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SHORT COMMUNICATION

Hemophagocytic lymphohistiocytosis as indication or sequel of hematopoietic stem cell transplantion in children: a single center experience

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) represents a life-threatening inflammatory condition with abnormal immune activation related to ineffective cytotoxic cell function. This results in excessive release of inflammatory cytokines leading to myelosuppression, vascular endothelium injury, and in consequence disseminated intravascular coagulation and organ damage [1]. Clinical manifestations indicative of HLH comprise spiky pattern fever, hepatosplenomegaly and cytopenias, with typical laboratory findings including an elevated level of ferritin, low fibrinogen, hypertriglyceridemia and liver injury, further neurological impairments, and rapid progression to multiorgan failure. HLH can be distinguished as either a primary (hereditary) or a secondary (acquired) syndrome.

Essentially, primary HLH (pHLH) is observed in children, although late-onset has also been described [2]. The main subtype of pHLH, referred to as familial HLH (FHL), is diagnosed typically in infants and is classified into five subtypes (FHL1–5) in accordance with underlying mutations of genes responsible for T lymphocyte and natural killer (NK) cells cytotoxic function. Causative gene mutations of other primary forms of HLH are related to a variety of effector T-cell and NK cell functions.

The secondary form of HLH (sHLH) lacks a clear genetic basis and arises in association with various stimuli i.e. infections, autoimmune disorders, immune deficiencies, malignant lymphoproliferations, or hematopoietic stem cell transplantation (HSCT) [1, 3].

Allogeneic HSCT is the only effective therapy in pHLH, and is required in sHLH that is refractory to immunochemotherapy or is relapsed. The results are suboptimal, with overall 5-year survival of 66–73% [3, 4]. On the other hand, the HSCT procedure itself may be a trigger of HLH, a severe complication with an especially high mortality rate in this setting. In patients with HLH post-HSCT, two forms of the disease can be distinguished. The more frequent form, early-onset post-HSCT HLH, occurs <30 days after HSCT, while late-onset post-HSCT HLH appears >30 days after transplantation. Late-onset post-HSCT HLH is usually associated with infection, but the pathogenesis of the early-onset disease remains unexplained [5].

We present below our experience of pHLH treatment with allogeneic bone marrow transplantation and, as a contrast, we describe a patient who developed sHLH as a complication after HSCT. The aim of this study was to analyze the various triggers of HLH in the context of seeking a prompt diagnosis and effective treatment.

Material and methods

Three children, among them two siblings, diagnosed with pHLH (FHL3 in all cases), consecutively treated with HSCT in our center, were enrolled into our study, along with a single patient recognized as post-HSCT sHLH, who had been transplanted for activated phosphoinositide 3-kinase delta syndrome (PI3K-δ) syndrome (APDS). All patients underwent HSCT in our center between 2011 and 2022.

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The diagnosis and management of primary and secondary HLH were based on the HLH-2004 Protocol with later updates [6, 7]. The parents of the four children provided written informed consent for their participation in this study.

Results

Detailed clinical data on the presented patients is set out in Table I.

Patient 1, a seven-week-old infant, revealed a septic-like picture with HLH features with a good response to methylprednisolone, but soon experienced a second (then diagnosed with FLH3) and a third severe flare of the disease. Severe multi-organ failure and the need for prolonged intensive care therapy postponed HSCT, which the patient underwent at the age of 12 months. Post-transplant course was unremarkable, with permanent recovery from HLH. Patient 1 had a younger brother (not included in the study) diagnosed with FHL3, who died of sepsis at the age of 2.5 months.

Patient 2, the younger sister of the aforementioned boys, presented with an HLH picture a few days after birth, and FHL3 was quickly confirmed. At the age of two weeks, she started standard HLH treatment and as a four-month-old infant she was subjected to HSCT. In 7-months of post-transplant observation, the child has remained in a good condition, free from HLH signs.

Patient 3 displayed an HLH picture at the age of 2 weeks. Because previously in his family an infant had died of FHL, the patient was quickly diagnosed with FHL3. Concomitantly, he revealed hypertrophic cardiomyopathy. He achieved remission of HLH and at the age of three months underwent HSCT. He died of cytomegaloviral disease in the early post-transplant course.

Patient 4 was a 5-year-old boy with APDS type 1, a kind of combined immunodeficiency with hyper IgM syndrome-like phenotype, diagnosed at the age of 4 years. Chronic Epstein-Bárr virus (EBV) infection was observed during the pre-transplant course. HSCT was performed and in the early post-transplant course the features of autoimmune hemolytic anemia (AIHA) were observed, although Coombs tests were negative. Atypical AIHA with negative antiglobulin tests was recognized regarding IgM/IgG switch impairment and the use of fludarabine and alemtuzumab in conditioning [8]. EBV detections in serum were repeatedly low. 3.5 months post-transplant, the boy developed HLH. A genetic background of lymphohistiocytosis was excluded (NGS screening). Prolonged neutropenia was complicated by *pseudomonas aeruginosa* sepsis with perianal inflammatory infiltration. The patient was treated with an HLH regimen together with intensive antimicrobial and supportive treatment. HLH features were alleviated after two months of HLH therapy, although the patient experienced graft insufficiency. A year after the transplant, he was given a CD34-cell-boost. In subsequent observation, he has had a normal graft function and has presented without any signs of HLH.

Discussion

The first objective in HLH is prompt recognition and efficient suppression of hyperinflammation, followed by HSCT if required. In the context of high post-transplant mortality in children with HLH, there is a need to distinguish more specifically between different forms of the disease, and it is recommended to have genetic tests included in pre-transplant analyses. It has been reported that HSCT treatment in genetically proven FHL results in a 71% 5-year overall survival (OS). However, HSCT in not-genetically verified disease has a 52% 5-year OS [3].

In the series of FHL3 cases we present here who underwent HSCT, two sibling children are alive and with satisfactory outcomes after transplant. Both were in a stable condition with hyperinflammatory signs partially settled when transplanted. Another brother of these siblings died of refractory HLH before the planned transplant. The third FHL case in our analysis, although diagnosed quickly due to a relevant family history, and with disease remission when transplanted, died of infectious complications and comorbidities.

It has been suggested that HLH should be distinguished considering its specific etiological associations, rather than focusing on the not always obvious distinction between primary and secondary forms. The subset of those with immune dysregulation as the core problem should be distinguished from those with HLH features but without underlying immune impairment. The latter group, referred to as HLH disease mimics, applies usually to infections or undiagnosed malignancies [9]. The specific diagnostic challenge is HLH occurring post HSCT.

The HLH diagnostic strategy is substantially based on the HLH-2004 guidelines [6]. In HLH occurring post HSCT, the clinical picture can overlap i.e. by a high baseline pre-HSCT ferritin due to transfusion iron overload, or high triglyceride levels attributed to total parenteral nutrition. In the post-transplant course, NK cells activity and sCD25 levels are usually found outside the normal ranges. In addition, other clinical conditions observed after transplant can mimic HLH, among them sepsis, engraftment syndrome, cytokine release syndrome, capillary leak syndrome, and thrombotic microangiopathy [10]. Nevertheless, HLH after allogeneic HSCT occurs in c.1% of cases, posing a high risk of a fatal outcome (c.80% in adult settings). It is frequently triggered by EBV and other herpes virus reactivations. There is a lack of uniform diagnostic criteria for HLH after HSCT. Commonly used parameters include persistent or aggravating fever in patients treated for infection, two or three lineage cytopenia, a high serum ferritin level

Table I. Clinical data of patients

Clinical data	Patient 1 — FHL3	Patient 2 — FHL3	Patient 3 — FHL3	Patient 4 — APDS, post-transplant HLH
Mutation	*UNC13D* gene: c.753+1G>T; biallelic	*UNC13D* gene: c.753+1G>T; biallelic	*UNC13D* gene: c.753+1G>T; biallelic	PIK3CD GOF: PIK3CD:3061G>A; NGS screening for pHLH-negative
Age at start of HLH	7 weeks	1 week	2 weeks	4 years 9 months (3.5 months after HSCT)
Clinical presentation* (cm inferior to costal margins in physical exam)	Fever, septic presentation, hepatomegaly (5 cm), splenomegaly (6 cm), generalized edema	Hepatomegaly (2 cm), splenomegaly (2 cm)	Fever, hepatomegaly (2 cm), splenomegaly (4 cm), hypertrophic cardiomyopathy	Fever, disseminated skin changes (non-itchy papuli), hepatomegaly (4 cm), splenomegaly (2 cm)
Hemoglobin [g/dL]/ /WBC/neutrophiles/ /platelets [/μL]*	7.7/950/0/1,000	16.9/7,500/ /730/24,000	9.4/4,700/610/ /19,000	7.4/690/300/35,000
ALT/AST* [U/L]	67/50	17/57	208/284	360/137
Triglycerides* [mmol/L]	3.77	1.78	2.18	4.09
Ferritin* [μg/L]	From 8,788 to >82,000	925	From 3,450 to >40,000	8,616
Fibrinogen* [g/L]	0.7	1.01	1.52	2.08
Hemophagocytosis	Phagocytes in bone marrow, bone marrow aplasia, phagocytes in CSF	Phagocytes in bone marrow, bone marrow aplasia	Phagocytes in bone marrow	Phagocytes in bone marrow, bone marrow dysplasia
Functional NK/CTL test	NK cytotoxic activity impaired, degranulation defective	nd	Cytotoxic activity impaired, degranulation defective	nd
sIL-2R/IFNγ	IFNγ in MNC supernatant 857 pg/mL (highly elevated)	sIL-2R — 6.907 U/mL	nd	sIL-2R — 3639 U/mL
HLH therapy	Dexamethasone, cyclosporin A, etoposide, intrathecal methotrexate	Dexamethasone, cyclosporin A, etoposide, intrathecal methotrexate	Dexamethasone, cyclosporin A, etoposide	Methylprednisolone, tacrolimus, mycophenolate mofetil, etoposide
HLH course/follow-up	2 weeks after discharge home: progressive HLH relapse, ARDS, mechanical ventilation, dialysis, cardiac insufficiency. Cured after 4-month-intensive care with HLH-2004 retreatment, then HSCT	HLH remission; febrile state with rhino/ /enteroviral infection, mucosal damage, anemia; when cured — HSCT	HLH stable partial remission, at that time HSCT	In course of HLH therapy: *Pseudomonas aeruginosa* perianal inflammatory infiltration; *P. aeruginosa* sepsis; HLH remission
Age at MUD-HSCT	12 months	4 months	3 months	4 years 6 months (3.5 months before HLH)
HSCT conditioning	Fludarabine, melphalan, alemtuzumab	Fludarabine, melphalan, alemtuzumab	Intravenous busulfan, fludarabine, alemtuzumab	Intravenous busulfan, fludarabine, alemtuzumab
Outcome	Alive 12 years after transplant; good condition, discrete mental retardation, carbamazepine-controlled epilepsy; donor chimerism — 38%	Post-transplant CMV reactivation; alive 7 months after transplant, in good condition, without other complications; donor chimerism — 82%	Died on 48th day after HSCT of MOF due to CMV disease and cardiac insufficiency	Graft insufficiency after HLH treatment; CD34 boost; alive 19 months after HLH, in good condition; donor chimerism — 93%

*At hemophagocytic lymphohistiocytosis (HLH) diagnosis; WBC — white blood cells; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CSF — cerebrospinal fluid; NK — natural killer; CTL — cytotoxic T-lymphocyte; nd — not done; sIL-2R — soluble interleukin 2 receptor; IFNγ — interferon γ; ARDS — acute respiratory distress syndrome; MUD-HSCT — matched unrelated donor hematopoietic stem cell transplantation; MOF — multiorgan failure; CMV — cytomegalovirus

(>10,000 µg/L has 90% sensitivity and 96% specificity for HLH), an elevated soluble interleukin 2 receptor concentration (although not validated in post-transplant HLH), high triglycerides, and low fibrinogen [11].

The presented patient with APDS developed a late form of post-HSCT HLH. As is typical in APDS, he had been affected with chronic EBV infection, although at the time of HLH diagnosis the EBV detection in his serum was low. APDS itself is attributable to HLH susceptibility, as PIK3CD GOF mutation is related to exhaustion and ineffectiveness of lymphocyte response due to persistent antigen presentation. HLH-like phenotype can occur as the first manifestation of APDS [12]. Chronically active EBV infections have been reported as a common feature in APDS and are responsible for triggering HLH [13]. In our patient, the influence of underlying recipient impairments over post-transplant immunity is unclear. Referring to EBV reactivation as an HLH trigger after HSCT, there is a report of a patient with DOCK2 deficiency in whom HLH was diagnosed three months after HSCT with underlying EBV reactivation and with a rapidly progressive course and fatal outcome [14].

According to the literature, the most strongly determining factor of post-HSCT HLH outcome is the effective resolution of the inflammatory process with HLH treatment, regardless of the underlying disease. In a multicenter analysis published in 2012, 69% of children with early onset post-transplant HLH achieved remission after standard therapy. Overall survival in this group was 59%, but was only 14% in those who did not respond [5].

Conclusions

The results of HLH treatment in the case series described in this paper seem to parallel those with a 60–70% general survival rate presented elsewhere. In our group of four patients, we lost one child, even though he had been promptly diagnosed and intensively treated. The current results of standard immunosuppression and chemotherapy of HLH, particularly in its post-HSCT form, are not satisfactory. In this context, the increasingly common use of specific targeted cytokine blockade agents, with the most published evidence regarding JAK1 and JAK2 protein kinases inhibitor, interleukin 6 inhibiting monoclonal antibody, anti-interferon gamma antibody and PI3K inhibitors, carries with it hope of improving outcomes in this disease [10, 13, 15].

Authors' contributions

AKK, JG — study design. AKK — collection and analysis of data, manuscript writing. All authors — revision of manuscript, final approval.

Conflict of interest

The authors declare no conflict of interest.

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None.

Ethics

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

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