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Case Report

Hemophagocytic lymphohistiocytosis in patients with acute myeloid leukemia: a report of three cases and literature review

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Abstract: *Background:* The aim of this case report was to analyze clinical diagnosis, treatment, and prognosis of 3 patients with acute myeloid leukemia and hemophagocytic lymphohistiocytosis. Literature review was also performed. *Case presentation:* Hemophagocytic phenomenon was evidenced by bone marrow aspiration in 3 eligible patients. One patient was infected with Epstein-Barr virus. Two patients survived for only 19 and 27 days, respectively. One patient survived for 4 months with treatment including dexamethasone, cyclosporin A, and etoposide. *Conclusion:* Hemophagocytic lymphohistiocytosis is a disease with rapid onset and high mortality. Early diagnosis and control of the cytokine storm by chemotherapy should be adopted for patients with acute myeloid leukemia and hemophagocytic lymphohistiocytosis.

Keywords: Hemophagocytic, lymphohistiocytosis, acute myeloid leukemia

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and fatal hematological disease, mainly affecting the mononuclear phagocyte system [1]. A large number of inflammatory factors may cause severe or even fatal inflammatory responses [2]. HLH is categorized by primary and secondary types. Secondary HLH is the most common cause of infection and malignant cancer [2]. Incidence of leukemia with HLH is relatively rare and has been seldom reported [3]. Clinical manifestations of HLH vary. Thus, it is easily misdiagnosed and early diagnosis is often difficult [4]. Delayed diagnosis may lead to delayed treatment or even early death [5]. Here, this study reports the clinical information of 3 patients with acute myeloid leukemia (AML) and HLH after chemotherapy. Literature review was conducted in an attempt to improve the understanding of such cases.

Case presentation

Case 1

A 58-year-old male with a 1-year history of myelodysplastic syndromes (MDS) was admitted, due to fever, for 1 day. Physical examination showed mild fever (37.5°C), increased respiratory rate (23 beats/min), pale skin and mucous, and non-remarkable findings upon physical examination. Routine blood tests showed a decreased number of red blood cells (RBCs) (1.69×10^{12}/L), decreased hemoglobin (51×10^{9}/L), increased lymphocyte ratio (22.4%), and increased monocyte ratio (10.9%). Bone marrow cytology showed abnormal proliferation of mononuclear cells, including 32% of primitive and immature mononuclear cells. Bone marrow flow cytometry showed 75.98% of CD34, 75.65% of CD13, 64.71% of CD33, 91.58% of CD38, 37.89% of CD117, 78.36% of HLA-DR, 17.60% of myeloid derived immature cells, and 16.89% of mononuclear cells. Chromosome examination in bone marrow showed that G-banded karyotype was 46XY (20). Thus, diagnosis was confirmed as AML which had transformed from MDS. Anti-infection drugs (mezlocillin sodium sulbactam and levofloxacin) were given and patient temperature dropped to normal. Decitabine + CAG regimen was given (Decitabine 25 mg d1-4, aclarubicin 12 mg d1-8, cytarabine 20 mg q12

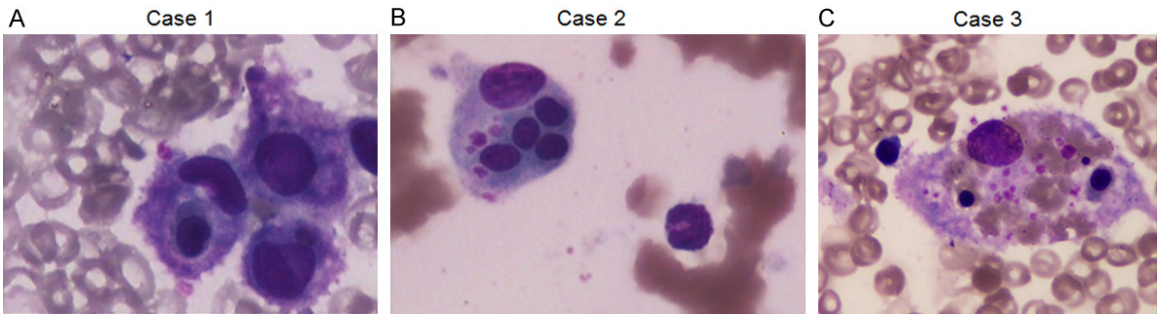

Figure 1. Bone marrow smear. Wright-Giemsa staining was performed. Representative images are shown. Magnification: 1 × 1000. A: Case 1. B: Case 2. C: Case 3.

Table 1. Dynamic changes of routine blood and coagulation tests in Case 1

Date	WBC (× 10^9/l)	Hb (g/L)	PLT (× 10^9/l)	Mon (%)	PT (s)	APTT (s)	FIB (g/l)
1st day	0.79	45	7	12.7	13.1	49.6	1.79
4th day	1.15	56	2	12.2	14.7	59.7	1.84
8th day	1.95	69	2	14.4	14.9	65.3	0.97
12th day	0.35	61	2	15.7	15.5	62.8	0.88
18th day	0.35	39	3	23.8	16.9	103.0	1.40
20th day	0.52	34	1	32.7	23.8	126.2	1.17

Note: WBC: white blood cell; Hb: hemoglobin; PLT: blood platelet; PT: prothrombin time; APTT: active partial thromboplastin time; FIB: fibrinogen metaglobulin.

h d1-14, and G-CSF 300 ug d1-14). During the course of chemotherapy, this patient experienced high fever (max 39.3°C) with fibrosis on both lungs, as detected by chest CT scan. Tests for active infections were all negative but serum ferritin (2886.53 ng/mL) and triglycerides (6.13 mmol/l) were high. PT (14.70 s) and APTT (59.70 s) prolonged, FIB remained, and NK cell activity decreased (4.1%). Many cells were observed in bone marrow smear and 28% of them were hemophagocytic cells (**Figure 1A**). Dynamic changes of blood tests are shown in **Table 1**. PRF1, STX1, STXBP2, and MUNC13-4 gene mutations were not found. Therefore, secondary HLH was diagnosed. Routine anti-infection treatment showed no obvious effects. Anti-viral infection treatment was prescribed (foscernet sodium 3 g q8 h), along with cyclosporine (125 mg bid), dexamethasone (10 mg), gamma globulin (5-10 g, 150 mg/m^2, biw), and supportive treatment. The following week, VP16 was given. Fever, hematocypenia, dysfunction coagulation, and hemophagocytic phenomenon persisted, however, and the patient died after 19 days.

Case 2

A 59-year-old male was admitted due to fatigue and anorexia for more than 20 days and fever for 10 days. This patient had mild fever (37.6°C), two palpable (0.5 × 0.5 cm in size) axillary lymph nodes but no other remarkable findings upon physical examination. Blood tests showed low Hb (89 g/L), low PLT (72 × 10^9/L), decreased neutrophils (17.0%), decreased lymphocytes (9.0%), increased mononuclear cells (15.1%), immature cells (54%), and high lactate dehydrogenase (1116.0 U/L). Bone marrow cytology showed bone marrow hyperplasia, reduced granulocyte proliferation, increased primitive granulocytes, increased mononuclear cells, increased ratio of primitive and immature mononuclear cells (54%), decreased proliferation of lymphocytes and erythroid, and weak positive POX. The karyotype of bone marrow chromosome was 46XY (20). Flow cytometry showed that abnormal cells mainly expressed CD13, CD33, HLA-DR, CD38, and CD15. They partially expressed CD15 and CD117 and few expressed CD7, CD14, and cyMPO. Thus, the diagnosis was AML (M5). For treatment, DA regimen (daunorubicin 60 mg d1-3, cytarabine 150 mg d1-7) was given. However, fever and hematocytopenia persisted until 3 weeks after chemotherapy. EB virus DNA was 1.57 × 10^4 Copies/mL. Broad-spectrum antibiotic and empirical antifungal treatments showed no improvement, therefore, antiviral therapy was given. Bone marrow examination (**Figure 1B**) showed reduced bone marrow hyperplasia, reduced granulocyte erythroid hyperplasia, increased lymphocyte ratio (mostly mature lymphocytes), increased monocytes ratio, increased primitive myelomonocytes

Table 2. Dynamic changes of routine blood and coagulation tests in Case 2

Date	WBC (× 10^9/l)	Hb (g/L)	PLT (× 10^9/l)	Mon (%)	PT (s)	APTT (s)	FIB (g/l)
1st day	1.23	64	3	8.9	18.1	56.5	2.43
5th day	1.08	49	2	6.5	14.7	53.1	1.57
10th day	0.87	52	1	5.7	15.5	59.8	0.97
13th day	0.57	42	0	5.6	17.6	58.5	0.78
17th day	0.70	23	0	11.3	26.1	59.6	1.19

Note: WBC: white blood cell; Hb: hemoglobin; PLT: blood platelet; PT: prothrombin time; APTT: active partial thromboplastin time; FIB: fibrinogen metaglobulin.

Table 3. Dynamic changes of routine blood and coagulation tests in Case 3

Date	WBC (× 10^9/l)	Hb (g/L)	PLT (× 10^9/l)	Mon (%)	PT (s)	APTT (s)	FIB (g/l)
1st day	0.26	56	3	11.5	14.3	49.2	3.03
7th day	1.16	51	4	43.1	12.7	41.8	2.19
13th day	0.57	65	25	17.5	11.0	35.8	1.71
18th day	1.23	53	22	12.3	11.0	26.4	1.06
28th day	2.73	83	109	2.3	11.1	28.6	1.89

Note: WBC: white blood cell; Hb: hemoglobin; PLT: blood platelet; PT: prothrombin time; APTT: active partial thromboplastin time; FIB: fibrinogen metaglobulin

(7.5%), increased plasma cells, increased histocytes, and visible hemophagocytic cells (3%). Dynamic changes of blood tests are shown in **Table 2**. Serum ferritin (2915.23 ng/m), NK cell activity (3.5%), and triglycerides (6.95 mmol/l) all increased. PRF1, STX1, STXBP2, and MUNC13-4 gene mutations were not found. Therefore, secondary HLH was clinically diagnosed. Intravenous infusions of dexamethasone (20 mg d1-14) and etoposide (0.2 g, d1, d4), oral intake of cyclosporine (150 mg q12 h), and supportive care were given. The patient's symptoms aggregated, however, and he died 7 days after diagnosis of HLH.

Case 3

A 28-year-old female was admitted because of an intermittent fever for 1 month and skin bleeding and ecchymosis for 4 days. Physical examinations showed mild fever (38.5°C) and ecchymosis but no other remarkable findings. Blood tests showed decreased levels of RBC (1.96 × 10^{12}/L), Hb (67 g/L), and PLT (49 × 10^9/L) and increased ratio of monocyte (41.0%) and immature cells (40%). Flow cytometry showed abnormal cells expressing CD13, CD14, CD15, CD33, and HLA-DR. The patient was diagnosed with AML (M4) based on bone marrow pathology and flow cytometry. AML-related fusion genes were negative and bone marrow chromosome showed 46XX (20). DA regimen (daunorubicin 40 mg/m^2, cytarabine 150 mg/m^2) was given. Bone marrow puncture, after chemotherapy, was performed and showed increased primitive granulocytes (17%), primary monocytes (12.0%), and immature mononuclear cells (28%). Following the IA regimen (daunorubicin 10 mg/m^2, cytarabine 150 mg/m^2), patient showed fever (max 39.3°C), increased levels of ESR (40 mm/h), serum ferritin (2250.10 ng/mL), and lactate dehydrogenase (278 U/L) as well as decreased levels of RBC (2.23 × 10^{12}/L), Hb (73 g/L), and PLT (15 × 10^9/L). Patient showed no evidence for active infections. After 6 weeks, bone marrow cytology showed hemophagocytic phenomenon (**Figure 1C**). Blood tests showed abnormal coagulation functions, increased serum triglyceride (3.82 mmol/L), increased serum ferritin (2810.24 ng/mL), and increased NK cell activity (4.7%). Dynamic changes of blood tests are shown in **Table 3**. PRF1, STX1, STXBP2, and MUNC13-4 gene mutations were not found. Therefore, secondary HLH was diagnosed. Treatment of dexamethasone (10 mg), cyclosporine A (125 mg q12 h), VPI6 (200 mg for 1st week and 100 mg for 2nd week), and gamma globulin (0.4 g/kg for 5 d) was given. The patient's temperature decreased. Results of blood tests and bone marrow cytology showed gradual recovery to normal levels. One month later, this patient received cytarabine chemotherapy. Currently, the patient is preparing for hematopoietic stem cell transplantation.

Discussion

HLH, a kind of histiocytosis disease, was first reported in 1979 by Risdall et al. [6]. It presents with fever, hepatosplenomegaly, hemocytopenia, abnormal liver function and coagulation, and hemophagocytic cells in the bone marrow [7]. HLH can be categorized by primary and secondary types. The former mainly attacks newborns and infants while the latter attacks people at all stages of disease [8]. Secondary HLH may be caused by a variety of reasons, includ-

ing infections and malignancies (such as lymphoma and leukemia) [9]. A multi-center clinical study showed that 50% of HLH is caused by infections and 36.1% is caused by malignancies [10]. Among malignancies, non-Hodgkin's lymphoma induced HLH accounts for 31.9%, MDS accounts for 4.2%, rheumatic diseases account for 7.0%, and the remaining 6.9% of HLH is due to unclear reasons [10]. Similar to another report [11], infections account for 62.2% of HLH, malignancies account for 24.3%, and rheumatic disease accounts for 13.5%. Most common malignancies are lymphoma and aggressive NK cell leukemia, while AML is relatively rare [12], The pathogenesis of this disease may result from high T lymphocyte activity, leading to large numbers of inflammatory cytokines, macrophage proliferation and differentiation, and pathological damage [13]. The common clinical manifestations of HLH are non-specific and are similar to leukemia. They include persistent fever, hepatosplenomegaly, pancytopenia, and bleeding [14], leading to delayed diagnosis and high mortality rate.

Common presentations of the 3 cases in this study are as follows. First, patients had underlying diseases such as acute monocytic leukemia or acute myelomonocytic leukemia (abnormal proliferation of mononuclear system), without hemophagocytic phenomenon at initial diagnosis. Second, hemophagocytic phenomenon occurred during chemotherapy-induced myelosuppression, therefore, infection was the leading cause for HLH, not leukemia. Third, patients mainly presented with fever and hemocytopenia, which are usually misdiagnosed as infections or bone marrow suppression. Mechanisms underlying acute monocytic leukemia and acute myelomonocytic leukemia induced HLH should be further studied with larger sample sizes.

HLH development is a dynamic process. Early bone marrow examinations only show a small amount of hemophagocytic cells in focal distribution [15]. Therefore, bone marrow puncture should be performed at multiple sites when suspecting HLH [9]. Wang et al. [16] reported that only 86.1% patients with hemophagocytic phenomenon could be detected at first diagnosis. Therefore, bone marrow puncture should be performed repeatedly to improve the diagnostic rate. In this care report, hemophagocytic cells were found in the bone marrow smear of 2 patients (Cases 1 and 2), upon initial suspicion, and in 1 patient (Case 3) after multiple punctures. HLH was timely diagnosed in Case 3 and prompt treatment was given.

Current treatment for HLH is mainly based on HLH-2004 recommendations [17], considering the pathogenesis and underlying diseases. The cytokine storm can be treated by dexamethasone-based regimens or etoposide (VP16) -based regimens [18]. Recently, rituximab has also been used to control cytokine storms in HLH [19]. Lymphoma-related HLH and EBV-related HLH use CHOP or modified CHOP regimens [20]. Only a small number of patients have had hematopoietic stem cell transplantation [21]. However, whether to perform chemotherapy for the primary disease or treat HLH first is hard to determine. The successful outcome for Case 3, in this study, was dependent on timely diagnosis and treatment.

In addition to infection control, immunosuppressive therapy and large doses of gamma globulin should be used to control the cytokine storm and reduce phagocytosis. Timely control of HLH combined with VP16 regimen leads to successful treatment. Therefore, control of deadly hyperinflammatory factors caused by HLH should be first, then subsequent treatment of infections or leukemia is recommended.

In summary, the clinical progress of HLH is rapid with high mortality. AML combined with HLH is easily misdiagnosed and multiple bone marrow punctures should be performed for suspected cases. Timely diagnosis and effective control of cytokine storms are of great importance.

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Disclosure of conflict of interest

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