

Hemophagocytic Lymphohistiocytosis Due to Acute Myeloid Leukemia Relapse: A Very Unusual Association

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) diagnosed in the course of acute myeloid leukemia (AML) is generally triggered by treatment-induced infections. AML-induced HLH is a very rare situation for which no diagnostic or therapeutic guidelines are available. We report the occurrence of HLH in an AML5 post-transplant relapse. In our case, the absence of detectable pathogen and the parallel evolution between HLH and leukemia burden suggested a direct link between AML and HLH. We suggest that the diagnostic of AML-related HLH should be promptly considered in front of unexplained fever, cytopenia, liver dysfunction or neurological symptoms as therapeutic intervention is urgent in this life-threatening situation.

Keywords: AML; HLH

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and frequently fatal disease. Primary HLH are familial disorders due to a range of genetic mutations affecting perforin genes. Secondary HLH occur in the course of infections or malignancies, particularly in lymphoma patients including T-cell, NK-cell, diffuse large B-cell lymphoma and Hodgkin lymphoma. However, leukemia represents only 6% of cancer-related HLH [1]. In acute leukemia patients, HLH is triggered in most cases by infection due to bacterial, viral or fungal pathogens [2]. We report here a case of HLH due to acute myeloid leukemia (AML) relapse.

Case Report

A 65-year-old male patient was diagnosed with normal karyotype AML (AML5 FAB subtype) with unfavorable genotype including FLT3-ITD and DNMT3A R882H mutations and absence of NPM1 mutation. He underwent matched-unrelated donor reduced-intensity allogeneic stem-cell transplantation (SCT) in first complete remission after induction by cytarabine and daunorubicine. Strikingly, no clinical or biological symptom of HLH was detected at diagnosis or during the course of allogeneic transplant. While he had a poor hematologic reconstitution after SCT resulting in a chronic pancytopenia, his general condition gradually improved. However, bone marrow failure suddenly worsened 5 months after SCT. Few days later he was admitted for jaundice and abnormal liver enzyme levels including AST 342 U/l (normal range 10-45 U/l), ALT 736 U/l (normal range 10-45 U/l), GGT 377U/l (normal range 7-55 U/l), APL 315U/l (normal

range 35-120 UI/l), and total bilirubin 66.3 $\mu\text{mol/l}$ (3-17 $\mu\text{mol/l}$). The complete blood count was: leukocyte count $0.21 \times 10^9/\text{l}$, hemoglobin 76g/l, platelet count $17 \times 10^9/\text{l}$. HLH was suspected due to hypertriglyceridemia at 3.24 mmol/l and hyperferritinemia at 60 194 $\mu\text{g/l}$. Bone marrow biopsy revealed AML relapse as shown by the presence of 30% blast cells and also features of hemophagocytosis (Figure 1). Based on HLH-2004 criteria [3] he was diagnosed with HLH and immediately treated with etoposide 75 mg/m² during two consecutive days and all HLH clinical and biological symptoms resolved within 72 h. Extensive search for pathogens was negative and included total-body CT/scan, blood cultures, and serum antibodies for HIV, hepatitis A, B, C and E, aspergillus, and PCR for CMV, EBV, HHV6 and HHV8. After clinical improvement, AML therapy started with cytarabine 3000 mg/m² every 12 h at days 1, 3 and 5. Bone marrow examination performed 30 days after salvage therapy showed hypocellularity and 4% blast cells without HLH features (data not shown). Forty days after high-dose cytarabine, he had seizures and electroencephalography-proven encephalitis. At this point, ferritin level was 10 000 $\mu\text{g/l}$ and bone marrow biopsy showed 20% blast cells along with hemophagocytosis. A new search for infectious agents was negative including in the cerebrospinal fluid. Brain MRI did not reveal significant abnormalities. However, he received 1000 mg of intravenous acyclovir three times a day to cover for potential HSV or VZV infection. In the absence of clinical improvement after one week, he received intrathecal methotrexate assuming that his neurological manifestations might have been due to HLH with a limited efficacy. Then he successively received etoposide, sorafenib and gemtuzumab ozogamicin without improvement of encephalopathy or pancytopenia and he unfortunately died from intracranial bleeding in a context of refractory thrombocytopenia.

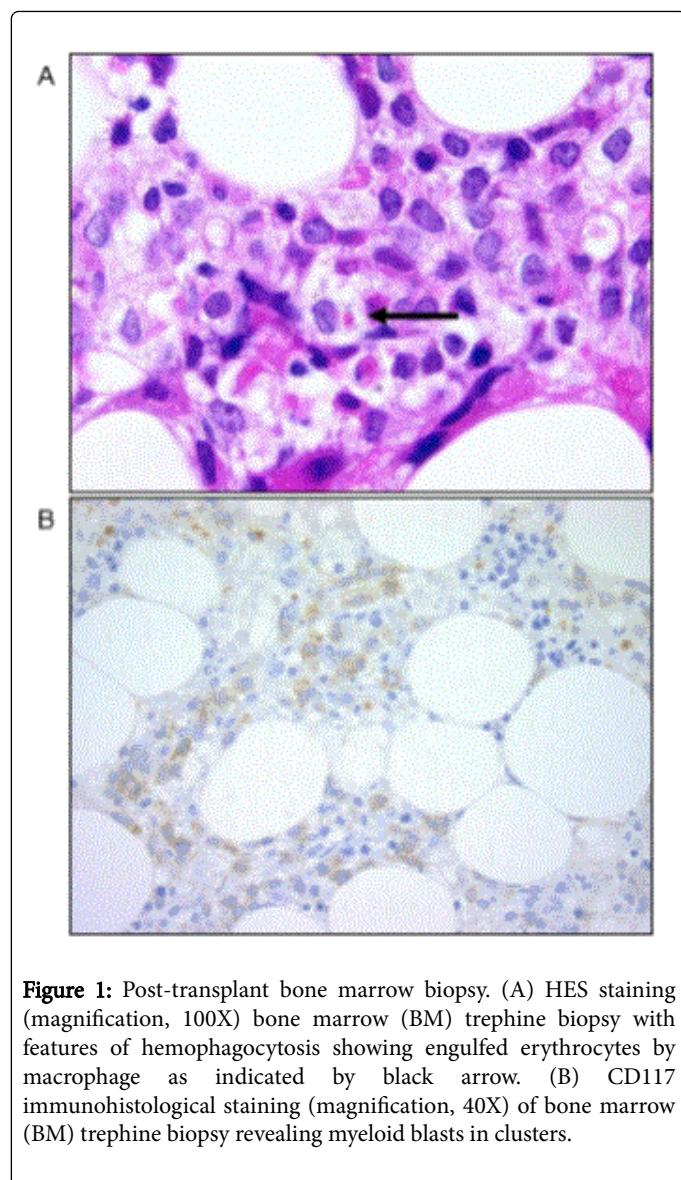


Figure 1: Post-transplant bone marrow biopsy. (A) HES staining (magnification, 100X) bone marrow (BM) trephine biopsy with features of hemophagocytosis showing engulfed erythrocytes by macrophage as indicated by black arrow. (B) CD117 immunohistological staining (magnification, 40X) of bone marrow (BM) trephine biopsy revealing myeloid blasts in clusters.

Discussion and Conclusion

In AML, Delavigne et al. reported that HLH may be detected in up to 10% of patients during induction therapy but in virtually all cases HLH was due to therapy-related infection and resolved with adapted antimicrobial therapy [2]. However, HLH is seldom reported in direct association with AML blast cells, in contrast to other malignancies such as non-Hodgkin lymphoma [4]. Among the limited number of AML-associated HLH cases reported, the presence of a monocytic component (AML4 and AML5 subtypes of the FAB classification) may represent a predisposing condition. Indeed, Hatano et al. reported an increased phagocytic functions of the leukemic cells thereby directly responsible for HLH [4]. While blast cells from our patient arose from the myelomonocytic lineage (AML5 subtype, Table 1), we did not find evidence that blast cells were directly involved in hematopoietic cell phagocytosis (Figure 1A). Some cytogenetic abnormalities involving 8p11 and 16p13 seem more frequent in AML-associated HLH [4] but our patient leukemic cells had a normal karyotype. Finally, Jekarl et al. found a positive correlation between CD56

expression and hemophagocytosis features of the leukemic blast cells [5]. In our case, leukemic cells were CD56 negative in agreement with the fact that HLH was not directly due to the leukemic burden in our patient. To our best knowledge, we report here the first case of HLH occurring in a context of relapsing AML. When focusing on AML-associated HLH without evidence for concurrent infection, we found only several reports and in those cases HLH mainly occurred at the time of initial diagnosis (Table 2). Interestingly in our patient, we were able to directly link HLH to the presence of AML blast cells as both diseases displayed a parallel evolution (Figure 2). We hypothesized that changes in blast cell functions may have occurred between AML diagnosis and relapse and accounted for induction of hemophagocytosis by AML blast cells. Interestingly, our patient developed encephalopathy and seizure. While we could not exclude that an undetected pathogen might have contributed to the symptoms, we hypothesized that HLH may have involved the central nervous system (CNS). Neurological symptoms of HLH are mostly described in genetic HLH but Gratton et al. recently observed neurological manifestations of acquired HLH in 7 patients with encephalopathy and seizures as the most frequent clinical manifestations of the disease [6]. While we could not provide definitive conclusions regarding CNS involvement by HLH in our case, we suggest considering neurological symptoms as possibly related to HLH in this situation and to use therapies with broad CNS diffusion as well as intrathecal chemotherapy. Due to the rarity of this condition, no guidelines are available for the treatment of AML-related HLH. HLH-2004 guidelines propose extensive search and treatment of concurrent infection that may also trigger HLH but the choice of a chemotherapy regimen has to be done on case-by-case basis. In our case, we used etoposide first as we anticipated that this drug may induce a rapid control of HLH-related biological abnormalities that precluded the use of cytarabine or gemtuzumab ozogamicin. Our current case illustrates the rarity but also the severity of AML-related HLH, particularly in a context of relapsing disease. Rapid diagnosis and personalized management may help to improve the prognostic of this critical situation.

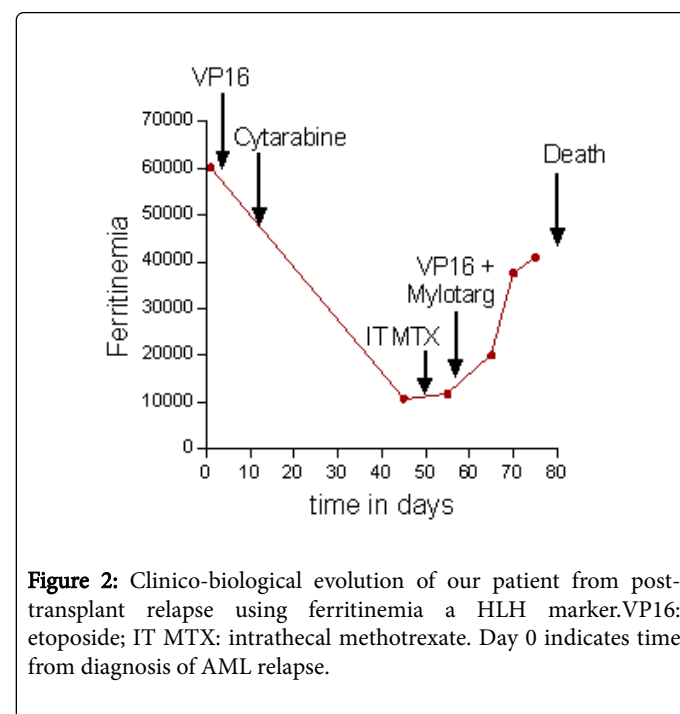


Figure 2: Clinico-biological evolution of our patient from post-transplant relapse using ferritinemia a HLH marker. VP16: etoposide; IT MTX: intrathecal methotrexate. Day 0 indicates time from diagnosis of AML relapse.

	Immunophenotype
Myeloid markers	CD34- CD38+ CD123+ CD117+ HLA-DRlow CD13+ CD33+ MPO+
Monocytic markers	CD4 (75%) CD11b (35%) CD36 (30%) CD64 (20%)

Table 1: Immunophenotype of the blast cell population

N	Year	Comments	References
1	2000	Child with t(4;7)(q21;q36)	Kumar M, et al. [7]
1	2006	Child with t(7:17) and deletions in chromosomes 7, 17, and 5	Tadmor T, et al. [8]
1	2007	Child with inv(8) (p11q13) and MOZ-TIF2 fusion transcript	Abdelhaleem M, et al. [9]
1	2009	Adult with pure erythroidleukemia	Kitigawa J, et al. [10]
1	2010	Adult with Initial isolated HLH. Concurrent normal karyotype AML at HLH relapse.	Wang L, et al. [11]
1	2010	Adult with normal karyotype AML with HLH occurring during AML on-therapy progression successfully treated with decitabine.	Sudhanshu M, et al. [12]
1	2015	Adult with direct phagocytosis by normal karyotype AML monocytic blast cells	Hatano K, et al. [4]

Table 2: Reported cases of AML-related HLH

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