

Acute Monoblastic Leukemia (AML-M5) with concomitant Hemophagocytic Lymphohistiocytosis: Presenting as Pancytopenia

Dr. Sonal, Dr. Deepti Gupta, Dr. Nupur Trivedi, Dr. Shefali Agarwal, Dr. Archana Agarwal, Dr. Anjali Tewari, Dr. Priyanka Verma

Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is an aggressive hyperinflammatory condition characterized by prolonged fever, cytopenias, hepatosplenomegaly and hemophagocytosis with a high rate of mortality. Its diagnosis is a challenge for pathologists as well as clinicians due to variable overlap of symptoms with other severe diseases. AML-associated hemophagocytic lymphohistiocytosis is a rare event, reported only in limited members.

We, hereby report a case of 14 year old male child who came to our hematology department with a history of prolonged fever, pancytopenia and history of 40 transfusions in last one year. Peripheral blood counts showed 15 % blastoid atypical cells. Bone marrow revealed acute leukaemia with evidence of haemophagocytosis. A diagnosis of AML-M5 with HLH was made after flow cytometry and completion of clinico-biochemical criteria for HLH.

Patients with HLH in acute leukaemia may have low blast counts on peripheral blood leading to much delay in the diagnosis. This case report provides helpful clinical experience related to diagnosis of this rare entity.

Keywords

Hemophagocytic Lymphohistiocytosis (HLH), hyperinflammatory condition, AML-associated, secondary HLH, cytopenias.

Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is an aggressive hyperinflammatory condition characterized by prolonged fever, cytopenias, hepatosplenomegaly and hemophagocytosis with a high rate of mortality. There are two forms; familial and secondary HLH. Familial HLH is an autosomal recessive syndrome with an estimated prevalence of 1/50,000 live births.⁽¹⁾ Secondary HLH is a well recognized entity and is associated with infections, autoimmune diseases, immune deficiencies, metabolic diseases, drugs or malignancies.⁽²⁾ Usually HLH develops during the course of treatment of haematological malignancies and its diagnosis is difficult because the findings of HLH are masked by malignant process or because the findings of these two processes may be indistinguishable. Rare cases of leukaemias with HLH have been reported.⁽³⁾ However, when HLH is present concomitantly with acute leukaemias, HLH induced cytopenias reduce the peripheral blood blasts counts, masking acute leukaemia leading to much delay in the diagnosis. We, hereby, report a rare

case of AML in a 14 year old male, who had persistent pancytopenia due to concomitant presence of HLH.

Case Report

A 14-year-old boy came to our hospital OPD with complaints of prolonged fever, anaemia, thrombocytopenia, history of 40 transfusions in last one year and a diagnosis of megaloblastic/hypoplastic anemia. Patient appeared lethargic but his vitals were stable. On P/A examination, there was mild splenomegaly. Initial CBC showed Hb-4.8g/dl, RBC count- $1.78 \times 10^6/\mu\text{L}$, PCV-14.2%, TLC- $3.85 \times 10^3/\mu\text{L}$, DLC revealed 15% atypical blastoid cells and platelet count -1000/uL. On the basis of this, an impression of pancytopenia with few atypical cells was made. On 2 day of admission CBC was Hb-4.7g/dl, RBC count - $1.60 \times 10^6/\mu\text{L}$, PCV-14.1%, TLC- $1.43 \times 10^3/\mu\text{L}$, DLC- 05% blastoid cells and platelets - 2000/uL. Bone marrow aspiration and biopsy were done. Bone marrow showed mildly hypocellular marrow fragments with 25% blasts (morphologically resembling Myeloblasts) having high N:C ratio, round to oval nucleus, opened up chromatin, prominent nucleoli and scant cytoplasm (Figure 1). Erythropoiesis and megakaryopoiesis were suppressed and histiocytes were markedly increased in number with evidence of hemophagocytosis (Figure 2). Bone marrow iron stores were increased (Grade III-IV) (Figure 3). Findings were suggestive of Acute leukemia with marked Hemophagocytosis. The patient was then worked up for Acute leukaemia and HLH. On flow cytometry, 30 % blasts were reported, positive for CD13, CD33, CD14,CD11c, CD64 and HLA-DR. Biochemical Investigations for HLH workup revealed Serum Ferritin level - 7030 ng/dl, Hs-CRP – 10gm/dl, S.Triglyceride-144.5mg/dl, S.LDH-685.3U/L, Total bilirubin-2.45mg/dl, Direct-1.94mg/dl, Indirect-0.51mg/dl. Coagulation profile showed Prothrombin Time 19.4seconds. Hence, a diagnosis of AML-M5 with coexisting Secondary HLH was made.

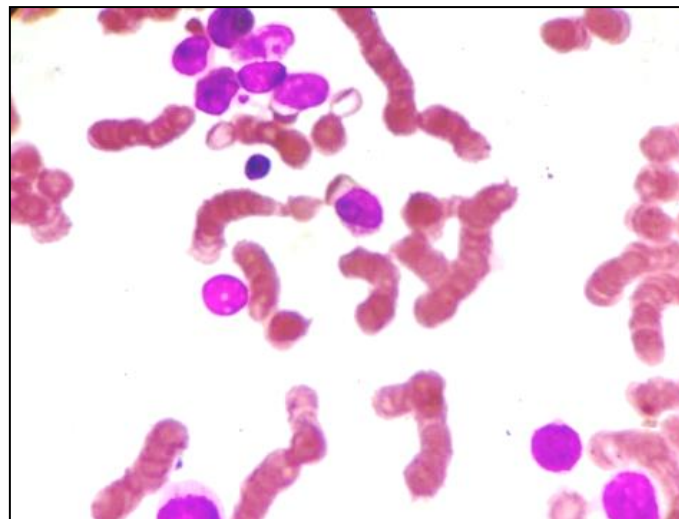


Figure 1: Bone marrow aspirate showing blasts having high N:C ratio, round to oval nucleus, opened up chromatin, prominent nucleoli and scant cytoplasm. (x1000 magnification)

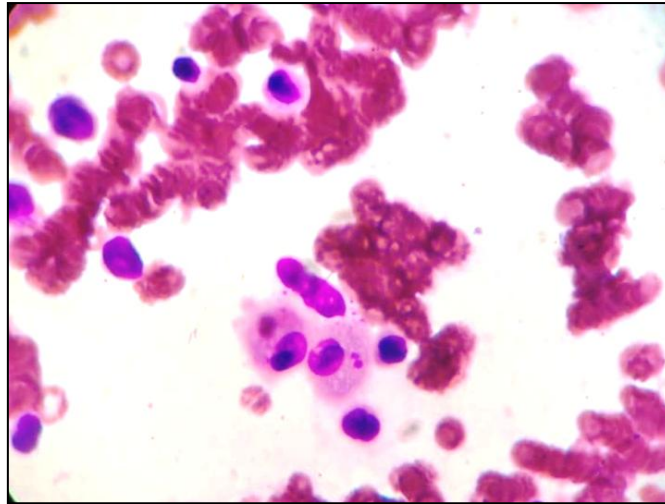


Figure 2: Bone marrow aspirate showing haemophagocytic cells (x1000 magnification)

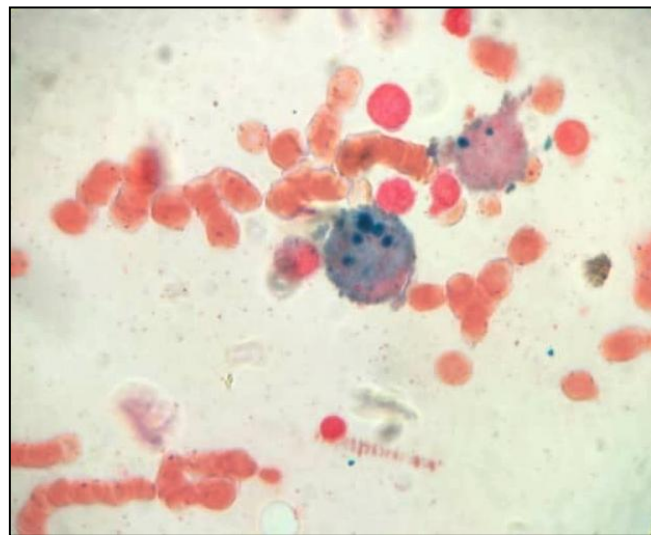


Figure 3: Bone marrow aspirate showing haemophagocytic cells with increased iron stores on Pearls' Prussian Blue staining (x1000 magnification)

Discussion

HLH is classified as either primary familial HLH, with a genetic etiology, or secondary HLH which is associated with malignancies, autoimmune diseases and infections. Genetic forms appear early in life, even in infants, while other forms are sporadic and may affect people of any age. HLH is characterized by uncontrolled cytokine production resulting in persistent cytotoxic T-cell activation, macrophage proliferation and hemophagocytosis.⁽⁴⁾ Genetic form occurs due to defect in perforin gene on chromosome 9q21, the MUNC13-4 gene on chromosome 17q25 or mutation in syntaxin 11 gene on chromosome 6q24. The perforin and Fas system maintain homeostasis of dendritic cells and restrict T-cell activation from antigen presentation. This uncontrolled activation of antigen-presentation cells and T cells results in a cytokine storm with secretion of proinflammatory cytokines such as TNF α , IL1 and IL6. This activates macrophages and causes tissue damage that leads to multi-organ failure.⁽⁵⁾

Secondary HLH comprise of two main groups: Malignancy associated and non-malignancy associated HLH. Non-malignancy associated HLH is most commonly associated with viral, bacterial, parasitic or fungal infections. CMV and EBV are the most common viral infections.⁽⁶⁾ Malignancy-related HLH is most commonly associated with NK- or T cell malignancies (35.2%), followed by B-cell lymphoma (31.8%), Hodgkin lymphoma (5.8%), acute leukemia (6.4%) and other hematologic neoplasms (14.4%).⁽⁷⁾

AML-associated HLH is only seen in some cases reports without accurate data. A nationwide survey was conducted in Japan from 2001 to 2005. Out of 567 patients of HLH analyzed, the incidence of HLH associated with leukaemia was reported, 0.5% for ALL and 1.5% for AML.⁽⁸⁾ Presumably, high concentrations of inflammatory cytokines (interleukin 1, interleukin 6 TNF alpha and interferon gamma) secreted by malignant cells play an important role in the pathogenesis.⁽⁹⁾ It is questionable whether chemotherapeutic drugs also trigger HLH. It is possible that the development of leukemia in patient with genetic HLH mutations may trigger overt HLH, particularly when combined with infections.⁽¹⁰⁾

In accordance with the International Histiocyte Society guidelines, five out of eight diagnostic criterias are required for a diagnosis of secondary HLH: Fever ≥ 38.5 C, splenomegaly, cytopenia affecting ≥ 2 of 3 lineages in peripheral blood, Hypertriglyceridemia (Fasting triglyceride ≥ 3 mmol/l) and/or hypofibrinogenemia (≤ 1.5 g/l), evidence of haemophagocytosis in bone marrow or spleen or lymph nodes (No evidence of any malignancy), low or absent natural killer cell activity, Serum ferritin ≥ 500 ug/l and elevated soluble CD25 ≥ 2400 U/ml.⁽¹¹⁾

HLH diagnosis in leukaemia is difficult because of clinical and laboratory tests similarities of the two entities. For example, it is difficult to determine whether splenomegaly, fever and cytopenias developed related to HLH or resulted from leukaemia itself. Similarly, HLH symptoms are confused with myelosuppression induced by chemotherapy or sepsis. HLH related to leukaemia usually develops after the diagnosis of leukaemia is made due to the release of cytokines by the blasts or during the course of treatment because of chemotherapeutic drugs.

In our case, the two pathologies coexisted from the very beginning leading to marked delay in the diagnosis of either/both. The young male patient was treated for one year on the grounds of pancytopenia/ macrocytic anaemia with repeated transfusions. Only, when he reached our tertiary care hospital, the haematologist suspected leukaemia. However, the peripheral blood counts report was not helpful and a bone marrow aspiration- biopsy was performed, which revealed marked haemophagocytosis with 25% leukaemic blasts. Hence, a diagnosis of AML-M5 with coexisting Secondary HLH was made after flow cytometry and fulfilment of HLH diagnostic criteria.

Initial goal of therapy in HLH has been to suppress the overactive immune system, thus preventing immune-mediated organ damage. Induction therapy is often followed by allogeneic stem cell transplant in most cases of primary HLH if a suitable donor is available. However, there is no consensus on the treatment of HLH when it is concomitant with AML.

Jordan et al recommend initiating immunochemotherapy first and then administering chemotherapeutic drugs once the inflammatory markers have normalised.⁽¹²⁾

Conclusion

Patients with HLH and acute leukemia may have low blast counts on peripheral blood leading to delay in the diagnosis. This case report provides helpful clinical experience related to diagnosis of this rare entity. Although there is no substitute for maintaining a high index of suspicion in appropriate patients, we think that a better understanding of the clinical patterns of HLH and underlying pathophysiology would lead to more prompt and accurate diagnoses.

Consent Disclaimer:

As per international standard or university standard, parent's consent of the child has been collected and preserved by the authors.

References

1. Janka G, Henter JI, Imashuku S. Clinical aspects and therapy of hemophagocytic lymphohistiocytosis. CambridgeUK: Cambridge University Press; 2005.
2. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection-and malignancy-associated hemophagocytic syndromes: secondary hemophagocytic lymphohistiocytosis. Hematology/oncology clinics of North America. 1998 Apr 1;12(2):435-44.
3. Akyay A, Celkan T, Iskender G, Tukun A, Ogan C, Olcay L. Two acute myeloblastic leukemia cases concomitant with hemophagocytic lymphohistiocytosis and review of the literature. Annals of Clinical & Laboratory Science. 2013 Dec 21;43(1):85-90.
4. Janka GE. Hemophagocytic syndromes. Blood reviews. 2007 Sep 1;21(5):245-53.
5. Szyper-Kravitz M. The hemophagocytic syndrome/macrophage activation syndrome: a final common pathway of a cytokine storm. The Israel Medical Association Journal. 2009 Oct 1;11(10):633.
6. Komp DM, McNamara J, Buckley P. Elevated soluble interleukin-2 receptor in childhood hemophagocytic histiocytic syndromes. Blood. 1989 Jun 1;73(8):2128-32.
7. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. The Lancet. 2014 Apr 26;383(9927):1503-16.
8. Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, Yamamoto K, Horiuchi H, Takada K, Ohshima K, Nakamura S. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. International journal of hematology. 2007 Jul 1;86(1):58-65.

9. Majluf-Cruz A, Sosa-Camas R, Perez-Ramirez O, Rosas-Cabral A, Vargas-Vorackova F, Labardini-Mendez J. Hemophagocytic syndrome associated with hematological neoplasias. *Leukemia research*. 1998 Oct 1;22(10):893-8.
10. O'Brien MM, Lee-Kim Y, George TI, McClain KL, Twist CJ, Jeng M. Precursor B-cell acute lymphoblastic leukemia presenting with hemophagocytic lymphohistiocytosis. *Pediatric blood & cancer*. 2008 Feb;50(2):381-3.
11. Meki A, O'Connor D, Roberts C, Murray J. Hemophagocytic lymphohistiocytosis in chronic lymphocytic leukemia. *Journal of Clinical Oncology*. 2011 Jun 27;29(24):e685-7.
12. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011 Oct 13;118(15):4041-52.