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Haemophagocytic Lymphohistiocytosis and Acute Myeloid Leukemia: A Case Report

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ABSTRACT

We report a case of haemophagocytic lymphohistiocytosis associated with acute myeloid leukemia. The usual etiologies of haemophagocytic lymphohistiocytosis, including viral infections, were negative. Haemophagocytic lymphohistiocytosis secondary to acute myeloid leukemia is often underestimated and undiagnosed. Haemophagocytic lymphohistiocytosis may be masked by the tumour process, often making the diagnosis difficult.

KEYWORDS

Acute myeloid leukemia; Haemophagocytic lymphohistiocytosis; Hemophagocytosis; Leukemias

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is an aberrant immune response syndrome characterized by uncontrolled activation of lymphocytes and macrophages, hypersecretion of pro-inflammatory cytokines and multi-organ dysfunction [1]. Familial or primary HLH is conferred by genetic defects in cytotoxic immune function, usually occurring in childhood. Secondary or acquired HLH is mainly related to acquired factors, such as infection, chronic inflammation or malignancy.

HLH in the context of malignancy is encountered in about half of all adult cases and occurs in 1% of hematological malignancies [2,3]. T-cell or natural killer lymphomas (35%) and B-cell lymphomas (32%) are the most commonly reported. Other tumours include leukemia (6%), Hodgkin's lymphoma (6%), other hematological malignancies (14%), solid tumours (3%) and other non-specific neoplasms (3%) [2,4].

The association between HLH and acute myeloid leukemia (AML) is unusual. Rare cases and a few series have been reported [5,6]. We report a case of HLH simultaneously diagnosed with acute erythroid leukemia, in a patient followed for polycythemia vera.

CASE REPORT

A patient aged 69-years of Malagasy origin, was admitted to the Oncology Department in May 2022 after the

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discovery of blasts and haemophagocytes on the bone marrow smear.

In his history, he was followed by the Hematology department for polycythemia vera diagnosed in 2015. He was initially treated with hydroxyurea which was discontinued due to digestive intolerance. During follow-up, regular blood count monitoring and phlebotomy episodes were performed.

In February 2022, he had anemia and thrombocytopenia. The bone marrow smear was normal. In May 2022, the blood count showed 46% blast count with persistent cytopenias. The second bone marrow smear revealed blasts and haemophagocytes.

His other history was marked by alcoholism and smoking that had been weaned 30-years ago, no use of other toxic substances and no exposure to ionizing radiation. He had no history of immunodepression and no history of cancer.

On admission, he reported moderate dyspnea that was slightly relieved when sitting. Peripheral oxygen saturation was 80%. He had a fever of 39.5ºC and his general condition was altered with a performance status of 3. On examination, the patient was found to have mucocutaneous pallor, painless hepatomegaly and Hackett's stage 3 splenomegaly. Pulmonary auscultation revealed diffuse crackling rales. There was no peripheral lymphadenopathy. The rest of the examination was unremarkable.

On the second day of hospitalization, he presented with episodes of moderate melena, hemorrhagic bullae of the oral mucosa and petechial lesions on the plantar surface of the feet [4].

The blood count showed a haemoglobin level of 6.8 g/dL, a white blood cell count of 93.87 G/L, a platelet count of 3 G/L, a lymphocyte count of 7,51 G/L and a blast count of 37%. Serum ionogram, calcium and albumin levels were normal. Serum creatinine level was 184 µmol/L (clearance 36 mL/min). Hepatitis B, C and HIV serologies were negative. Serum protein electrophoresis showed polyclonal hypergammaglobulinemia.

Cytological examination from bone marrow aspiration showed 21% blasts, erythroblastic hyperplasia and hemophagocytosis. The results are summarized in Table 1 and illustrated in Figure 1.

	Result
Granular cell lineage	26 %
Promyelocytes	02
Myelocytes	03
Metamyelocytes	05
Polynuclear neutrophils	16
⎯⎯ *Granulocytic dysplasia*	
Erythroblastic lineage	52 %
Basophilic erythroblasts	10
Polychromatophilic erythroblasts	20
Acidophilic erythroblasts	22
⎯⎯ *Erythroblastic dysplasia*	
Lymphocytes	01
Macrophages	+++
⎯⎯ *Hemophagocytosis*	
Blasts	21 %

Table 1: Result of cytological examination from bone marrow aspiration.

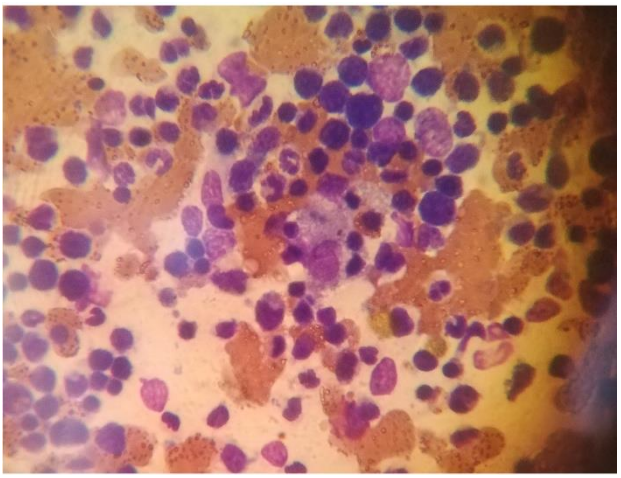

Figure 1: Images of haemophagocytes on bone marrow aspiration (May-Giemsa staining).

Additional investigations for HLH were performed. Ferritin level was 477.96 ng/mL and fibrinogen was 1.87 g/L. Triglyceride level was 5.12 g/L. Serologies for Epstein-Barr virus, parvovirus B19, cytomegalovirus and human herpes virus-8 were negative. Plasmodium was not

detected on thick and thin blood smears. Blood culture and urine cytobacteriological examination were negative.

Acute erythroid leukemia was diagnosed. The leukemia was secondary to the acuitization of polycythemia vera. The diagnosis of concomitant HLH was evoked with an H-score of 240. Bleeding syndrome, respiratory distress and acute renal failure were associated with HLH.

The patient received corticosteroid therapy with methylprednisolone IV 1 mg/kg per day, antibiotic therapy with amoxicillin/clavulanic acid IV 3 g per day for 7 days, omeprazole IV 240 mg per day, transfusion support and oxygen therapy. After multidisciplinary consultation, no specific treatment for AML or HLH was initiated.

The short-term evolution was marked by improvement of the dyspnea and disappearance of the bleeding syndrome at one week of admission. The haemoglobin level was corrected within one week and the platelet count remained below 15 G/L. Unfortunately, the patient died at home a few weeks after hospitalization.

DISCUSSION

We report a case of HLH concomitant with acute erythroid leukemia or M-6 AML according to the French-American-British classification [7]. HLH occurring during leukemia is unusual. In a Japanese study by Ishii E et al., the incidence was 0.5% for acute lymphoblastic leukemia and 1.5% for AML [8]. It can occur before, during or after the onset of malignancy [3].

The pathophysiological mechanism of leukemia-related HLH is multifactorial. Tumour cells secrete triggering pro-inflammatory cytokines. Certain inherited immune disorders predispose not only to HLH but also to cancer. Chemotherapy may be involved, either through immunomodulatory effects or through infection in the context of immunosuppression [9]. Some authors have reported the presence of predisposing clonal abnormalities [10,11].

In our case, investigation for the usual triggers of HLH was performed, and the only finding was AML. Cytogenetic analysis could not be performed due to lack of technical facilities.

HLH usually presents with high fever, hepatomegaly, splenomegaly, lymphadenopathy, liver abnormalities and coagulation disorders. Non-specific gastrointestinal symptoms are common. Pulmonary, cardiac and renal involvement is encountered in severe forms. In rare cases, digestive hemorrhage is observed, as presented by our patient.

The diagnosis of HLH is based on clinical-biological criteria. The HLH-2004 criteria have been the most widely used, requiring at least five of the eight proposed criteria [1]. However, some of the HLH-2004 parameters are not specific. The H-Score was then created to accurately identify secondary HLH [12]. This score consists of nine variables and is used to calculate the probability of HLH. In our case, five HLH-2004 criteria were present and the H-score was 240, giving a probability of 98%-99%.

The diagnosis of HLH in the context of leukemia is often difficult because of the similarities between the two diseases. Fever, hepatomegaly, splenomegaly and cytopenias are often found in leukemia. It should be noted that hemophagocytosis is not specific to HLH. It can be seen in infection, autoimmune disease and blood transfusions.

There is no standard consensus for the therapeutic management of HLH in the setting of malignancy. The authors recommend initiating treatment to control inflammation, including corticosteroids in the first line and etoposide in case of severe visceral damage [13].

Specific treatment for malignancy is only initiated after inflammatory markers have returned to normal. However, management is based on a multidisciplinary approach and varies according to the patient's comorbidities and visceral lesions. In our case, we chose not to initiate immunochemotherapy.

The prognosis of HLH remains poor. Mortality rates vary between 42 and 88% [14]. Malignancy-related HLH has the worst prognosis of all HLH subgroups. Older age and underlying lymphoma are predictive of mortality [4,15].

CONCLUSION

HLH associated with AML is unusual. This association is often underestimated and under-diagnosed. HLH should be considered in patients diagnosed with AML who present with fever and persistent cytopenias. Its diagnosis is based on clinical and biological criteria.

CONSENT FOR PUBLICATION

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient.

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AUTHORS CONTRIBUTIONS

RMF Randrianarisoa: drafting the work. NOTF Andrianandrasana, MI Rahantamalala: revised critically the work for important intellectual content. HMD Vololontiana, F Rafaramino: approved the version to be published.

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