation without the supply of oxygen was 89–91 %, the pronounced generalized weakness remained.

A trephine biopsy of the bone marrow was carried out (15.02.2019). Histopathological and immunohistochemical impression: changes corresponded to bone marrow failure from two processes; the most probable were chronic idiopathic myelofibrosis (sclerotic phase) and well-differentiated B-cell lymphoma. Considering the absence of the final diagnosis of the first histopathological study, the biopsy was revised by another specialist. Conclusion: histopathological

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.

Table 1. Dynamics of the laboratory indicators of the patient

Indicator, units of measurement	13.02.2019 (upon admission)	18.02.2019	22.02.2019	IVIG 29.02.2019	Normal range
Leukocytes, G/l (incl. % of band neutrophils)	8.55 (27 %)	5.5 (18 %)	2.71 (8 %)	6.2 (7 %)	4–9 (1–5 %)
Hemoglobin, g/l	76	89	80	87	120–150
Platelets, G/l	115	119	119	152	150–450
ESR, mm/hour	15	25	24	18	2–30
AST, units/l	46.2	52	43.4	39.8	<32
LDH, units/l	1 004.20	1080	885.8	869.9	<247
Creatinine, μmol/l	181.06	105.23	86	92	44–80
CRP, mg/l	177	192.3	85.66	56.3	<5
Ferritin, ng/ml	>1500	–	>1500	>1500	5–148
Procalcitonin, ng/ml	0.57	0.38	0.16	–	0.1

Triglycerides – 5.65 mmol/l (normal range – ≤1.5 mmol/l); sIL-2R >7500 U/ml (normal range 122–496 U/ml); Antibodies to HIV – not detected. ANA i ANCA were negative; blood culture for sterility – negative (no growth). **IVIG:** administering of intravenous immunoglobulin.

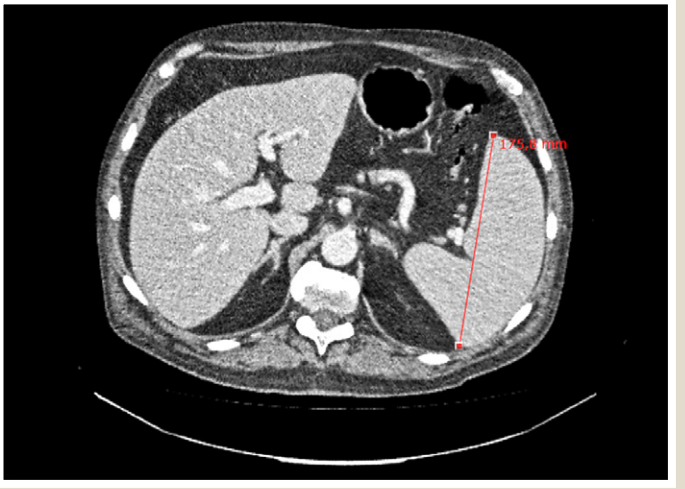

Fig. 1. Abdominal MSCT (14.02.2019).

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 histiocytes/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]

Mutation characteristic of HLH confirmed by molecular diagnostics (pathologic mutations PRF1, UNC13D, STXBP2, Rab27a, STX11, SH2D1A, XIAP) or Presence of 5 out of the 8 diagnostic criteria listed below:
1. Fever ≥38.3 °C
2. Splenomegaly
3. Cytopenias affecting ≥2 of 3 lineages in the peripheral blood: Hemoglobin <90 g/l (for infants up to 4 weeks old <100 g/L); Platelets <100 × 10^9/l; Neutrophils <1.0 × 10^9/l
4. Hypertriglyceridemia and/or hypofibrinogenemia: Triglycerides fasting ≥ 3.0 mmol/l; Fibrinogen ≤ 1.5 g/l
5. Hemophagocytosis in the bone marrow or lymph nodes or spleen
6. Low or absent NK cell activity
7. Ferritin ≥500 mg/l
8. Soluble CD25 (sIL-2R) ≥2,400 IU/ml

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 antibacterial 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 bilineage in peripheral blood), hyperferritinemia, hypertriglyceridemia (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 hemophagocyte syndrome, while its increase >10 000 ng/ml has 90 % sensitivity 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 considered, 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 immunosuppressive status with *Pneumocystis jirovecii* infection in line with exclusion of probability of HIV and other viral (including herpes and hepatitis viruses) and bacterial infections, significantly 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/m^2, halved every two weeks), etoposide (150 mg/m^2 per dose, twice weekly for 1–2 weeks with the further tapering of administration frequency), cyclosporin A and intrathecal 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/m^2 [19]. The presence of cytopenia and/or liver dysfunction are not contraindications 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. Nonspecific 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.

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References

[1] Al-Samkari, H., & Berliner, N. (2018). Hemophagocytic Lymphohistiocytosis. *Annual review of pathology*, *13*, 27-49. https://doi.org/10.1146/annurev-pathol-020117-043625

[2] Bhatt, N. S., Oshrine, B., & An Talano, J. (2019). Hemophagocytic lymphohistiocytosis in adults. *Leukemia & lymphoma*, *60*(1), 19-28. https://doi.org/10.1080/10428194.2018.1482543

[3] Campo, M., & Berliner, N. (2015). Hemophagocytic Lymphohistiocytosis in Adults. *Hematology/Oncology Clinics of North America*, *29*(5), 915-925. https://doi.org/10.1016/j.hoc.2015.06.009

[4] Carter, S. J., Tattersall, R. S., & Ramanan, A. V. (2019). Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology*, *58*(1), 5-17. https://doi.org/10.1093/rheumatology/key006

[5] Daver, N., McClain, K., Allen, C. E., Parikh, S. A., Otrock, Z., Rojas-Hernandez, C., Blechacz, B., Wang, S., Minkov, M., Jordan, M. B., La Rosée, P., & Kantarjian, H M. (2017). A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. *Cancer*, *123*(17), 3229-3240. https://doi.org/10.1002/cncr.30826

[6] De Saint Basile, G., Moshous, D., & Fischer, A. (2017). Genetics and pathogenesis of hemophagocytic lymphohistiocytosis. In *Histiocytic Disorders* (pp. 197-214). Springer International Publishing. https://doi.org/10.1007/978-3-319-59632-7_11

[7] Ehl, S., Astigarraga, I., von Bahr Greenwood, T., Hines, M., Horne, A., Ishii, E., Janka, G., Jordan, M. B., La Rosée, P., Lehmberg, K., Machowicz, R., Nichols, K. E., Sieni, E., Wang, Z., & Henter, J. I. (2018). Recommendations for the Use of Etoposide-Based Therapy and Bone Marrow Transplantation for the Treatment of HLH: Consensus Statements by the HLH Steering Committee of the Histiocyte Society. *The journal of allergy and clinical immunology. In practice*, *6*(5), 1508-1517. https://doi.org/10.1016/j.jaip.2018.05.031

[8] Emile, J. F., Abla, O., Fraitag, S., Horne, A., Haroche, J., Donadieu, J., Requena-Caballero, L., Jordan, M. B., Abdel-Wahab, O., Allen, C. E., Charlotte, F., Diamond, E. L., Egeler, R. M., Fischer, A., Herrera, J. G., Henter, J. I., Janku, F., Merad, M., Picarsic, J., Rodriguez-Galindo, C., … Histiocyte Society (2016). Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood*, *127*(22), 2672-2681. https://doi.org/10.1182/blood-2016-01-690636

[9] Esteban, Y. M., de Jong, J., & Tesher, M. S. (2017). An Overview of Hemophagocytic Lymphohistiocytosis. *Pediatric annals*, *46*(8), e309-e313. https://doi.org/10.3928/19382359-20170717-01

[10] George, M. R. (2014). Hemophagocytic lymphohistiocytosis: review of etiologies and management. *Journal of blood medicine*, *5*, 69-86. https://doi.org/10.2147/JBM.S46255

[11] Griffin, G., Shenoi, S., & Hughes, G. C. (2020). Hemophagocytic lymphohistiocytosis: An update on pathogenesis, diagnosis, and therapy. Best practice & research. *Clinical rheumatology*, *34*(4), 101515. https://doi.org/10.1016/j.berh.2020.101515

[12] Henderson, L. A., & Cron, R. Q. (2020). Macrophage Activation Syndrome and Secondary Hemophagocytic Lymphohistiocytosis in Childhood Inflammatory Disorders: Diagnosis and Management. *Paediatric drugs*, *22*(1), 29-44. https://doi.org/10.1007/s40272-019-00367-1

[13] Henter, J. I., Horne, A., Aricó, M., Egeler, R. M., Filipovich, A. H., Imashuku, S., Ladisch, S., McClain, K., Webb, D., Winiarski, J., & Janka, G. (2007). HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatric blood & cancer*, *48*(2), 124-131. https://doi.org/10.1002/pbc.21039

[14] Hutchinson, M., Tattersall, R. S., & Manson, J. J. (2019). Haemophagocytic lymphohisticytosis-an underrecognized hyperinflammatory syndrome. *Rheumatology*, *58*(Suppl 6), vi23-vi30. https://doi.org/10.1093/rheumatology/kez379

[15] Janka, G. E., & Lehmberg, K. (2013). Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematology. American Society of Hematology. *Education Program*, *2013*, 605-611. https://doi.org/10.1182/asheducation-2013.1.605

[16] Jordan, M. B., Allen, C. E., Greenberg, J., Henry, M., Hermiston, M. L., Kumar, A., Hines, M., Eckstein, O., Ladisch, S., Nichols, K. E., Rodriguez-Galindo, C., Wistinghausen, B., & McClain, K. L. (2019). Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium for Histiocytosis (NACHO). *Pediatric blood & cancer*, *66*(11), e27929. https://doi.org/10.1002/pbc.27929

[17] Jordan, M. B., Allen, C. E., Weitzman, S., Filipovich, A. H., & McClain, K. L. (2011). How I treat hemophagocytic lymphohistiocytosis. *Blood*, *118*(15), 4041-4052. https://doi.org/10.1182/blood-2011-03-278127

[18] Kleynberg, R. L., & Schiller, G. J. (2012). Secondary hemophagocytic lymphohistiocytosis in adults: an update on diagnosis and therapy. *Clinical advances in hematology & oncology : H&O*, *10*(11), 726-732.

[19] La Rosée, P., Horne, A., Hines, M., von Bahr Greenwood, T., Machowicz, R., Berliner, N., Birndt, S., Gil-Herrera, J., Girschikofsky, M., Jordan, M. B., Kumar, A., van Laar, J., Lachmann, G., Nichols, K. E., Ramanan, A. V., Wang, Y., Wang, Z., Janka, G., & Henter, J. I. (2019). Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*, *133*(23), 2465-2477. https://doi.org/10.1182/blood.2018894618

[20] Larroche, C. (2012). Hemophagocytic lymphohistiocytosis in adults: diagnosis and treatment. *Joint bone spine*, *79*(4), 356-361. https://doi.org/10.1016/j.jbspin.2011.10.015

[21] Lerkvaleekul, B., & Vilaiyuk, S. (2018). Macrophage activation syndrome: early diagnosis is key. *Open access rheumatology : research and reviews*, *10*, 117128. https://doi.org/10.2147/OARRR.S151013

[22] Machowicz, R., Janka, G., & Wiktor-Jedrzejczak, W. (2017). Similar but not the same: Differential diagnosis of HLH and sepsis. *Critical reviews in oncology/hematology*, *114*, 112. https://doi.org/10.1016/j.critrevonc.2017.03.023

[23] Madkaikar, M., Shabrish, S., & Desai, M. (2016). Current Updates on Classification, Diagnosis and Treatment of Hemophagocytic Lymphohistiocytosis (HLH). *Indian journal of pediatrics*, *83*(5), 434-443. https://doi.org/10.1007/s12098-016-2037-y

[24] Marsh, R. A., Allen, C. E., McClain, K. L., Weinstein, J. L., Kanter, J., Skiles, J., Lee, N. D., Khan, S. P., Lawrence, J., Mo, J. Q., Bleesing, J. J., Filipovich, A. H., & Jordan, M. B. (2013). Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. *Pediatric blood & cancer*, *60*(1), 101-109. https://doi.org/10.1002/pbc.24188

[25] McClain, K. L. (2020). Treatment of hemophagocytic lymphohistiocytosis in the era of new biologics. *Pediatric blood & cancer*, *67*(10), e28631. https://doi.org/10.1002/pbc.28631

[26] Morimoto, A., Nakazawa, Y., & Ishii, E. (2016). Hemophagocytic lymphohistiocytosis: Pathogenesis, diagnosis, and management. *Pediatrics international*, *58*(9), 817-825. https://doi.org/10.1111/ped.13064

[27] Okamoto, M., Yamaguchi, H., Isobe, Y., Yokose, N., Mizuki, T., Tajika, K., Gomi, S., Hamaguchi, H., Inokuchi, K., Oshimi, K., & Dan, K. (2009). Analysis of triglyceride value in the diagnosis and treatment response of secondary hemophagocytic syndrome. *Internal medicine*, *48*(10), 775-781. https://doi.org/10.2169/internalmedicine.48.1677

[28] Osińska, I., Popko, K., & Demkow, U. (2014). Perforin: an important player in immune response. *Central-European journal of immunology*, *39*(1), 109-115. https://doi.org/10.5114/ceji.2014.42135

[29] Otrock, Z. K., Daver, N., Kantarjian, H. M., & Eby, C. S. (2017). Diagnostic Challenges of Hemophagocytic Lymphohistiocytosis. *Clinical lymphoma, myeloma & leukemia*, *17S*, S105-S110. https://doi.org/10.1016/j.clml.2017.02.017

[30] Parikh, S. A., Kapoor, P., Letendre, L., Kumar, S., & Wolanskyj, A. P. (2014). Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. *Mayo Clinic proceedings*, *89*(4), 484-492. https://doi.org/10.1016/j.mayocp.2013.12.012

[31] Risma, K. A., & Marsh, R. A. (2019). Hemophagocytic Lymphohistiocytosis: Clinical Presentations and Diagnosis. *The journal of allergy and clinical immunology. In practice*, *7*(3), 824-832. https://doi.org/10.1016/j.jaip.2018.11.050

[32] Rosado, F. G., & Kim, A. S. (2013). Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *American journal of clinical pathology*, *139*(6), 713-727. https://doi.org/10.1309/AJCP4ZDKJ4ICOUAT

[33] Sen, E. S., Clarke, S. L., & Ramanan, A. V. (2016). Macrophage Activation Syndrome. *Indian journal of pediatrics*, *83*(3), 248-253. https://doi.org/10.1007/s12098-015-1877-1

[34] Sen, E. S., Steward, C. G., & Ramanan, A. V. (2017). Diagnosing haemophagocytic syndrome. *Archives of disease in childhood*, *102*(3), 279-284. https://doi.org/10.1136/archdischild-2016-310772

[35] Soy, M., Atagündüz, P., Atagündüz, I., & Sucak, G. T. (2021). Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. *Rheumatology international*, *41*(1), 7-18. https://doi.org/10.1007/s00296-020-04636-y

[36] Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I., & Kayhan, S. (2020). Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clinical rheumatology*, *39*(7), 2085-2094. https://doi.org/10.1007/s10067-020-05190-5

[37] Thomas, W., Veer, M. V., & Besser, M. (2016). Haemophagocytic lymphohistiocytosis: an elusive syndrome. *Clinical medicine*, *16*(5), 432-436. https://doi.org/10.7861/clinmedicine.16-5-432

[38] Valade, S., Mariotte, E., & Azoulay, E. (2020). Coagulation Disorders in Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome. *Critical care clinics*, *36*(2), 415-426. https://doi.org/10.1016/j.ccc.2019.12.004

[39] Verma, M., Gupta, N., Dass, J., Kotwal, J., & Sharma, A. (2020). HLH Masquerading Lymphoma: Diagnostic Dilemma and Treatment Outcomes. *Indian journal of hematology & blood transfusion*, *36*(4), 635-639. https://doi.org/10.1007/s12288-019-01250-2

[40] Zhou, M., Li, L., Zhang, Q., Ma, S., Sun, J., Zhu, L., Lu, D., Zhu, J., Zhou, D., Zheng, Y., Yang, X., Xie, M., Zhu, M., Ye, X., & Xie, W. (2018). Clinical features and outcomes in secondary adult hemophagocytic lymphohistiocytosis. *QJM : monthly journal of the Association of Physicians*, *111*(1), 23-31. https://doi.org/10.1093/qjmed/hcx183