VIA MEDICA

CASE REPORT

Hematology in Clinical Practice
2022, vol. 13, no. 3–4, 130–137
DOI: 10.5603/HCP.a2022.0015

ISSN: 2720–1015
e-ISSN: 2720–2690

Haemophagocytic lymphohistiocytosis: case series. Serum ferritin level as an indicator of treatment effectiveness

Daria Majowicz, Konrad Kostrzewa, Tomasz Gromek, Bożena Sokołowska, Marek Hus

Department of Haemato-Oncology and Bone Marrow Transplantation, Medical University in Lublin, Poland

Abstract

Introduction: *Haemophagocytic lymphohistiocytosis (HLH) is a medical condition associated with the over-activation of the immune system. HLH results from the inactivity of natural killer cells and uncontrolled activity of cytotoxic T lymphocytes and macrophages, with a massive cytokine response. Cytohistological examinations might show haemophagocytes in different tissues (e.g., bone marrow). Among laboratory findings especially(particularly) high ferritin level is often seen. Due to the aggressive course of the disease mortality rate is extremely high.*

Material and methods: *The study presented three patients with an acquired form of HLH treated successfully in the Haemato-Oncology Department Medical University of Lublin from September 2018 to April 2021. In case 1 HLH developed during pregnancy. Patient 2 was first hospitalized in the Intensive Care Unit and 10 therapeutic plasma exchanges were carried out. In both patients, stabilization of ferritin levels and remission of the disease were achieved soon after the application of treatment according to the HLH-2004 protocol. Case 3 presents a patient in whom HLH was induced by Epstein-Bárr virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. In the first stage of treatment, the patient received drugs according to the HLH-2004 protocol, but the serum ferritin did not normalize. The reinfection with SARS-CoV-2 occurred again during the treatment. Due to the disease resistance and the inability to continue the HLH-2004 protocol, it was decided to start ruxolitinib therapy, which resulted in the stabilization of the serum ferritin and improvement of the general condition. The patient was qualified for allogeneic bone marrow transplantation.*

Conclusions: *HLH is a difficult and interdisciplinary diagnostic and treatment problem. It is necessary to popularize knowledge about fast and targeted diagnostics. Among laboratory finding the ferritin concentration seemed to be especially helpful as a predictor of treatment effectiveness. Proper diagnosis and treatment introduced as early as possible could save patients' life.*

Key words: haemophagocytic lymphohistiocytosis (HLH), haemophagocytes, serum ferritin, EBV, SARS CoV-2

Hematology in Clinical Practice 2022; 13, 3–4: 130–137

Address for correspondence: Marek Hus, Klinika Hematoonkologii i Transplantacji Szpiku, Uniwersytet Medyczny w Lublinie, ul. Staszica 11, 20–080 Lublin, Poland, phone +48 81 534 54 68, fax +41 81 534 56 05, e-mail: markhus@o2.pl

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a medical condition associated with the overactivation of the immune system. HLH results from the inactivity of natural killer (NK) cells and uncontrolled activity of cytotoxic T lymphocytes and macrophages, with a massive cytokine response [1]. HLH as a disorder of childhood immune regulation was first described in 1952 under the name of 'familial haemophagocytic reticulosis' [2]. The following years brought progress in research on the pathogenesis of the disease. In 1996 the first papers were published, in which there were proven that the impaired function of cellular immunity played a leading role, but humoral immunity activity is essentially intact [3]. The first reports related to the genetic background of HLH appeared in 1999, in which Stepp et al. [4] showed the association of familial HLH with a defect in the perforin gene.

Two forms of HLH are distinguished: congenital and acquired.

In the congenital form, the subset of genetic HLH disorders named familial haemophagocytic lymphohistiocytosis (fHLH) was extracted in which the presence of biallelic pathogenic variants not only in perforin gene (*PRF1*) but also in other three genes: *STX11, STXBP2* and *UNC13D* were found. All these genes regulate granule-dependent cytotoxicity. Based on the genetic background mentioned above four subtypes of fHLH have been identified: *PRF1*-related familial HLH (*PRF1*--fHLH: perforin deficiency), *STX11*-related familial HLH (*STX11*-fHLH: syntaxin-11 deficiency), *STXBP2*-related familial HLH (*STXBP2*-fHLH: Munc 18-2 deficiency), *UNC13D*-related familial HLH (*UNC13D*-fHLH: Munc 13-4 deficiency) [5]. Diagnostics of fHLH are based not only on the identification of pathogenic variants in one of four genes but also on suggestive clinical and laboratory findings. The acquired form is associated mainly with underlying diseases (most often neoplasms of the haematopoietic and lymphatic systems), infections [most often with Epstein-Bár virus (EBV)], and drugs. Since 2004 was known that the mechanism of HLH development is associated with the 'paralysis' of natural killers (NK) cells, cytotoxic T lymphocytes and the excessive activity of proinflammatory cytokines [6].

In HLH-94, the first prospective international study organized to investigate and treat HLH, the diagnosis was based on five criteria (fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and haemophagocytosis) [7]. In HLH-2004, a modification of the diagnostics criteria was introduced and three additional criteria were added: low or no NK cell activity, hyperferritinaemia, and high levels of soluble interleukin (IL)-2 receptor [7].

Without the treatment mortality rate during HLH is extremely high even at 100%. The introduction of the HLH-94 protocol and the subsequent modification of HLH-2004 allowed for the reduction of the mortality rate to 20–88% [1].

The study aimed to present three patients with an acquired form of HLH successfully treated in the Haemato-Oncology Department from September 2018 to April 2021.

Case reports

Case 1

A 31-year-old woman was admitted to the Department of Obstetrics and Perinatology because of complications in the pregnancy. It was her second pregnancy the advancement of which was: 34/ /35 weeks (according to OM) or 35/36 weeks (according to ultrasound [USG]). The patient reported headache and fever for about a week (> 38°C), periodically itchy skin and dry cough. After the first week of the hospital stay, the patient was qualified to complete the pregnancy by caesarean section. The decision was made based on some abnormalities found in the foetus: oligohydramnios, abnormal flows in the middle cerebral artery, oedema and tachycardia. Simultaneously the patient also presented tachycardia, abnormal values of transaminases, fever and high values of inflammatory parameters [C-reactive protein (CRP) 111 mg/ /L]. Viral infections such as hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human immonodeficiency virus (HIV) were excluded. Anti-cytomegalovirus (CMV), anti--EBV, and anti-Parvovirus B19 antibodies in the IgG class were positive but in the IgM class, they were negative. A CMV and EBV polymerase chain reaction (PCR) test were performed, which were negative. Imaging examinations were performed. USG evaluation of the abdominal cavity revealed a liver of border size with features of steatosis and no obvious focal changes, spleen was enlarged to 165 mm. In the abdominal computed tomography (CT) scan — the enlarged liver was also found, the left lobe overlapped the spleen, and the spleen was enlarged with a bipolar dimension of approximately 172 mm. An additional 26 mm spleen was presented too.

Due to the deteriorating of the patient's general condition, no improvement after the use of

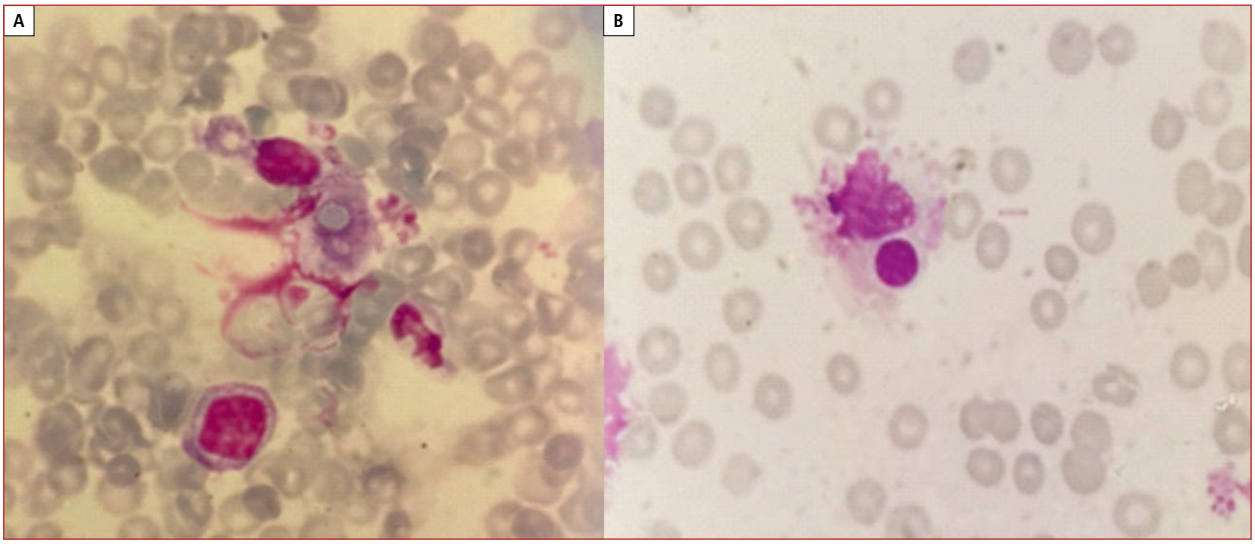

Figure 1A. Haemophagocytes in the cytological examination of the bone marrow; **B.** Single scattered CD68+ cells, which may correspond to haemophagocytes in the pathomorphological examination of the bone marrow

broad-spectrum antibiotics and based on symptoms (fever > 38°C, hyperferritinaemia, splenomegaly, pancytopenia, deterioration of liver function parameters), a HLH was suspected. The patient was urgently transferred to the Haemato-Oncology Department. First, the bone marrow trephine biopsy was performed and the material was secured for cytological and pathomorphological evaluation. Haemophagocytes were visualized in the cytological examination of the bone marrow. Single scattered CD68+ cells, which may correspond to haemophagocytes were present in the pathomorphological examination of the bone marrow (Figure 1A, B).

The patient met 6/8 criteria for the diagnosis of haemophagocytic lymphohistiocytosis: fever, splenomegaly, cytopenia in 3 cell lines (of peripheral blood), hyperferritinaemia (29,410 μg/L), hypertriglyceridemia, haemophagocytosis in the bone marrow. The patient was treated according to the HLH-2004 protocol with the use of intravenous etoposide, oral cyclosporine, and oral dexamethasone. Because the patient was in the postnatal period, inhibition of lactation with bromocriptine and anticoagulant prophylaxis with enoxaparin was recommended. After introducing the proper treatment, meaning the HLH protocol, the patient's clinical condition improved quickly. The patient was in the hospital only for the first two weeks of treatment. The treatment lasted 8 weeks and was completed on August 30, 2019. Based on blood count and biochemical tests — disease remission was achieved. The patient remains under observation in an outpatient clinic. In this case, probably the pregnancy was an HLH trigger.

Figure 2 presents serum ferritin levels during the treatment period in case 1.

Case 2

A 31-year-old man was admitted to the hospital in July 2018 due to a fever > 38°C lasting 3 weeks and hepatosplenomegaly. Imaging examinations (USG of the abdominal cavity) revealed the liver was enlarged to 165 mm in the right midclavicular line, homogeneous, normoechogenic, without focal changes, the spleen was also enlarged 140 × 50 mm, homogeneous and normoechogenic. CT of the abdominal cavity revealed enlarged liver of 170 mm in the craniocaudal view dimension, homogeneous, with the features of steatosis, in segment VIII there was calcification of the size of 10 × 5 mm. Single lymph nodes were visible around the hilum of the liver, the size of the largest one was 16 × 11 mm. There was also shown a homogeneous, enlarged spleen (150 × 50 mm).

Based on the clinical picture and laboratory tests, a HLH was suspected. Ferritin concentration during diagnosis was high (62,335 μg/L). The patient was circulatory insufficient with a tendency to hypotension, The fluid in the pleural cavities, the pericardium, and the peritoneal cavity was found. Additionally, features of liver damage were observed and because of this, the patient was transferred to the Intensive Care Unit (ICU) and

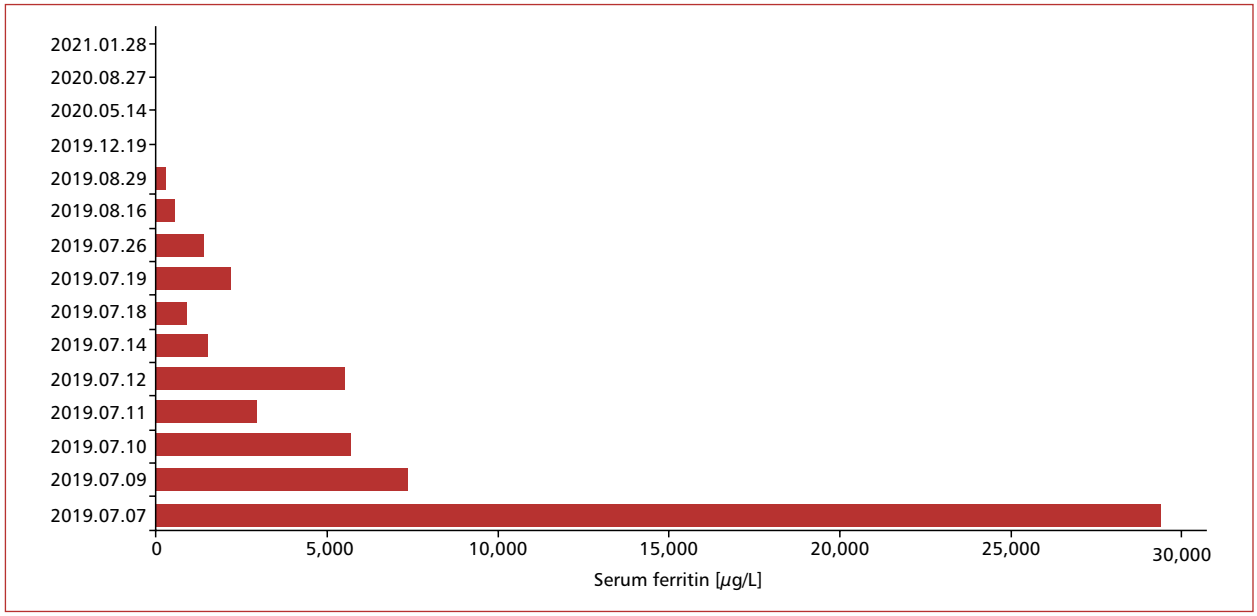

Figure 2. Serum ferritin levels during the treatment period in case 1

qualified for therapeutic plasma exchange (TPE). He developed also pancytopenia in the blood count.

After a haematological consultation, the patient initially received: dexamethasone 20 mg + + immunoglobulin 15 g. Then therapy with steroids was continued and cyclosporine and etoposide were added according to the HLH-2004 protocol. During the ICU stay, 10 TPE procedures were performed. The patient received additionally a total of 11 packed red blood cell units, 14 infusions of platelet pools, and 10 units of cryoprecipitate. After achieving a stable general condition, the patient was transferred to the Department of Haemato-Oncology where the therapy according to the HLH-2004 protocol was continued. Due to the unacceptable toxicity of the treatment, prolonged periods of neutropenia, and deterioration of kidney function, the decision was made to terminate the treatment. It was in April 2019, in week 32 of the protocol. In laboratory tests, the concentration of ferritin was stabilized at the level of 1,361 μg/L. Currently, the patient is in remission of the disease, under the care of the Haematology Clinic. The concentration of ferritin is still above the upper limit of the normal range.

In this case, the infection was probably a trigger of HLH although several blood cultures were performed during hospitalization and the microbes could not be grown.

Figure 3 presents serum ferritin levels during the treatment period in case 2.

Case 3

A 46-year-old man was admitted to the Department of Haemato-Oncology in July 2020. Previously he was hospitalized in the ICU due to sepsis and acute kidney injury requiring renal replacement therapy. Based on the diagnostic tests performed (finding of haemophagocytes in myelogram, hyperferritinaemia — 100,372 μg/L, hypertriglyceridaemia) and presence of fever as a general symptom a HLH was suspected. The treatment initially included steroid therapy and etoposide according to the HLH-2004 protocol. The dose of etoposide was reduced due to the severe general condition of the patient. What's more, cyclosporine was not administered due to acute kidney damage. The applied treatment improved the patient's condition so there was no need to continue renal replacement therapy. In the control examination of the bone marrow, which was performed twice, no haemophagocytes were present.

After several days of observation, the patient's general condition deteriorated again. There was a fever, and laboratory data revealed increased levels of ferritin (203,220 μg/L) and triglycerides (726 mg/dL). The haemophagocytes appeared again in the bone marrow smear. The patient met the criteria for the diagnosis of relapsed haemophagocytic lymphohistiocytosis. EBV DNA was detected in the blood PCR test. EBV infection as well as the previous SARS-CoV-2 infection could

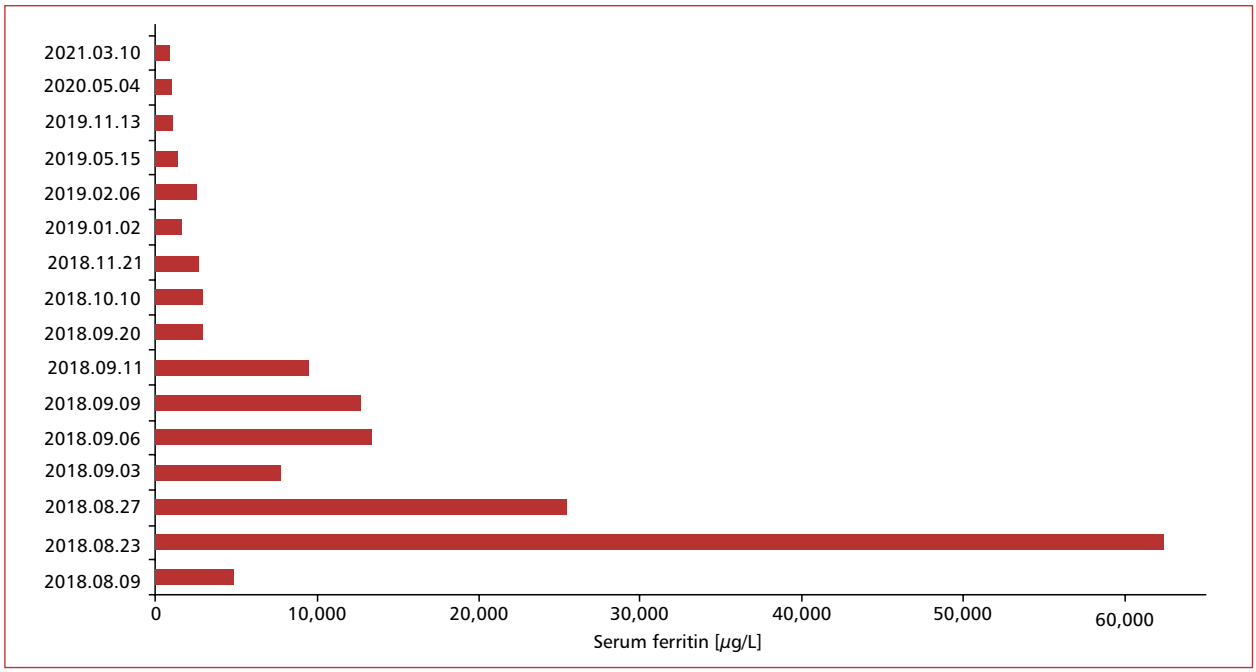

Figure 3. Serum ferritin levels during the treatment period in case 2

be the causes of the induction of haemophagocytic lymphohistiocytosis. The treatment according to the HLH-2004 protocol was started again. Additionally, rituximab was used to eradicate the EBV. In the third month of hospitalization, CMV reactivation was also diagnosed. Ganciclovir was used in the treatment at a dose adjusted to the creatinine clearance and finally, the virus was eradicated. The patient's hospitalization was complicated by septic shock induced by *Klebsiella pneumoniae* extended-spectrum beta-lactamases (ESBL)(+) and an episode of atrial fibrillation with symptoms of acute heart failure requiring electrical cardioversion.

During the next hospitalization In December 2020, the patient was diagnosed with reinfection with the SARS-CoV-2. The infection period was uneventful. Due to the biochemical features of the HLH and the patient's poor general condition, it was decided to start treatment with ruxolitinib off-label. The patient has been receiving ruxolitinib at a dose of 20 mg/daily since January 2021 and partial remission was achieved. Currently, the patient is qualified for allogeneic bone marrow transplantation from an unrelated donor. The search for a donor is ongoing.

Figure 4 presents serum ferritin levels during the treatment period in case 3.

Discussion

HLH is a medical condition associated with the over-activation of the immune system. Haematopoietic and lymphoid tissues are directly involved while other organs are secondarily damaged by circulating cytokines and chemokines, the production of which is excessive [8]. Stimulated lymphocytes and macrophages produce pro-inflammatory cytokines including IL-1, IL-6, IL-18, and tumour necrosis factor alpha (TNFα). Fever is caused by endogenous pyrogens IL-1, IL-6 and TNFα [1, 8]. Pro-inflammatory cytokines, mainly TNFα and interferon gamma (IFNγ), can strongly inhibit the activity of lipoprotein lipase and consequently lead to the stimulation of triglyceride synthesis [8, 9]. Patients with HLH also often suffer from coagulation disorders in the form of an isolated decrease in fibrinogen concentration, most likely resulting from increased fibrinolysis. Occasionally, hypofibrinogenaemia may be associated with disseminated intravascular coagulation that may occur in severe HLH [10].

HLH should be included in the differential diagnosis of sepsis, systemic connective tissue diseases, and systemic inflammatory response syndrome (SIRS). The study by Jordan and col-

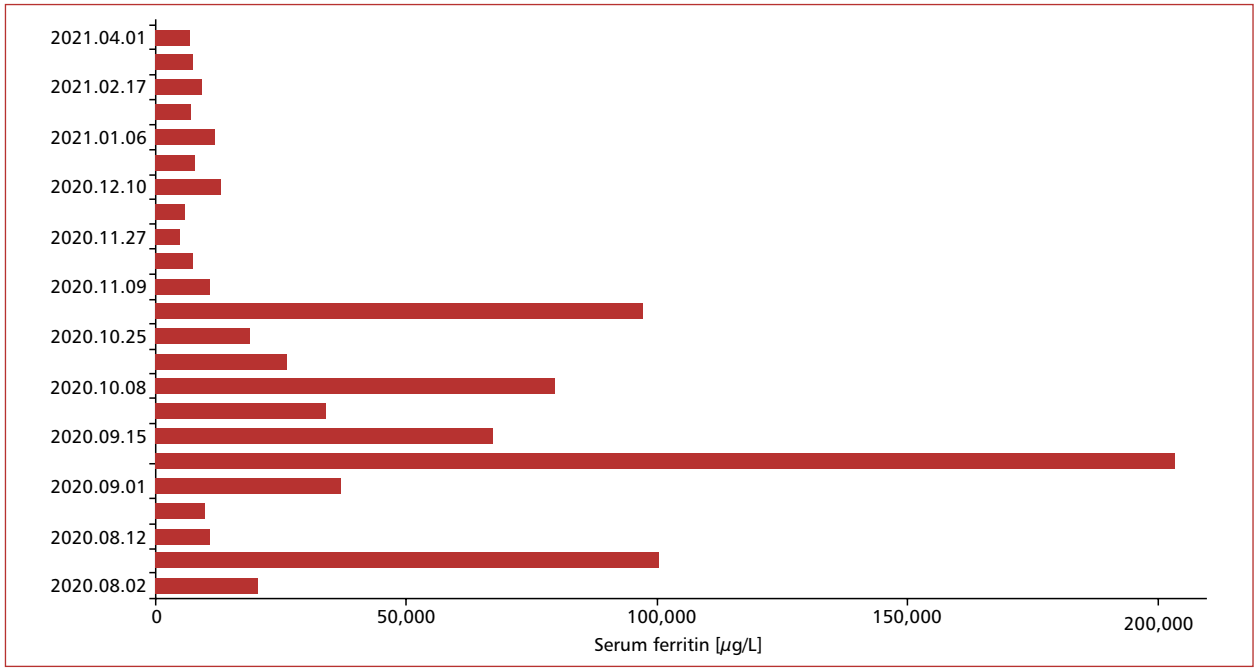

Figure 4. Serum ferritin levels during the treatment period in case 3

leagues analysed the problem of difficulties in the differential diagnostics of HLH [11]. A very important aspect during the diagnostic process is the time factor, making the diagnosis and starting treatment as soon as possible from the first symptoms to treat patients successfully — it means saving patients' lives.

The pathogenesis of HLH is most often a multifactorial process. One possible cause of HLH is EBV infection [12]. There are also reports related to the occurrence of HLH in the course of SARS-CoV-2 infection or after coronavirus disease 2019 (COVID-19) vaccination. Dewaele et al. [13] presented a case of a patient with acute respiratory failure in the course of SARS-CoV-2 infection [13]. Lubnow et al. [14] described a 21-year-old woman who was hospitalized due to coronavirus disease COVID-19-associated respiratory and hepatic impairment with severe haemolytic anaemia. HLH was additionally diagnosed, and immunosuppression was introduced. Because of the deterioration of the patient's general status immunosuppression was stopped and convalescent donor plasma was given with good results [14]. Tang and Hu [15] published a case of HLH developing in a healthy individual after COVID-19 vaccination. Laboratory evaluation shows among other abnormalities positive test for EBV DNA. After confirmation of HLH diagnosis steroids (dexamethasone acetate) were immediately prescribed and the patient's status improved. The authors emphasized how important is to exclude the presence of active EBV infection or other common viruses before COVID-19 vaccination [15].

In current diagnostics it is necessary to use the diagnostic criteria according to the HLH Study Group 2004, which consider all: laboratory criteria [cytopenia, hypertriglyceridaemia, hyperferritinaemia, hypofibrinogenemia, low or no NK cell cytotoxic activity, high concentration for the soluble IL-2 receptor (sCD25)], clinical criteria (fever, splenomegaly) and histopathological criteria — haemophagocytosis in the bone marrow, lymph node or cerebrospinal fluid [16]. NK cell function assay and evaluation of soluble IL-2Rα levels are unavailable in most haematology laboratories, unlike ferritin levels which are easier to evaluate, and the results may be available on the day of testing [17]. The concentration of ferritin is a very sensitive and best parameter for monitoring disease activity both at the time of diagnosis and during treatment. Allen and colleagues showed that ferritin levels above 10,000 μg/L may be specific and sensitive to HLH. However, he emphasized the need for the exclusion of an underlying medical history that could increase the concentration of ferritin [18].

On the one hand, Sandnes et al. [19] in 2021 published their work concerning causes of hyper-

ferritinaemia in routine medical practice. According to their results, only 10% of hyperferritinaemia is associated with iron overload. Among the rest, there is inflammation metabolic syndrome, chronic alcohol consumption, cellular damage and malignancy. Primary and secondary HLH present rare causes of hyperferritinaemia without iron overload [20].

On the other hand, evaluation of the ferritin concentration in HLH could provide very important information. In the presented cases 1 and 2, a trend was observed to decrease ferritin concentration after 2–3 weeks from the start of treatment and finally, remission of the disease was achieved. Case No. 3 is an example of a patient in whom overlapping viral infections (SARS-CoV-2, EBV, CMV) caused continuous activity of the HLH, consistently high concentration of ferritin, despite the cytostatic and immunosuppressive treatment. Lin et al. [21] presented the usefulness of regular ferritin measurements in predicting treatment outcomes in patients with HLH. Additionally, Kohli et al. [22] showed that high serum ferritin levels are highly predictive of mortality and morbidity.

The introduction of the HLH-94 protocol to the treatment of HLH, with a modification in HLH--2004, significantly reduced the mortality rate in the course of the disease. Both protocols developed for children are commonly applied but are not validated for adults. In the HLH-2004 protocol cyclosporine (CSA) was administered upfront instead of after 8 weeks as in HLH-94 [23]. CSA is associated with side effects as well as contraindications, so HLH-94 remains the recommended standard of care because is less toxic [24, 25]. The HLH-2004 protocol was chosen because the first patient was severe ill (in a very poor condition) and the good results of this treatment encouraged the introduction of these protocols in the remaining two patients, although using the HLH-2004 protocol there were made some modifications (for example in second patients) resembling HLH-94 protocol. In a paper published in 2013 by prof Machaczka [26] based on his own experience, there is a proposal for HLH treatment according to the HLH-2004 protocol in the authors' modification for the therapy of adults. In patients with first-line treatment failure or relapse of the underlying disease, allogeneic bone marrow transplantation with ruxolitinib bridging treatment is the option. Wang et al. [27] showed the above use of ruxolitinib and noted that in China there are ongoing studies on the validation of the DEP-R (doxorubicin, etoposide, methylprednisolone, ruxolitinib) regimen. Currently, patient 3 in whom the first-line chemotherapy failed has been receiving ruxolitinib. The patient achieved partial remission, and stabilization of ferritin level — 6,555 μg/L, without reactivation of CMV, EBV and SARS-CoV-2. The patient does not require hospitalization and is currently looking for a donor unrelated to allogeneic bone marrow transplantation.

Research is also ongoing on targeted therapies for HLH. Currently, the first reports from 2019 refer to alemtuzumab as the first-line approach in the treatment of primary HLH. The first prospective studies indicate that alemtuzumab enables the control of HLH activity with a favourable safety and tolerability profile [28].

Conclusion

HLH is a difficult and interdisciplinary diagnostic and treatment problem. It is necessary to popularize knowledge about fast and targeted diagnostics. Among laboratory finding the ferritin concentration seemed to be especially helpful as a predictor of treatment effectiveness. Proper diagnosis and treatment introduced as early as possible could save patients' life.

Conflict of interest

The authors declare no conflict of interest.

Financing

None.

References

1. Jędrzejczak W, Machowicz R, Ochrem B. Histiocytozy zapalne i nowotworowe; Limfohistiocytoza hemofagocytowa. In: Gajewski P. ed. Interna Szczeklika. Duży podręcznik. Medycyna Praktyczna, Kraków 2020: 1909–1911.
2. Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. Arch Dis Child. 1952; 27(136): 519–525, doi: 10.1136/adc.27.136.519, indexed in Pubmed: 13008468.
3. Egeler RM, Shapiro R, Loechelt B, et al. Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. J Pediatr Hematol Oncol. 1996; 18(4): 340–345, doi: 10.1097/00043426-199611000-00002, indexed in Pubmed: 8888739.
4. Stepp SE, Dufourcq-Lagelouse R, Kumar V, et al. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science. 1999; 286(5446): 1957–1959, doi: 10.1126/science.286.5446.1957, indexed in Pubmed: 10583959.
5. Zhang K, Astigarraga I, Bryceson Y et al. Familial hemophagocytic lymphohistiocytosis. In: Adam MP, Mirzaa GM, Pagon RA et al., eds. GeneReviews. University of Washington, Seattle 2006: 1993–2022. https://pubmed.ncbi.nlm.nih.gov/20301617/ (September 30, 2021).

6. Jordan MB, Hildeman D, Kappler J, et al. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood. 2004; 104(3): 735–743, doi: 10.1182/blood-2003-10-3413, indexed in Pubmed: 15069016.
7. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48(2): 124–131, doi: 10.1002/pbc.21039, indexed in Pubmed: 16937360.
8. Usmani GN, Woda BA, Newburger PE. Advances in understanding the pathogenesis of HLH. Br J Haematol. 2013; 161(5): 609–622, doi: 10.1111/bjh.12293, indexed in Pubmed: 23577835.
9. Henter JI, Carlson LA, Söder O, et al. Lipoprotein alterations and plasma lipoprotein lipase reduction in familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1991; 80(6-7): 675–681, doi: 10.1111/j.1651-2227.1991.tb11928.x, indexed in Pubmed: 1867086.
10. Valade S, Azoulay E, Galicier L, et al. Coagulation disorders and bleedings in critically ill patients with hemophagocytic lymphohistiocytosis. Medicine (Baltimore). 2015; 94(40): e1692, doi: 10.1097/MD.0000000000001692, indexed in Pubmed: 26448017.
11. Jordan MB, Allen CE, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011; 118(15): 4041–4052, doi: 10.1182/blood-2011-03-278127.
12. Rouphael NG, Talati NJ, Vaughan C, et al. Infections associated with haemophagocytic syndrome. Lancet Infect Dis. 2007; 7(12): 814–822, doi: 10.1016/S1473-3099(07)70290-6, indexed in Pubmed: 18045564.
13. Dewaele K, Claeys R. Hemophagocytic lymphohistiocytosis in SARS-CoV-2 infection. Blood. 2020; 135(25): 2323, doi: 10.1182/blood.2020006505, indexed in Pubmed: 32556137.
14. Lubnow M, Schmidt B, Fleck M, et al. Secondary hemophagocytic lymphohistiocytosis and severe liver injury induced by hepatic SARS-CoV-2 infection unmasking Wilson's disease: Balancing immunosuppression. Int J Infect Dis. 2021; 103: 624–627, doi: 10.1016/j.ijid.2020.12.047, indexed in Pubmed: 33412272.
15. Tang LV, Hu Yu. Hemophagocytic lymphohistiocytosis after COVID-19 vaccination. J Hematol Oncol. 2021; 14(1): 87, doi: 10.1186/s13045-021-01100-7, indexed in Pubmed: 34088334.
16. La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019; 133(23): 2465–2477, doi: 10.1182/blood.2018894618, indexed in Pubmed: 30992265.
17. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48(2): 124–131, doi: 10.1002/pbc.21039, indexed in Pubmed: 16937360.
18. Allen CE, Yu X, Kozinetz CA, et al. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008; 50(6): 1227–1235, doi: 10.1002/pbc.21423, indexed in Pubmed: 18085676.
19. Sandnes M, Ulvik R, Vorland M, et al. Hyperferritinemia — a clinical overview. J Clin Med. 2021; 10(9): 2008, doi: 10.3390/jcm10092008.
20. Hearnshaw S, Thompson NP, McGill A. The epidemiology of hyperferritinaemia. World J Gastroenterol. 2006; 12(36): 5866–5869, doi: 10.3748/wjg.v12.i36.5866, indexed in Pubmed: 17007054.
21. Lin TF, Ferlic-Stark LL, Allen CE, et al. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. Pediatr Blood Cancer. 2011; 56(1): 154–155, doi: 10.1002/pbc.22774, indexed in Pubmed: 20842751.
22. Kohli S, Chadha R, Rastogi N, et al. High serum ferritin alone as a predictor of mortality and hemophagocytic lymphohistiocytosis. EJHaem. 2021; 2(1): 136–138, doi: 10.1002/jha2.153, indexed in Pubmed: 35846094.
23. La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019; 133(23): 2465–2477, doi: 10.1182/blood.2018894618, indexed in Pubmed: 30992265.
24. Ehl S, Astigarraga I, von Bahr Greenwood T, et al. 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. J Allergy Clin Immunol Pract. 2018; 6(5): 1508–1517, doi: 10.1016/j.jaip.2018.05.031, indexed in Pubmed: 30201097.
25. Bergsten E, Horne A, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood. 2017; 130(25): 2728–2738, doi: 10.1182/blood-2017-06-788349, indexed in Pubmed: 28935695.
26. Machaczka M. Specyfika występowania limfohistiocytozy hemofagocytarnej w okresie wieku dorosłego. Acta Haematol Pol. 2013; 44(3): 307–313, doi: 10.1016/j.achaem.2013.07.020.
27. Wang J, Wang Y, Wu L, et al. [Refractory/relapsed hemophagocytic lymphohistiocytosis treated with ruxolitinib: three cases report and literatures review]. Zhonghua Xue Ye Xue Za Zhi. 2019; 40(1): 73–75, doi: 10.3760/cma.j.issn.0253-2727.2019.01.014, indexed in Pubmed: 30704233.
28. Moshous D, Briand C, Castelle M, et al. Alemtuzumab as first line treatment in children with familial lymphohistiocytosis. Blood. 2019; 134(Suppl_1): 80–80, doi: 10.1182/blood-2019-124477.