Leukemia Research Reports 9 (2018) 5–8

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

# Alemtuzumab-based therapy for Secondary Malignant Histiocytosis arising from Pre-B-ALL

Muhammad Bilal Abid[a,b,*], Karan Wadera[a], Jenny M. Bird[a], Joya Pawade[c], David I. Marks[a]

[a] Division of Hematology & Bone Marrow Transplantation, University Hospitals of Bristol NHS Foundation Trust, Bristol, United Kingdom
[b] Division of Internal Medicine, Medical College of Wisconsin (MCW), Milwaukee, WI, USA
[c] Division of Pathology, University Hospitals of Bristol NHS Foundation Trust, Bristol, United Kingdom

ARTICLE INFO

*Keywords:*
Secondary Malignant Histiocytosis (SMH)
Pre-B-Cell Acute Lymphoblastic Leukemia (Pre-B-ALL)
Transdifferentiation
C/EBPα
PAX5

*Clinical Practice Points:*

- Secondary Malignant Histiocytosis (SMH) is an exceedingly rare, life-threatening condition that invariably occurs in the presence of an underlying monoclonal hematologic disorder. Prognosis of SMH remains dismal and there is no established treatment.
- We report a case of a patient who developed SMH during induction chemotherapy for his underlying pre-B-ALL, that caused persistently high fevers and was only diagnosed by a marrow while cytopenic in phase 2 induction. He was treated with alemtuzumab-based therapy that reduced the histiocytic infiltration of the bone marrow from 80% to 15% and made him eligible to undergo T-cell replete allogeneic stem transplantation from his sibling.
- This report is the first to highlight the role of alemtuzumab, an anti-CD52 monoclonal antibody, in clonal disorders originating from transdifferentiation.
- The alemtuzumab-based regimen should be reserved only for carefully selected allogeneic transplant patients.

## 1. Introduction

Secondary Malignant Histiocytosis (SMH) is a distinct entity and forms part of a spectrum of disorders of the monocyte-phagocytic lineage, categorised into five main groups in the current WHO classification. It includes conditions such as Langerhans Cell Histiocytosis (LCH), Hemophagocytic Lymphohistiocytosis (HLH), Rosai-Dorfman disease, cutaneous and mucocutaneous manifestations of these disorders and primary and secondary malignant histiocytosis [1–3]. It can occur either as a sporadic illness or secondary to clonally-related hematological malignancies. Pathogenesis of SMH remains unclear but it is derived from cells of the Macrophage/Dendritic Cell (DC) system and is most commonly associated with Acute Lymphoblastic Leukemia (ALL) and Follicular Lymphomas, as well as myeloid disorders like Chronic Myelomonocytic Leukemia (CMML) and Acute Myeloid Leukemia (AML). SMH is diagnosed based on anaplastic morphology, expression of macrophage and DC markers, a definite temporal and a probable clonal relationship with the primary hematologic neoplasm [1]. The marked hyperferritinemia, triglyceridemia and hemophagocytosis in the bone marrow, typical of HLH, are generally not seen in SMH.

## 2. Case report

A 40-year-old male, with no past medical history of significance other than smoking, attended the general practitioner's clinic with three weeks' history of feeling generally unwell and one-week history of night sweats. At presentation, the patient did not manifest any signs or symptoms of marrow failure. He also did not have pallor, jaundice, lymphadenopathy, or hepatosplenomegaly. Initial full blood count (FBC) showed a hemoglobin of 14.4 g/dL, platelets of 59 × $10^9$/L, white cell count of 38.8 × $10^9$/L and neutrophils of 4.11 × $10^9$/L.

* Correspondence to: Division of Internal Medicine, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226, USA.
*E-mail addresses:* bilal_abid@hotmail.com, mabid@mcw.edu (M.B. Abid).

https://doi.org/10.1016/j.lrr.2017.11.003
Received 20 May 2017; Received in revised form 30 September 2017; Accepted 26 November 2017
Available online 05 December 2017

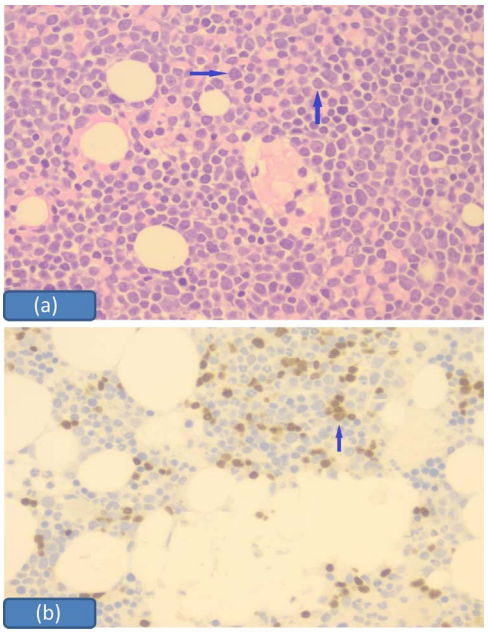


**Fig. 1.** (a): Bone Marrow Aspirate (H&E X 100) shows the presence of lymphoblasts (arrows), consistent with ALL. (b): Bone Marrow Trephine (H&E X 100) shows the persistence of lymphoblasts, highlighted with TDT staining (arrow), post-induction chemotherapy

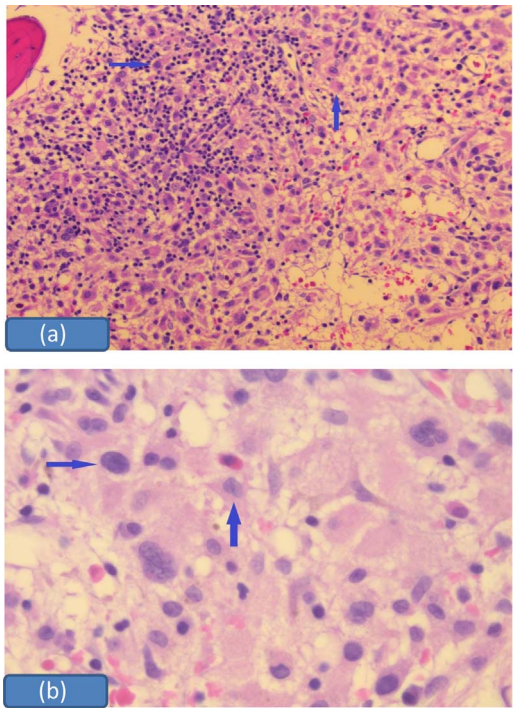


**Fig. 2.** (a & b): Bone Marrow Trephine shows pleomorphic histiocytes (arrows), consistent with Secondary Malignant Histiocytosis

Liver function tests, lactate dehydrogenase (LDH), creatinine, electrolytes and coagulation screen were normal. A peripheral blood film revealed lymphoblasts.

Bone marrow aspirate and trephine showed a hypercellular marrow with decreased tri-lineage hematopoiesis and 90% blasts [Fig. 1(a)]. Flow cytometry confirmed Pre-B-Cell Acute Lymphoblastic Leukemia (Pre-B-ALL) and karyotyping met the criteria for complex cytogenetics [4]. Molecular analyses were negative for a bcr-abl1 transcript (both p190 and p210 variants).

The patient was enrolled in the UKALL14 trial (09/H0711/90) in May 2016 and was randomized to receive 4 doses of rituximab in phase-1 induction. Bone marrow assessment after phase-1 of 4-drug induction chemotherapy revealed the persistence of 13% blasts by flow cytometry and 15% on trephine [Fig. 1(b)]. As per protocol, it was decided that he should continue with phase-2 of induction therapy (cyclophosphamide, cytosine arabinoside and 6-mercaptopurine). He then developed persistently high fevers and was treated with broad-spectrum antibiotics for neutropenic fever. Anti-viral and anti-fungal prophylaxis was continued during this time. Microbiological investigations for viral, fungal and bacterial pathogens were repeatedly negative. Imaging studies including a CT and PET scans did not show lymphadenopathy, hepatosplenomegaly, or other organ involvement. In view of his persistent fever, a mid-cycle bone marrow aspirate and trephine were performed which showed a reduction in lymphoblasts to 5% by flow cytometry and an extensive infiltration of malignant histiocytes, amounting to nearly 80%, with no associated hemophagocytosis [Figs. 2(a) & (b); 3(a) & (b)]. This 'secondary malignant histiocytosis' (SMH) was considered to be the cause of his persistent fevers, based on flow cytometric analysis. Karyotyping was not performed on the marrow at this stage. There was mild hepatomegaly, no splenomegaly, ferritin levels were 1197 microgram/L (normal 10–400 mcg/L), whereas LDH and triglyceride levels were normal. Other differential diagnoses which were ruled out included: Anaplastic large cell lymphoma (negative staining for CD30 and ALK1), carcinoma (negative staining for cytokeratin) and dendritic cell neoplasms (negative staining for CD23 and S100 as well as morphology). Phase-2 induction chemotherapy was discontinued.

His secondary malignant histiocytosis was treated with alemtuzumab (Campath) 2.4 mg/kg over 5 days [5], intravenous immunoglobulins (IVIG) 1 gm/kg for 2 days and methylprednisolone 2 mg/kg for 5 days. He defervesce after 48 h and became well and ambulant. Assessment of bone marrow on day 15, 2 weeks after receiving alemtuzumab, showed a decrease in histiocytes to less than 15% and lymphoblasts to 0.1% by flow cytometry.

With an excellent performance status, normalization of blood counts and a partial response of his SMH, it was decided to proceed to T-cell replete allogeneic stem transplantation from his sibling with fludarabine (40 mg/m2/day) on days − 7 to − 3 and IV busulfan (130 mg/m2/day) conditioning on days − 6 to − 3 [6]. His bone marrow examination, 70 days' post-allogeneic stem cell transplantation, showed a complete morphological [Fig. 4], flow cytometric and cytogenetic remission. He developed features of mild skin graft versus host disease (GVHD), 2 months' post-transplant, which was treated with topical steroids. The patient maintained complete remission for 8 months' post-allogeneic stem cell transplant but has relapsed with ALL in thigh muscles, the middle ear and the leptomeninges. Biopsies from two sites reveal no evidence of SMH.

## 3. Discussion

Histiocytoses encompass a rare, heterogeneous group of disorders characterized by the aggregation of cells of mononuclear-phagocytic lineage and occur more commonly in children. Histiocytes, a morphological term for tissue-dweller macrophages, perform the phagocytic function whereas dendritic cells (DC) are involved in antigen presentation and T-cell activation. Nomenclature for this rare entity has evolved since 1987 and most recent classification group > 100 subtypes into 5 categories [1,2].

Secondary Malignant Histiocytosis (SMH) is a neoplastic disorder occurring simultaneously or after another hematologic malignancy and is classified under "M group (MH: Malignant Histiocytoses)" according to the revised classification of histiocytic disorders. SMH is diagnosed based on anaplastic morphology, expression of macrophage and DC markers, a definite temporal and a probable clonal relationship with the primary hematologic neoplasm [2,3].

Differential diagnosis mainly includes high-grade lymphoma,