REVIEW ARTICLE

How can an internal medicine specialist save a patient with hemophagocytic lymphohistiocytosis (HLH)?

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KEY WORDS

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH; also, hemophagocytic syndrome) occurs when an inflammatory reaction cannot stop on its own but continues to self-accelerate with positive feedback loops. If not interrupted, this pathomechanism leads to death. HLH in adults is usually diagnosed based on the HLH-2004 criteria, but its confirmation should not stop the diagnostic process. Finding the triggering factor (especially malignancy) is of utmost importance. Treatment strongly depends on the established trigger and it is often based on the etoposide HLH-94 protocol (adjusted for adults). Diagnostic workup should not unnecessarily delay the treatment since patients in severe or quickly deteriorating clinical condition require its fast initiation. Considering the progressive nature of HLH, time is extremely important. Prompt diagnosis and treatment, frequently made by an internal medicine specialist, is life-saving. The aim of this review is to raise HLH awareness among internal medicine specialists and to provide advice on HLH management tailored for this group of physicians. Suggested approach is based on the latest recommendations by the Histiocyte Society and include novel insights from the authors' experience.

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Why is HLH important for internal medicine specialists?

Hemophagocytic lymphohistiocytosis (HLH; also, hemophagocytic syndrome) is a syndrome of uncontrolled hyperinflammation, which leads to death when left untreated.1 Its symptoms essentially resemble infection without obvious characteristic differences, and patients are usually treated for sepsis but have no chance to be cured with antibacterial therapy. In effect, HLH remains severely underdiagnosed and many patients die without any attempt of effective treatment (which is widely available). The role of internal medicine specialists in saving patients with HLH is crucial as frequently they are the first who can suspect HLH, diagnose it, and if possible, start treatment.

Hemophagocytic lymphohistiocytosis is a rare syndrome—data for adults from Sweden show 3.6 cases per million inhabitants annually,2 but these data include only HLH associated with malignancy, which suggests it may be at least 2-fold more frequent. It is also heavily underdiagnosed. In Poland, at least 250 new cases of HLH in adults may be expected every year, but unfortunately, the majority of those patients are not diagnosed and eventually die untreated.

The aim of this review is to raise HLH awareness among internal medicine specialists and to provide advice on HLH management tailored for this group of physicians. Suggested approach is based on the latest recommendations by the Histiocyte Society and include novel insights based on the authors' experience.3

What is HLH?

Hemophagocytic lymphohistiocytosis occurs when an inflammatory reaction cannot stop on its own but continues to self-accelerate with positive feedback loops. Its mechanism is well described in primary HLH in which a genetic defect in the cytotoxic granule pathway causes lack of cytotoxic activity of T lymphocytes and natural killer (NK) cells. Although unable to kill target cells, they retain ability to release cytokines that stimulate macrophages, which in turn stimulate cytotoxic cells causing a vicious circle of positive feedback loops. Genes involved in this process are shown in FIGURE 1. A severe biallelic

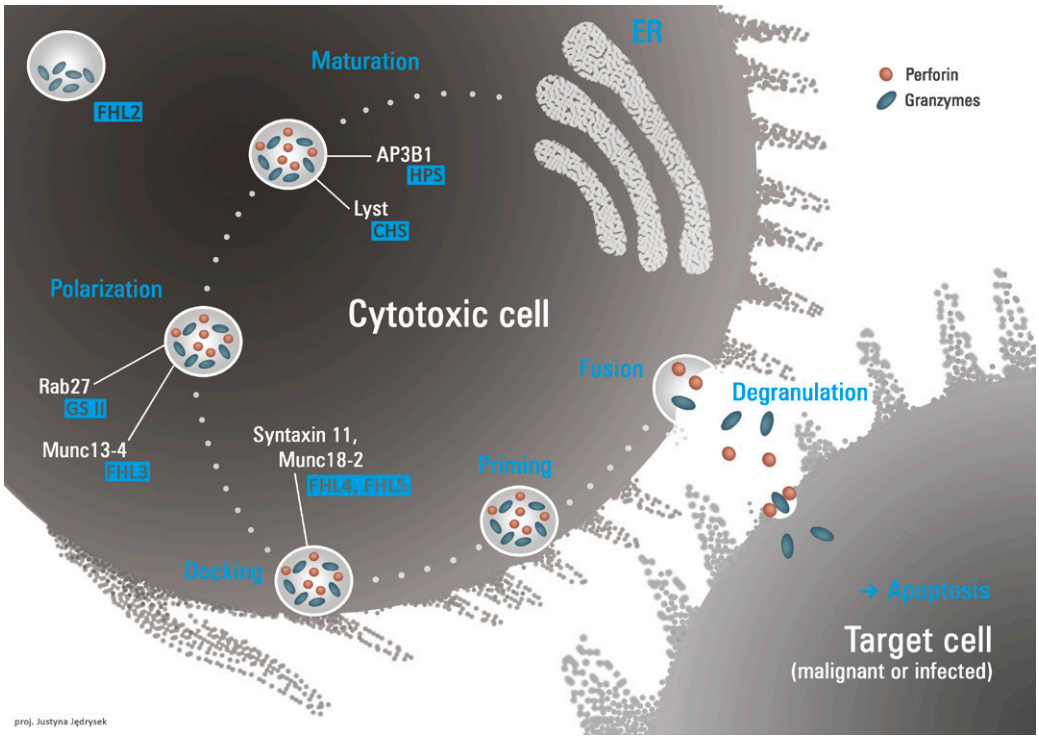

FIGURE 1 Genetic background of primary HLH: cytotoxic granule pathway. Syndromes (blue boxes) are presented next to proteins defect of which causes each syndrome (in white). Abbreviations: CHS, Chédiak–Higashi syndrome; ER, endoplasmic reticulum; FHL, familial hemophagocytic lymphohistiocytosis; GS II, Griscelli syndrome type II; HPS, Heřmanský–Pudlák syndrome (Figure designed by Justyna Jędrysek)

mutation in this pathway causes HLH onset in early childhood, but less severe defects were also found in adults.4,5

This mechanism is characteristic of familial (primary) HLH. Recently, also defects in inflammasome function were found to be associated with HLH, but a vast majority of adult patients do not have any identifiable genetic abnormality (but probably have some other, not yet known predisposition as HLH is very rare). In such a situation, HLH is described as secondary.

Pathologic inflammation has to be induced by a triggering factor. In case of lack of any cytotoxic activity, every infection can start HLH in an infant. Adults have a higher threshold for HLH induction. The most important triggering factors are: infections, malignancies, and autoinflammatory disorders. Among infections, they are usually viral, with a leading role of Epstein–Barr virus (EBV). Cytomegalovirus, parvovirus, or influenza A(H5N1) were also demonstrated as HLH triggers,6 as well as bacterial, fungal, or parasitic triggers.7 Malignancies inducing HLH are usually lymphomas, especially T cell, but also myeloid malignancies and solid tumors are frequently reported.8 Hemophagocytic lymphohistiocytosis may also occur in patients with immune suppression after chemotherapy, receiving immunosuppressive drugs, or with HIV infection. In such cases, it is usually caused by a secondary infection. Autoimmune disorders include Still disease, lupus, systemic juvenile idiopathic arthritis, and others. Such cases of HLH are frequently reported as macrophage activation syndrome (MAS).

The term MAS can be also used in cases of severe autoinflammation that are less severe compared with HLH. Hemophagocytic lymphohistiocytosis is always at the far end of the inflammatory continuum. Different, often misleading, names used for description of similar symptoms are summarized in TABLE 1.

When should I suspect HLH? Hemophagocytic lymphohistiocytosis should be suspected in a patient with intense, progressive inflammation with recurrent fever, cytopenia, and splenomegaly9 or coagulopathy. These manifestations can be accompanied by organomegaly, lymphadenopathy, rash, arthralgia, icterus, purpura, edema, dyspnea, and progress to multiorgan failure. These symptoms may be produced by both a triggering factor and HLH itself, but their presence should raise suspicion of HLH. Laboratory results frequently include hypertriglyceridemia, hyperbilirubinemia, transaminitis, elevated lactate dehydrogenase and D-dimer levels.

Patients, despite looking "septic," do not respond to empiric antimicrobial therapy. Symptom progression, which can become rapid, is an important trait—HLH is also diagnosed at the intensive care unit.10 Hemophagocytic lymphohistiocytosis, as a severe inflammation, is unlikely in an afebrile patient.

Is there any single pathognomonic symptom of HLH? No single clinical or laboratory feature is pathognomonic for HLH. Extreme hyperferritinemia is the only commonly present abnormality which may be, to some extent, characteristic. Patients with HLH may present with ferritin concentrations exceeding 10 000 ng/ml (sometimes even 100 000 ng/ml; values in ng/ml are the same as in μg/l). Only a subset of patients have such high values, and hyperferritinemia may have multiple other causes in adults, for example, hemochromatosis, transfusions, or liver failure. Although its predictive value is not satisfactory,11 disproportionately

TABLE 1 Similar symptoms, different names

HLH	Hemophagocytic lymphohistiocytosis; usually defined as fulfilling the HLH-2004 criteria
Hemophagocytic syndrome	A slightly wider term than HLH, incorporates also patients diagnosed, eg, with the HScore
MAS	Macrophage Activation Syndrome; hyperinflammation syndrome caused by autoimmune/autoinflammatrory disease. The term MAS-HLH is also in use. It can be much milder than HLH (eg, when diagnosed with the Ravelli criteria) or, much less frequently fulfill the HLH-2004 criteria. Historically, it used to be a synonym for HLH/hemophagocytic syndrome.
MAS-sepsis, hyperferritinemic sepsis	These and other similar terms describe hyperinflammatory variant of sepsis, which is much more common than HLH, and should not be mistaken with HLH or MAS as defined above.
CRS	Cytokine release syndrome; occurs after the use of certain novel immunotherapies (blinatumomab, chimeric antigen receptor T cells)
Cytokine storm syndrome	Probably the widest and least defined term; may include all of the above

The terms may have different meanings in various studies and are sometimes used interchangeably. Caution and verification of the exact definition in every paper is advised.

TABLE 2 The HLH-2004 diagnostic criteria

A	Molecular diagnosis consistent with HLH
B	5 out of the 8 following criteria • Fever • Splenomegaly • Cytopenia of ≥2 out of 3 lineages: neutrophils $<1.0\times10^9$/l; Hb <9 g/dl; PLT $<100\times10^9$/l • Hypofibrinogenemia and/or hypertriglyceridemia: fibrinogen ≤1.5 g/l (150 mg/dl); triglycerides ≥3 mmol/l (265 mg/dl) • Hemophagocytosis • Ferritin ≥500 ng/ml • Low NK-cell activity • sCD25 (sIL-2R) ≥2400 U/ml

Abbreviations: Hb, hemoglobin; HLH, hemophagocytic lymphohistiocytosis; NK, natural killer; PLT, platelet count; sCD25, soluble cluster of differentiation 25; sIL-2R, soluble interleukin 2 receptor

high hyperferritinemia in a febrile patient should always raise a suspicion of HLH.

Hemophagocytosis is the phagocytosis of blood cells by activated macrophages observed in a microscopic examination of biological material, most commonly bone marrow smear. It is a base for the name hemophagocytic syndrome, but confirmation of its presence is neither required nor sufficient for the diagnosis of HLH. Hemophagocytosis can be present in many inflammatory conditions: sepsis, influenza, leishmaniasis, malaria, active rheumatoid disorders, and after blood transfusions.12 Overdiagnosing hemophagocytic syndrome based on the presence of hemophagocytosis and selected other symptoms in a patient who is, however, not fulfilling the remaining diagnostic criteria may have detrimental consequences, leading to an unsuccessful treatment of HLH without making the right diagnosis.

On the other hand, hemophagocytosis is considered one of the late HLH symptoms (it was found in 32% of children at admission and 85% at HLH diagnosis)13 and neglecting diagnosis of "hemophagocytic syndrome without hemophagocytosis" (which is not yet visible) is life-threatening.

An increased concentration of soluble interleukin 2 receptor, also known as soluble cluster of differentiation 25 (sCD25), although in clinical practice used mostly in the diagnostic workup of HLH, is also elevated in multiple other conditions such as autoimmune diseases, neoplasms (notably lymphoproliferations), and infections.14 Although by no means pathognomonic, its elevated concentration can help guide differential diagnosis towards HLH and low values are helpful in ruling HLH out.15 A high ratio of sCD25 to ferritin suggests lymphoma as HLH trigger.16 The key issue with this useful test is that it is available only in highly specialized centers.

The determination of NK cell activity (gradually replaced by the analysis of perforin and CD107a)17 is important mostly as a screening method of genetic defects responsible for familial HLH. Undoubtedly, its importance in adults is much lower than in children. Low NK cell activity, although key to the mechanism of familial HLH, is by no means pathognomonic for HLH—it was found also in 96% of patients with septic shock.18

How to make the diagnosis? The diagnosis of HLH is based on the presence of a constellation of hyperinflammation symptoms. However, the presence and intensity of each of them varies between patients. The most widely accepted is the fulfillment of at least 5 out of 8 HLH-2004 criteria19 (TABLE 2). They were created by a group of experts as inclusion criteria for a pediatric clinical trial, which is frequently underlined as their limitation in adults. Despite that, they are the most widely used standard also in this population. Two out of 8 HLH-2004 criteria (NK--cell activity and sCD25 concentration) are very difficult to test in the general practice, as discussed above. In a rapidly deteriorating patient, a prompt initiation of therapy is life-saving. In such cases, a simplified system was proposed by Jedrzejczak20: patient should convincingly fulfill at least 4 out of the 6 available HLH-2004 criteria, including ferritin concentrations higher than 2000 ng/ml, and he should not have causes for observed abnormalities other than HLH.

An independent system that overcomes the main limitations of the HLH-2004 is the HScore.21 It was designed using only widely

TABLE 3 Comparison of treatment regimens for hemophagocytic lymphohistiocytosis

Week	1–2	3–4	5–6	7–8
HLH-94				
VP-16	2 × 150 mg/m²/wk	← 1 × 150 mg/m²/wk →		
Dex	10 mg/m²/d	5 mg/m²/d	2.5 mg/m²/d	1.25 mg/m²/d
CsA				After 8 weeks
HLH-2004				
VP-16	2 × 150 mg/m²/wk	← 1 × 150 mg/m²/wk →		
Dex	Same as HLH-94			
CsA	← Concentration 200 µg/l →			
HLH-94 adjusted for adults				
VP-16	← 1 × 50–100 mg/m²/wk →			
Dex	Same as HLH-94			
CsA				Possible after 8 weeks

Abbreviations: CsA, cyclosporin A; Dex, dexamethasone; VP-16, etoposide; others, see TABLE 2

available parameters (established by a worldwide expert Delphi survey)22 and based on data for adult French patients. Its design is more complex than the HLH-2004 (parameters can have more than one threshold and each parameter has a different weight), moreover it establishes a probable, not definite, diagnosis. The HScore can be easily calculated online at http://saintantoine.aphp.fr/score.

There are different pediatric criteria for MAS (eg, the Ravelli criteria in systemic juvenile idiopathic arthritis23 or the MH Score)24 which allow diagnosis at much earlier stage than the HLH--2004, but in some patients with MAS, hyperinflammation also fulfills the HLH-2004 criteria.

The diagnostic workup has to be continued after the HLH diagnosis, which also does not indicate the necessity to start treatment. It only suggests that the inflammation is very intense and soon may become life-threatening. An aggressive diagnostic approach to establish the trigger is crucial for the choice of optimal treatment. A broad spectrum of infectious agents should be tested, always including EBV and HIV and other depending on patient history, including travel exposure. Screening for autoimmune diseases should also be initiated. Adult patients are at high risk of underlying malignancy and all effort should be made to diagnose it. In addition to bone marrow testing, other biopsies are usually required (guided by computed tomography and ideally by positron emission tomography with computed tomography). Moreover, repeated biopsies may be needed for occult difficult to diagnose lymphoma (such as intravascular B-cell lymphoma).

Patient fulfills the criteria. What should I do now? Consult a hematologist, if it has not been already done. Perform all suggested laboratory and imaging tests as well as biopsies (including trephine biopsy) as soon as possible. If you need to start treatment, store samples for genetic testing. If the patient is deteriorating, diagnostic process should not delay the treatment! Full treatment, at least in Poland, is available only on hematology wards.

A prompt initiation of all these actions is crucial, but requires a very cautious approach. While the current problem is the underdiagnosis of HLH, overdiagnosis is also possible. This may occur when 2 or 3 conditions together produce abnormalities in parameters used as HLH criteria. For example, patients with chronic liver failure frequently have splenomegaly (portal hypertension), hyperferritinemia (released from damaged liver), some degree of anemia and thrombocytopenia, and may occasionally have an infection with fever. Such patients would not benefit from HLH treatment.

Additionally, there are numerous disorders that mimic HLH25 which, despite fulfilling HLH criteria, require different treatment. They include infections such as visceral leishmaniasis, tuberculosis, mycobacteriosis, histoplasmosis, infection with *Ehrlichia*, *Bartonella*, and *Brucella* species, disseminated adenovirus, and disseminated herpes simplex virus. In these infections, the HLH-2004 criteria may be fulfilled, but they require antimicrobial treatment instead of immunosuppression needed in the treatment of HLH.

Initial treatment Steroids should be initiated if a patient is at risk of fast deterioration, and a prompt intervention of an internal medicine specialist can be life-saving. Depending on the clinical context, the treatment may include methylprednisolone pulses or dexamethasone 10 mg/m² as an initiation of the HLH-94 protocol.3 Another important treatment option, which may be delivered by an internal medicine specialist, is intravenous immunoglobulins (IVIGs, up to 1.6 g/kg split over 2–3 days).8,26 This treatment may stop moderate HLH or slow down the progression of more severe HLH, offering time for diagnostic procedures and further treatment in the hematology ward.

Hematological treatment Effective treatment of severe HLH is based on a cytostatic agent, etoposide (VP-16). The first widely used treatment protocol was the HLH-9427 (TABLE 3) consisting of etoposide, dexamethasone, and (after 8 weeks) cyclosporin A (CsA). In a similar HLH-2004 treatment protocol, the main difference was the use of CsA from the beginning of therapy.19 The HLH--2004 did not show significant survival advantage over the HLH-94,28 so the latter remains standard for HLH treatment in children. Cyclosporin A requires concentration measurements and toxicity assessment and can be replaced with tacrolimus.29

Apparently, pediatric protocols are overly toxic for adults. The adjustment of the HLH-94 is based on a regimen proposed by Henter et al6 for the treatment of HLH triggered by avian influenza. The dose of etoposide is reduced from 150 mg/m² to between 50 and 100 mg/m², additionally in the first 2 weeks, it is administered

once (not twice) a week (TABLE 3). Detailed recommendations of the Histiocyte Society on the use of etoposide in HLH (including dose reductions) were published in 2018.30

Etoposide is mutagenic and its use is associated with a risk of secondary leukemia. At present, experiences with this complication in adult HLH are limited, but this risk is lower than morbidity and mortality of severe HLH.30 Only 2 children in 2 large pediatric studies developed leukemia: 1 in 368 patients in the HLH-200428 and 1 in 249 patients in the HLH-94 study.31 These events were observed at a median follow-up of 5.2 and 6.2 years after etoposide exposure, respectively. In 81 Japanese patients with EBV-triggered HLH, one case of leukemia was described.32 In adult patients without malignancy, the cumulative dose of etoposide below 2 to 3 g/m^2 is recommended.32 Adult patients frequently do not need the full 8 week-course of therapy and later maintenance, so the cumulative dose of etoposide is much lower than in children.

Does the diagnosis of HLH always require etoposide treatment? The fulfillment of 5 or even 8 of the HLH-2004 criteria does not mean that the patient has to receive the HLH-94 protocol.30 The treatment should be tailored for each patient and depends on the underlying trigger. If HLH is diagnosed early enough, it may be stopped with steroids alone (with or without IVIG). Other important variations in the approach include the following situations.

Rituximab can be an important addition in HLH associated with EBV infection.33 Epstein–Barr virus viremia should be confirmed with polymerase chain reaction. Levels above >10^3 copies/ml were found in over 90% of patients at the first presentation.34

Malignancy-associated HLH may initially require a HLH-specific approach to stop the cytokine storm, but eventually, the therapy should be targeted against the triggering neoplasm. In lymphoma, treatment regimens containing etoposide can be chosen (eg, CHOEP [cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone], DA-EPOCH [dose-adjusted: etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin]).26

Hemophagocytic lymphohistiocytosis after chemotherapy or stem cell transplantation is difficult to diagnose. Additional cytotoxic activity of etoposide can prolong cytopenia and impair the potential to fight the underlying infection, which is the usual trigger in such cases. Antimicrobial treatment, steroids, and IVIG are preferred. Also, a suspected relapse of HLH may be associated with infection. Wide antimicrobial prophylaxis is recommended.

Cytokine release syndrome, a complication after the use of chimeric antigen receptor T cells or blinatumomab, is a specific form of iatrogenic HLH. It has own specific diagnostic criteria and treatment is based on steroids and tocilizumab (antibody against interleukin-6 receptor).35,36

Macrophage activation syndrome Macrophage activation syndrome is HLH in patients with an autoimmune / autoinflammatory disease. It can also be triggered by infection, not the disease itself.37 The first-line treatment is steroids (eg, pulses of methylprednisolone 1 g/d for 3–5 days).38 The specific treatment of MAS may include anakinra (anti–interleukin 1 therapy),39 tocilizumab,40 or CsA. Some patients with very severe or refractory MAS-HLH may require etoposide therapy.30

End-of-life HLH Many patients who are in the last days of their life due to various, but usually advanced diseases (eg, lymphoma or other malignancy progressing after several lines of treatment) can present with many symptoms of the HLH--2004 criteria, sometimes can even fulfill most of them. Obviously, this is not the emergence of HLH as an additional disease but progressing multiorgan failure causing multiple abnormalities, also those defined by the HLH-2004 criteria. Such patients will certainly not benefit from establishing such a diagnosis and etoposide treatment, which can only shorten their life. Steroids are used in palliative care alleviating some of these inflammatory symptoms without need for the diagnostic workup of HLH.

Also patients with newly diagnosed (or even not yet diagnosed) malignancy who seek professional help too late (eg, after neglecting alarming symptoms for extended periods) can be in a similar situation. They can fulfill some of the HLH--2004 criteria, but frequently, they are rather equivalent to their severe clinical condition rather than beginning of HLH. Some of such patients have already crossed the point of no return—their imminent death cannot be reversed with currently available methods. This tragic situation can also occur in patients with real HLH when cytokine storm is already so intense that it cannot be stopped with any currently available treatment.

Salvage therapy The reactivation of HLH may be caused by too moderate or too quickly tapered treatment. In such case, intensification of standard therapy may succeed. Caution is advised because there is always a risk of secondary infection falsely diagnosed as HLH relapse. The only HLH salvage therapy tested in adults in a prospective trial is the DEP regimen (liposomal doxorubicin, etoposide, and methylprednisolone).41

Plasmapheresis and cytokine adsorption columns can be of great help in fighting refractory HLH.42,43 Ruxolitinib (Janus kinase inhibitor) has a high potential in HLH and may be used in a refractory setting.44,45 As interferon γ (IFN-γ) was found to be the key agent in HLH cytokine storm,46 an anti–IFN-γ antibody was introduced. Emapalumab was approved by the Food and Drug Administration in November 2018 as

a second-line treatment of primary HLH in children and adults.47

Alemtuzumab (anti-CD52 antibody) was found effective both in the first-line therapy in children with familial HLH48 and as a salvage therapy in children49 and in adults,50 as a bridge to allogeneic hematopoietic stem cell transplantation (allo-HSCT). Allo-HSCT itself is indicated in adults with primary or relapsed / refractory disease.3,26,29 The diagnosis of primary HLH and indications for allo-HSCT based on genetic results should be carefully analyzed in adults to exclude genetic alterations without or with little clinical significance, such as the perforin A91V polymorphism present in 10% of the population.51

What if a patient with a history of HLH presents with fever? A febrile patient with previous history of HLH admitted to an internal medicine ward may constitute a diagnostic problem. The first step is to repeat all HLH-relevant tests to check if it is a relapse of HLH. The past history is important, but in case of (presumed) HLH relapse, it is crucial to always re-determine the trigger. A patient with an excellent response to HLH treatment may relapse with a different (eg, malignant) trigger. In our experience, a young man who had been previously treated in another center for EBV--triggered HLH, at relapse was diagnosed with T-cell lymphoma, even though EBV viremia was present again.

Should I diagnose and treat relatives? This relevant question has not been not fully answered in the adult population. In children, who usually have a strong genetic predisposition, it is crucial to investigate siblings for the same mutation as proband. It was shown that preemptive allo--HSCT in unaffected children has better outcomes than if treatment was started at the time of the first HLH symptoms.52 If the proband developed HLH after 18 years of age, the genetic predisposition in his siblings usually does not require up--front allo-HSCT.

A relative of a patient with HLH undergoing a severe febrile episode should have basic HLH parameters assessed (complete blood count with differential, ferritin, triglycerides, fibrinogen, transaminases, and presence of hepatosplenomegaly). Performing basic HLH tests in the siblings of a patient in order to have baseline results for comparison in case of a severe febrile episode is considered good practice. Adult siblings may have, for example, anemia, hyperferritinemia due to hemochromatosis, or hypertriglyceridemia due to dyslipidemia. All of these abnormalities, if found during a febrile episode, may cause unnecessary fear of HLH onset, therefore they should be reassessed at least every 2 to 3 years. An unaffected sibling negative for a genetic mutation may also benefit from such screening because predisposition in his family may be associated with a mutation in a different gene (not yet attributed to HLH).

Conclusions Hemophagocytic lymphohistiocytosis is a rare but life threatening syndrome, which when promptly diagnosed and managed may be resolved. It is a disease of vicious circle of hyperinflammation which, if not stopped, leads to multiple organ failure. In adults, it can be triggered by numerous diverse primary disorders such as neoplasia, viral, and less frequently, bacterial and fungal infections as well as autoimmune diseases. Additionally, especially in younger adults, it may still be due to inherited mutations of genes affecting activation of cytotoxic cells. The diagnosis is based on the confirmation of co-occurrence of several symptoms with hyperferritinemia being the most characteristic. In the majority of patients, only etoposide-based therapy is able to stop its progression and only when it is instituted prior passing into an irreversible stage. Hence, internists' awareness of HLH and its diagnostic work-up is critical.

ARTICLE INFORMATION

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