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CASE REPORT

# Successful treatment of recurrent malignancy-associated hemophagocytic lymphohistiocytosis with a modified HLH-94 immunochemotherapy and allogeneic stem cell transplantation

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**Abstract** Acquired hemophagocytic lymphohistiocytosis (HLH) triggered by a known or still to be recognized malignancy is a life-threatening hyperinflammatory syndrome due to massive cytokine release from activated lymphocytes and macrophages. Malignancy-associated HLH (M-HLH) often impedes adequate treatment of malignancy and has the worst outcome compared with any other form of HLH. The incidence of M-HLH is unknown, and there are no published treatment recommendations addressed to this HLH form. Here, we report the case of a young woman with recurrent ALK1-positive anaplastic large T-cell lymphoma and M-HLH successfully treated with a modified HLH-94 protocol, allogeneic stem cell transplantation (alloSCT) and donor lymphocyte infusion (DLI). More than 3 years after DLI, the patient is alive, in complete remission from her malignancy and HLH-free, although suffering from extensive chronic graft-versus-host disease. AlloSCT and, if needed, DLI performed to consolidate remission of malignancy and HLH may have a curative impact on both entities. We propose that when discussing possible treatment options for patients with M-HLH, alloSCT should be considered in eligible individuals.

**Keywords** Hemophagocytic lymphohistiocytosis · Hemophagocytic syndrome · Malignancy-associated · Malignancy · Lymphoma · Allogeneic · Stem cell transplantation

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## Introduction

Hemophagocytic lymphohistiocytosis (HLH), also called hemophagocytic syndrome, is a rare and critical immunohematologic condition caused by massive cytokine release from activated lymphocytes and macrophages [1, 2]. This multisystem inflammatory syndrome is potentially life-threatening and can be caused by a range of inherited or acquired factors. HLH is characterized by fever, cytopenia, hepatosplenomegaly, hyperferritinemia, jaundice, edema, disseminated intravascular coagulopathy, neurological symptoms, and hemophagocytosis in bone marrow (BM), liver, or lymph nodes [1–5]. The uncontrolled activation of immune cells is probably due to an immune response triggered by different stimulants (infectious organisms, tissue damage, metabolic products, etc.), and the underlying inherited (e.g., mutations in genes *PFR1*, *UNC13D*, *STX11*, *MUNC18-2*) or acquired (cytotoxic therapy, transplantation, malignancy) immune defect [3–5]. Macrophages and CD8+ cytotoxic lymphocytes release various pro-inflammatory mediators (TNF-$\alpha$, INF-$\gamma$, IL-6, IL-8, IL-10, IL-12, IL-18, MIP 1-$\alpha$) and hematopoietic growth factors [3–6]. Low or absent NK-cell function is often present and results in difficulties in termination of the exaggerated immune response [3–5].

The diagnosis of HLH is based on the criteria proposed by the HLH Study Group of the Histiocyte Society in 1991 and later updated in 2004 [7, 8]. According to the current guidelines (HLH-2004), five of the following eight criteria must be fulfilled for the diagnosis of HLH: (1) fever, (2) splenomegaly, (3) cytopenia affecting two or three lineages

(Hb <90 g/l; PLT <100 × $10^9$/l; neutrophils <1.0 × $10^9$/l), (4) hypofibrinogenemia (<1.5 g/l) and/or fasting hypertriglyceridemia (>3.0 mmol/l), (5) hemophagocytosis in BM, spleen, or lymph nodes, (6) hyperferritinemia (>500 μg/l), (7) low or absent NK-cell activity, (8) elevated level of sIL-2r also named sCD25 (>2,400 U/ml) [8].

HLH is divided into two distinct forms: an inherited, familial form (FHL) and an acquired, secondary form (sHLH) [1–5, 8]. The familial form of HLH was first described in two siblings by Farquhar and Claireaux in 1952 [9]. FHL has an autosomal recessive inheritance pattern and usually arises in infants (80% cases), but it can also occur in adults [1, 3–5, 10, 11]. Allogeneic stem cell transplantation (alloSCT) has an established role in FHL therapy as the only available treatment option with a curative potential [12]. The HLH-94 protocol, including etoposide and dexamethasone (DXM), or its updated form, the HLH-2004 protocol, including etoposide, DXM, and cyclosporine A (CyA), serves as induction remission therapy in FHL [7, 8].

The first report on sHLH is probably a paper by Tschistowitsch and Bykova published in 1928 [13]. In 1939, Scott and Robb-Smith reported four similar cases of adults with an HLH-like picture and proposed to term this condition histiocytic medullary reticulosis [14]. Acquired HLH can develop at any age as a result of intensive immunological activation due to infections, autoimmune inflammatory disorders, or malignancies [2, 4, 5, 15, 16]. Malignancy-associated HLH (M-HLH) can occur before or during the treatment of known malignancy, or as the first manifestation of an as yet unrecognized malignancy [2, 4, 5]. Several hematological malignancies (e.g., lymphomas) and solid cancers (e.g., thymoma, carcinoma, and germ cell tumor) have been associated with sHLH [2, 4, 16–24]. Patients with M-HLH are often refractory to FHL-like therapy, and there are virtually no published treatment recommendations addressed to this group of patients. So far, alloSCT has only been anecdotally performed in patients with sHLH [16, 25, 26].

Here, we report the case of a young woman with recurrent ALK1-positive anaplastic large T-cell lymphoma (ALTL) and M-HLH successfully treated by means of modified HLH-94 immunochemotherapy, alloSCT, and donor lymphocyte infusion (DLI).

## Case presentation

A 22-year-old Caucasian woman was admitted with a 6-week history of fever, exhaustion, night sweats, and diffuse abdominal pain. The patient had previously been healthy and family history was not contributory. Neither hepatosplenomegaly nor lymphadenopathy was detected on physical examination, but computed tomography (CT) imaging revealed abdominal lymphadenopathy (enlarged periaortal and pericaval lymph nodes up to 25 mm) and a slightly enlarged spleen (14 × 13 × 5 cm). Whole blood analysis showed a hemoglobin (Hb) concentration of 105 g/l, a white blood cell (WBC) count of 38.6 × $10^9$/l with the presence of immature lymphocytes, and a platelet (PLT) count of 150 × $10^9$/l. Immunohistological examination of the abdominal lymph node and fluorescence-activated cell sorting revealed ALK1-positive ALTL. Bone marrow examination disclosed that 30% of the cells were positive for ALK1 in fluorescence in situ hybridization, and BM cytogenetics showed a normal female karyotype (XX,46). Within a few days, the patient's WBC count rapidly increased to 130 × $10^9$/l and CHOEP-14 chemotherapy (consisting of cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone given every other week) with G-CSF support was initiated.

### M-HLH presentation, diagnosis, and initial outcome

After three cycles of CHOEP-14, the patient developed skin nodules showing involvement of ALTL, and shortly afterward her general status deteriorated, with the development of neurological symptoms (confusion, distraction, alternating euphoria and aggression, peripheral sensory and motor neuropathy in the lower extremities). Brain CT and magnetic resonance imaging (MRI) of the brain showed normal results. Lumbar puncture was performed, but analysis of cerebrospinal fluid (CSF) showed normal values, with no signs of ALTL involvement, pleocytosis, or elevated concentrations of CSF proteins. Abdominal CT disclosed progress of lymphadenopathy, and 3 days later the patient had a high fever (40.5°C). Blood cultures failed to reveal any bacteria or fungi, and whole blood Epstein–Barr virus (EBV) DNA and cytomegalovirus (CMV) DNA examined by means of real-time quantitative polymerase chain reactions showed negative results. The patient experienced rapid progression of hepatosplenomegaly, ascites, worsening of liver function, and pancytopenia. Serum ferritin concentrations promptly rose: 4,000–7,000–9,200 μg/l (normal range 20–300 μg/l). M-HLH was suspected and BM examination showed 3% lymphoma cells and an increased number of monocytes, with some activated macrophages and hemophagocytosis (Fig. 1). Six of eight diagnostic criteria of HLH proposed by the HLH study Group of the Histiocyte Society were fulfilled, but two further criteria were not determined (Table 1). Although treatment with intravenous immunoglobulin and corticosteroids was started, the patient developed hypoalbuminemia, fluid retention (10 kg), and cardiac failure with ejection fraction reduced to 20% and an elevated level of N-terminal pro-B-type natriuretic

peptide of >3,000 ng/l (age-adjusted normal values <150 ng/l). Because ALTL was believed to be a trigger of the patient's M-HLH, she received salvage chemotherapy with high-dose methotrexate (MTX; 1 g/m$^2$ × I) and high-dose cytosine arabinoside (Ara-C; 3 g/m$^2$ every 12 h × IV) (HD-MTX/HD-Ara-C). Afterward the patient developed acute respiratory failure, and she was admitted to the intensive care unit (ICU) and initially put on CPAP (continuous positive airway pressure), but 24 h later she required ventilator treatment. Her condition gradually improved, and after 8 days she was discharged from the ICU. One month later, the patient received a second course of HD-MTX/HD-Ara-C.

## HLH-94 therapy and consolidating treatment with alloSCT

One month later (6 months after ALTL diagnosis), the patient's general condition worsened and a new fever and skin involvement associated with ALTL were noted. Another CT examination disclosed pleural effusion, mediastinal infiltration, and multiple pathological mediastinal, cervical, and axillary lymph nodes. The treatment strategy was changed to modified HLH-94 chemotherapy with etoposide, a total of 13 doses over 15 weeks, 240–255 mg/dose i.v. (approximately 150 mg etoposide/m$^2$/dose, cumulative etoposide dose 3,180 mg) and high-dose corticosteroids. The patient's general status gradually improved, and after 2 months of HLH-94 therapy, she achieved remission of HLH and complete remission (CR) of ALTL (lymphadenopathy had resolved and spleen size had normalized). The patient qualified to receive consolidating therapy by means of alloSCT, using her HLA-identical brother as a donor. Pre-transplantation workup was initiated after the patient's initial response and continued under ongoing HLH therapy. Directly after cessation of HLH-94 treatment, she underwent myeloablative conditioning (cyclophosphamide 120 mg/kg plus fractionated total body irradiation 12 Gy) and allogeneic peripheral stem cell transplantation (6.2 × 10$^6$ CD34+ cells/kg of recipient body weight) 9 months after her ALTL diagnosis and 5 months after M-HLH diagnosis. Blood analyses before the start of conditioning showed Hb at 114 g/l, WBC count of 2.8 × 10$^9$/l, and PLT count of 109 × 10$^9$/l. Graft-versus-host disease (GVHD) prophylaxis consisted of standard MTX and CyA therapy. The post-transplantation period was complicated by grade 3 mucositis, *Enterococcus* sepsis, and diarrhea of unknown origin (*Clostridium*-negative, colonoscopy with negative biopsy results for both GVHD and CMV). Neutrophil engraftment was obtained on day +15 and platelet engraftment was achieved on day +14, respectively. The patient was discharged from hospital on day +39. Two months after alloSCT, she developed CMV infection, which was treated successfully with valganciclovir. Six months after alloSCT, the patient developed de novo chronic GVHD (cGVHD) in the mouth, liver, and stomach and started a corticosteroid course.

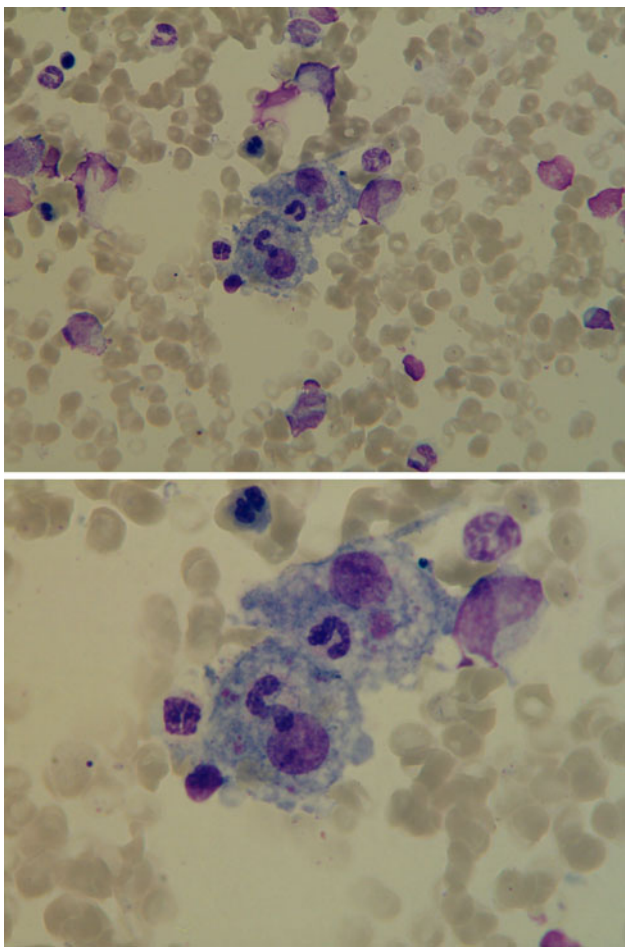

**Fig. 1** May–Grünwald–Giemsa stain of bone marrow aspirate smears (×1,000). The *centrally* placed macrophage shows hemophagocytosis of erythrocytes and myeloid cells. *Lower* and *higher* magnification (×400 and ×1,000, respectively)

## ALTL and M-HLH relapse and its treatment

One month later (16 months after ALTL diagnosis and 7 months after alloSCT), abdominal discomfort resembling menstrual pain, new skin nodules, and swelling of the left lower extremity appeared. Thoracic CT was normal, though abdominal CT disclosed pathological lymphoma infiltration (4 × 3 × 5 cm) pressing toward the left iliac vein. Biopsies showed ALTL relapse in lymph nodes and skin nodules, and hemophagocytosis in BM and skin. A course of palliative chemotherapy (etoposide 150 mg i.v. day 1–2; vinblastine 10 mg i.v. day 1), as initially intended, and oral corticosteroids given 4 times over a 2-month

**Table 1** Laboratory data at diagnosis of hemophagocytic lymphohistiocytosis

| Variable (units[a]) | Diagnostic criteria of HLH | Patient's results | Reference range[a] |
|---|---|---|---|
| Fever | Present | Present | Absent |
| Splenomegaly | Present | Present | Absent |
| Hemoglobin (g/l) | <90 | 81 | 117–153 |
| Neutrophils ($\times 10^9$/l) | <1.0 | 1.6 | 1.7–7.5 |
| Platelets ($\times 10^9$/l) | <100 | 17 | 165–387 |
| Triglycerides (mmol/l) | >3.0 | 3.9 | 0.5–2.6 |
| Fibrinogen (g/l) | <1.5 | 1.0 | 2.0–4.3 |
| Highest serum ferritin (μg/l) | >500 | 32.200 | 20–300 |
| Soluble CD25 (sIL-2) receptor (U/ml) | >2,400 | ND | 321–565 |
| Hemophagocytosis in biopsy | Present | Present | Absent |
| NK-cell activity | Low or absent | ND | Normal |
| CNS involvement | | Present | |
| Triggering infection | | Absent | |

*ND* not determined

[a] Where applicable

period led to remission of both M-HLH and ALTL, and one donor lymphocyte infusion of $10 \times 10^6$ CD3+ cells/kg of recipient body weight was given to consolidate therapy. After DLI, the patient developed acute GVHD (aGVHD) in the skin (generalized rash), and later extensive cGVHD in the skin, mouth, liver, and muscles. Treatment of cGVHD included local and oral corticosteroids, CyA, PUVA, and rehabilitation.

More than 3 years after DLI, the patient is alive, in CR from her malignancy and HLH-free, but suffering from extensive cGVHD. She still uses low-dose steroid therapy (10–15 mg prednisolone) but suffers from muscle and joint pain, gait difficulties, and sclerodermic skin (Fig. 2).

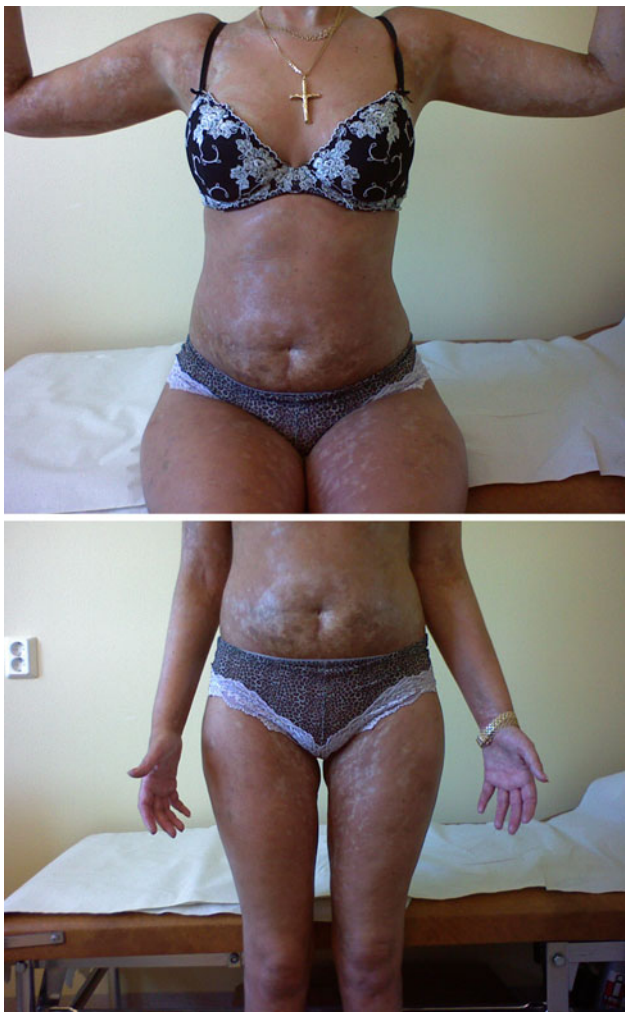

**Fig. 2** Chronic graft-versus-host disease with the development of sclerodermic skin after donor lymphocyte infusion

## Discussion

According to the results of a retrospective Japanese nationwide survey, M-HLH was the second most frequent form of HLH (after infection-associated HLH, the most frequent being EBV-associated HLH) diagnosed between 2001 and 2005 in all age-groups in Japan [19]. Although the same study revealed that malignant lymphomas were responsible for the majority of M-HLH cases, 24 out of 132 (18%) patients suffered from M-HLH caused by malignancies other than lymphoma, including 9 patients with acute myeloid leukemia and three patients with myelodysplastic syndromes.

Malignancy-associated HLH has the worst outcome in comparison with any other form of HLH [19–24]. The reported 5-year overall survival rate in the study by Ishii et al. [19] was highest in connection with infection-associated or autoimmune-associated HLH (83–90%),

intermediate in FHL (54%) and B-cell lymphoma-associated HLH (48%), and lowest in T/NK-cell lymphoma-associated HLH (12%). Tong et al. [22] published data in 2008 concerning the outcome of 28 patients suffering from aggressive T-NHL, presenting at diagnosis with concomitant HLH. All 28 patients died; 89% (25/28) died within 6 months of diagnosis, 7% (2/28) died 6–12 months after diagnosis, and one patient died 22 months after diagnosis of T-NHL and HLH. The median survival time was only 40 days (range 16 days to 22 months) for the entire group.

Although in some patients with M-HLH poor outcome depends on malignancy progression, in some patients the lack of effective M-HLH therapy may further impede adequate treatment of malignancy. Treatment of M-HLH is not standardized, and based on anecdote. Unless a more effective therapy is available, the HLH-94 or HLH-2004 protocol should serve as a basis for the treatment of M-HLH [7, 8]. However, adults with M-HLH are often refractory to FHL-like therapy, and a strategy for the management of M-HLH patients who fail to respond to the HLH-94 or HLH-2004 protocols needs to be developed [21, 24]. A better understanding of the pathogenesis of M-HLH will help plan more prompt and accurate treatment.

The first successful bone marrow transplant in a case of HLH was reported in 1986 [27]. Since then, information regarding the role of alloSCT in the treatment of HLH has mostly concerned FHL. Immunochemotherapy (e.g., HLH-94 and HLH-2004 protocols) is only temporarily effective in the control of FHL, and the outcome is uniformly fatal unless the patient undergoes alloSCT [8, 12]. In cases of FHL, different groups of investigators have reported 5-year overall survival rate of 50–70% with myeloablative conditioning [28–34], and 75–92% with reduced-intensity conditioning [35, 36]. Nevertheless, early treatment-related mortality (TRM) occurring within the first 100 days following alloSCT remains the major obstacle to the cure of FHL by alloSCT [28, 32–34]. Infections, veno-occlusive disease (VOD), pneumonitis, graft failure, and GVHD have been reported as the main causes of early TRM [28–36]. In some patients, TRM may depend on unsatisfactory control of HLH before alloSCT. Therefore, every reasonable effort must be made to ensure that these patients proceed to alloSCT with optimal control of their underlying FHL [12]. In particular, systemic and central nervous system manifestations of HLH should be carefully monitored and treated while preparing for alloSCT. On the other hand, significant excess mortality has also been seen in patients with apparently good control of their underlying FHL [12]. It is possible that occult liver or lung damage from HLH may predispose these patients to high rates of VOD or pneumonitis when treated with a busulfan-based conditioning regimen. Additionally, a significant number of deaths within the first 100 days after alloSCT are attributed to HLH reactivation [37]. In contrast, patients who survive beyond day +100 with durable engraftment usually experience long-term survival free of HLH [25, 34].

So far, alloSCT has been performed only occasionally in cases of acquired HLH, and its role in the treatment of sHLH is not yet established. Sporadic case reports have previously been published on refractory EBV-HLH successfully treated by means of alloSCT [38–40]. A recent Japanese survey revealed a curative effect of alloSCT on sHLH in 7 out of 11 patients (64%) with refractory EBV-HLH [25]. Similarly, Yoon et al. [26] reported in 2010 that alloSCT could be a curative treatment not only for FHL, but also for relapsed/refractory sHLH. Anecdotal reports, including the present one, have shown the efficacy of alloSCT in M-HLH therapy [41–43]. The role of DLI in M-HLH therapy is even less well known.

We report here what is to our knowledge the first published case of recurrent M-HLH (associated with lymphoma) successfully treated by means of alloSCT and DLI. This case confirms that alloSCT and, if needed, DLI may have a curative impact on both malignancy and M-HLH. Therefore, we think that when discussing possible treatment options for M-HLH, alloSCT should be considered in eligible patients. Nevertheless, to determine the optimal donor source and conditioning regimen before alloSCT for patients with M-HLH, prospective multicenter trials need to be conducted to evaluate new approaches for this rare condition. The best results following myeloablative conditioning for FHL have been achieved when HLA-matched related or unrelated donors have been used, and CNS disease has been absent or quiescent at the time of hematopoietic cell transplantation [12]. This should be taken into account in M-HLH patients proceeding to alloSCT. Another possible concern in the choice of donor source may be the high incidence of hemophagocytic syndrome following umbilical cord blood transplantation in adults, recently reported by Takagi et al. [44]. Last but not least, because patients with M-HLH represent a unique alloSCT population, with high morbidity/mortality and disease-specific complications, consideration should be given to referring these patients to centers with significant experience in the treatment and care of those with HLH.

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**Conflict of interest** The authors report no conflict of interest.

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