Pure Erythroid Leukemia with Hemophagocytosis

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Abstract

A 53-year-old man was admitted with pancytopenia, fever and splenomegaly. Biochemistry showed increased ferritin levels. Bone marrow examination revealed increased erythrocytic precursors (94.9%) and active hemophagocytosis. Pure erythroid leukemia with hemophagocytic syndrome (HPS) was diagnosed. Induction chemotherapy comprising idarubicin and cytarabine was administered and steroid pulse therapy was added. Complete remission was attained, and HPS also improved. However, leukemia relapsed during chemotherapy and the patient died. This is the first report of pure erythroid leukemia complicated with HPS.

Key words: pure erythroid leukemia, hemophagocytic syndrome (HPS)

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Introduction

Acute erythroid leukemias are characterized by a predominant erythroid population and account for approximately 2-5% of all cases of acute leukemia. Most authors agree that two main subtypes exist: the M6 acute leukemia according to the French-America-British (FAB) criteria, in which mixed granulocytic and erythroblastic cellular components are present; and a pure erythroid acute proliferation not taken into consideration in the FAB classification (1-4). The World Health Organization (WHO) classification of pure erythroid leukemia is >80% of marrow cells showing no evidence of any significant myeloblastic component (<3%) and usually <10% mature erythroblasts (5).

Hemophagocytic syndrome (HPS) is a reactive disorder of the mononuclear phagocytic system, characterized by benign, generalized histiocytic proliferation with marked hemophagocytosis in the bone marrow (6, 7). HPS was diagnosed based on fever, splenomegaly, cytopenias affecting at least two of three lineages in the peripheral blood, hypertriglyceridemia and/or hypoferibrinogenemia, hemophagocytosis (in bone marrow, spleen, or lymph nodes), low or absent NK-cell activity, hyperferritinemia, and high level of soluble interleukin 2 receptor. Altogether, five of the eight criteria must be fulfilled (8). Malignant neoplasm-associated HPS (MAHS) is categorized as a secondary hemophagocytic lymphohistiocytosis (HLH). MAHS has been reported in lymphomas and other carcinomas (9), but occurrence as a complication of acute myeloid leukemia (AML) is extremely rare. We report herein a case of pure erythroid leukemia with HPS.

Case Report

A 53-year-old man was admitted to our hospital with pancytopenia, high-grade fever for 12 days and a 3-week history of severe general fatigue. Laboratory data on admission are shown in Table 1. Peripheral blood nucleated cell count was 43.2×10⁹/L (erythroblasts 6,000/200; white blood cells, 1.39×10⁹/L). Composition of WBCs was as follows: neutrophils, 70%; lymphocytes, 8%; monocytes, 16%; eosinophils, 2%; and basophils, 4%. The patient also had anemia (hemoglobin, 3.8 g/dL) and thrombocytopenia (platelet count, 2.7×10⁹/L). Blood biochemistry showed increased levels of lactate dehydrogenase (LDH) (4,400 IU/L), triglycerides (179 mg/dL) and ferritin (7,014 ng/mL). Serum titers for parvovirus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, hepatitis B and C, and herpes simplex virus were all negative. Computed tomography (CT) revealed splenomegaly and no infectious signs. Bone marrow examination revealed increased numbers of erythrocytic precursors

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Table 1. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>Complete blood cell counts</th>
<th>Coagulation test</th>
<th>Immunological test</th>
<th>Cytokines</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC</strong> 1.39 × 10⁹ /L</td>
<td><strong>PT</strong> 42 %</td>
<td><strong>IgG</strong> 744 mg/dL</td>
<td><strong>sIL-2R</strong> 722 U/mL</td>
<td><strong>Erythroblast</strong> 94.8 %</td>
</tr>
<tr>
<td><strong>RBC</strong> 114 × 10¹⁰ /L</td>
<td><strong>Fibrinogen</strong> 561.3 mg/dL</td>
<td><strong>IgM</strong> 156 mg/dL</td>
<td><strong>EPO</strong> 300 mU/mL</td>
<td><strong>NCC</strong> 341 × 10⁹ /L</td>
</tr>
<tr>
<td><strong>Hb</strong> 3.8 g/dL</td>
<td><strong>FDP</strong> 5 µg/mL</td>
<td><strong>IgA</strong> 62 mg/dL</td>
<td><strong>γ-GTP</strong> 54 IU/L</td>
<td><strong>MgK</strong> 22 × 10⁶ /L</td>
</tr>
<tr>
<td><strong>Ht</strong> 11.8 %</td>
<td></td>
<td></td>
<td><strong>Mg</strong> 22 × 10⁶ /L</td>
<td></td>
</tr>
<tr>
<td><strong>Platelet</strong> 2.7 × 10¹⁰ /L</td>
<td></td>
<td></td>
<td><strong>Promyelocyte</strong> 0.0 %</td>
<td></td>
</tr>
</tbody>
</table>

**Hemogram**
- Blast 0 %
- stab 12 %
- segment 58 %
- monocyte 16 %
- eosinophil 2 %
- basophil 4 %
- lymphocyte 8 %
- Erythroblast 6000 /200

**Biochemistry**
- TP 5.3 g/dL
- Alb 3.4 g/dL
- TBil 1.5 mg/dL
- AST 151 IU/L
- ALT 24 IU/L
- LDH 4400 IU/L
- ALP 287 IU/L
- BUN 42.3 mg/dL
- Cre 1.9 mg/dL
- Na 144 mEq/L
- K 4.1 mEq/L
- Cl 106 mEq/L
- CRP 3.4 mg/dL
- Ferritin 7014 mg/dL

Leukemia purely comprising erythrocytic precursors was first described by Di Guglielmo in 1928 (10). Until recently, this fulminant acute leukemia was alternately classified as a myeloproliferative disorder or a myelodysplastic syndrome. Nevertheless, a number of articles and textbooks have described the complex cytogenetics and extremely poor outcomes associated with this leukemia, which represents a distinct disease entity. Response to chemotherapy and length of survival have been shown to depend on a number of factors, including cytogenetic aberrations [major karyotypic aberrations (MAKA)] and the rate of proerythroblasts at the time of the initial diagnosis. Pure erythroid leukemia identified as pure red cell or proerythroblast-rich leukemia often shows genetic MAKA, and this clinical feature was also present in our case. This patient was also diagnosed with HPS. No evidence of infection, collagen disease or adverse effects of pharmacotherapy was identified. This HPS was thus classified as MAHS according to HLH-2004 Diagnostic Guidelines (8). Leukemia-associated HPS is relatively rare. In fact, to the best of our knowledge, few reports have described AML associated with HPS (11, 12), and only one report has examined acute erythroid leukemia (13). The present de-

(94.8%) and multiple sites of active hemophagocytosis (Fig. 1). Blasts were positive for glycoporphin A (GP-A) and transferrin receptor (CD71), and negative for myeloid or lymphoid-lineage antigens in surface marker analysis. The karyotype has been interpreted as 63, XY,-X,+1,-3,-4,+del (5)(q?),+6,-9,-10,+add(11)(q13),-12,+13,+14,-15,-16,-17,-18,-19,del(20)(q11q13.3),-22, a severe complex karyotype with abnormalities on chromosome 5. Since the characteristic features included almost complete dominance of erythroblasts, a diagnosis of pure erythroid leukemia (WHO classification) was made. Combining bone marrow findings, hemophagocytosis, CT, splenomegaly, laboratory features, fever >7 days, 2-lineage cytopenia (platelets, RBCs) and hyperferritinemia (ferritin >500 µg/L), a diagnosis of HPS was established.

Induction chemotherapy consisting of idarubicin (12 mg/body 30 minutes div.; days 1-3) and cytarabine (100 mg/body continuous div days 1-7) was administered with steroid pulse therapy (methyl-prednisolone at 1 g/body 30 minutes div days 1-3) for HPS. Fever was resolved immediately, and complete remission was achieved thereafter. Hemophagocytosis disappeared in bone marrow after induction chemotherapy. The patient recovered to a good general condition, then underwent consolidation chemotherapy. However, leukemia relapsed after the third course of consolidation chemotherapy. Bone marrow examination at the time of relapse revealed increased blasts with a karyotype similar to that seen at onset. However, bone marrow examination did not reveal any increase in active hemophagocytosis. Subsequent salvage chemotherapy with high-dose cytarabine (Ara-C 3 g/m² 2 hours div days 1, 3 and 5) proved ineffective and the patient died 5 months after the initial diagnosis. Although bone marrow transplantation was planned, no appropriate donor was found before relapse.

Discussion

Leukemia purely comprising erythrocytic precursors was first described by Di Guglielmo in 1928 (10). Until recently, this fulminant acute leukemia was alternately classified as a myeloproliferative disorder or a myelodysplastic syndrome. Nevertheless, a number of articles and textbooks have described the complex cytogenetics and extremely poor outcomes associated with this leukemia, which represents a distinct disease entity. Response to chemotherapy and length of survival have been shown to depend on a number of factors, including cytogenetic aberrations [major karyotypic aberrations (MAKA)] and the rate of proerythroblasts at the time of the initial diagnosis. Pure erythroid leukemia identified as pure red cell or proerythroblast-rich leukemia often shows genetic MAKA, and this clinical feature was also present in our case. This patient was also diagnosed with HPS. No evidence of infection, collagen disease or adverse effects of pharmacotherapy was identified. This HPS was thus classified as MAHS according to HLH-2004 Diagnostic Guidelines (8). Leukemia-associated HPS is relatively rare. In fact, to the best of our knowledge, few reports have described AML associated with HPS (11, 12), and only one report has examined acute erythroid leukemia (13). The present de-
Figure 1. Bone marrow on admission. The majority of blasts are erythrocytic precursors and giant erythroblasts are apparent (May-Giemsa, original magnification: A) ×100; B) ×400). C) Reactive histiocytes in a cluster exhibit predominance of erythroblasts (May-Giemsa, original magnification ×400).

scription represents the first report of pure erythroid leukemia with HPS. Although macrophages might be activated by cytokines produced by T-cells stimulated by malignant cells in MAHS, whether MAKA is associated with T-cell stimulation by AML cells in present case remains unclear.

This patient displayed full erythroblast and active hemophagocytosis in bone marrow and karyotype showed MAKA. Although these factors suggest the likelihood of a very poor response to chemotherapy, complete remission was readily obtained after the first induction chemotherapy and hemophagocytes disappeared at the same time. The lack of clinical evidence of infection and resolution of reactive histiocytosis with treatment for leukemia suggest that HPS was probably directly related to the leukemic process.

Histiocytic activation may have resulted from macrophage-stimulating or related factors produced aberrantly by leukemia cells. In addition, steroid pulse therapy for HPS might have affected the response to induction chemotherapy in this case. Patients with acute erythroleukemia have traditionally been treated with the standard protocol for myeloid leukemia. Relapse and a rapid decline, however, occur very rapidly in pure erythroid leukemia, and the outcome is quite poor. Bone marrow transplantation had been planned for the present case, but could not be performed due to a rapid relapse. Appropriate treatment strategies, including hematopoietic stem cell transplantation at an early stage, should be defined for pure erythroid leukemia.

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syndrome preceding acute myeloid leukemia with der t [7:17](q12;
qu11), monosomy, 17 and 5p-. J Pediatr Hematol Oncol 28: