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LETTER TO THE EDITOR

Hemophagocytic lymphohistiocytosis associated with myelodysplastic syndromes

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Hemophagocytic lymphohistiocytosis/hemophagocytic syndrome (HLH/HPS) is a reactive disorder of the mononuclear phagocytic system, characterized by generalized histiocytic proliferation with marked hemophagocytosis in the bone marrow [1]. It comprises two different categories: a primary (genetic) and a secondary (acquired) form. Malignant neoplasm-associated HPS (MAHS) is categorized as a secondary HLH. MAHS is mainly associated with lymphoma and rarely with other carcinomas [2]. To our knowledge, HLH associated with myelodysplastic syndromes (MDS) has not been described, although MDS with hemophagocytosis has been observed. Here, we describe a case of HLH associated with MDS, which presented with abundant $CD8^+$ T cells in the bone marrow and elevated plasma-soluble interleukin 2 receptor (sIL-2R).

A 60-year-old Japanese man was admitted with pancytopenia, epitaxis, fever and general fatigue. A hematological examination showed a hemoglobin concentration of 6.5 g/dL, a platelet count of 14,000/μL and a leukocyte count of 3,200/μL with 42.8% atypical lymphocytes (Fig. 1a). Blood biochemistry showed increased levels of lactate dehydrogenase (LDH) (331 IU/L), ferritin (649 ng/mL) and sIL-2R (4,054 U/mL). NK cytolytic activity was measured by the standard 51-chromium (Cr) release assay. NK cytolytic activity was not reduced at both the E/T ratios of 10:1 (13.1%, normal range 8.9–29.5%) and 20:1 (22.5%, normal range 17.1–48.7%). Serological studies for hepatitis B, hepatitis C and HTLV-1 were negative. IgM antibodies to parvovirus were negative. Serological test for EBV revealed that anti-viral capsid antigen IgM was negative in the presence of anti-viral capsid antigen IgG (160×) and anti-EBV nuclear antigen antibody (40×). The number of EBV DNA copies in serum was under 2.0×10^2 copies/mL (normal <200 copies/mL). Computed tomography (CT) revealed hepato-splenomegaly, ascites and bilateral pleural effusion. Bone marrow aspirate showed dyserythropoietic changes (abnormally lobulated nuclei) (Fig. 1c) and dysplastic megakaryocytes (micromegakaryocytes) (Fig. 1d). Erythrocytic precursors were 10.4% and bone marrow myeloblasts were 2.0% (Fig. 1e). Chromosome analysis showed severe complex karyotype: 54–57XY, +1[2],+3[2],+4[4],+6[4],+8[4],add(9)(p22)[2],+11[3],add(15)(p11.2)[4],add(16)(q24)[4],add(19)(p13.1)[4],add(20)(p13)[4],+21[2],2–5mar[cp4]/46,XY[8]. A diagnosis of refractory anemia with excess blasts-1 (WHO classification) was made. In addition, bone marrow examination revealed increased numbers of atypical lymphocytes (Fig. 1b) and multiple sites of active hemophagocytosis (Fig. 2a–c). Atypical lymphocytes in bone marrow were positive for CD2, CD3 (surface, cytoplasmic), CD5, CD7, CD8, HLA-DR, TCR-$\alpha\beta$, and negative for CD4. No monoclonal rearrangement of TCR beta, gamma and delta chain genes was detected by Southern blotting. These findings suggested that the atypical lymphocytes were reactive $CD8^+$ T cells. Combining fever, hemophagocytosis, splenomegaly, increased levels of ferritin and sIL-2R, a diagnosis of HLH was established. Although steroid therapy was administered for HLH, pancytopenia was not improved. Two months after the initial diagnosis, the levels of LDH and ferritin were further elevated (LDH 1,474 U/mL, ferritin 4,347 ng/mL). Bone marrow examination

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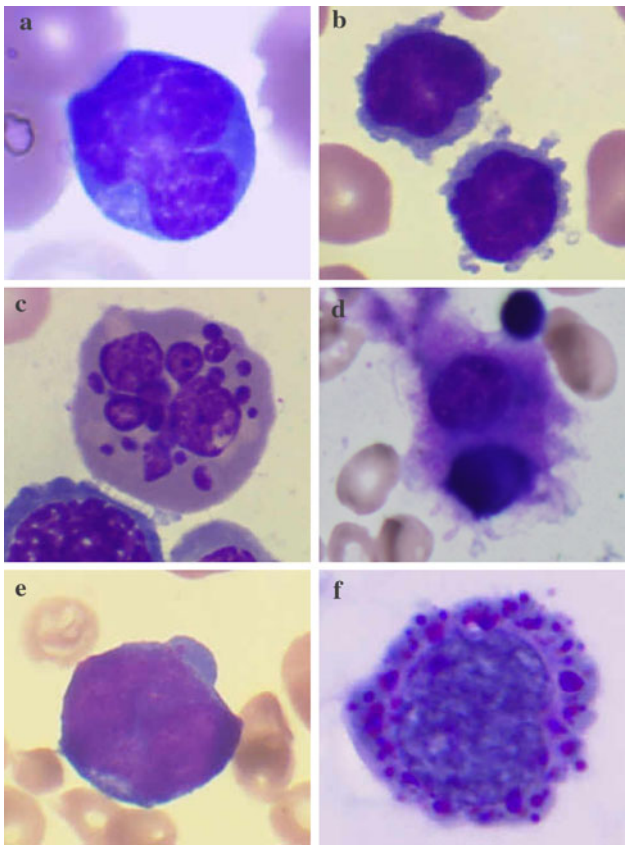

Fig. 1 Peripheral blood (**a**), and bone marrow (**b**) smear demonstrate the presence of atypical lymphocytes. Bone marrow smear, on diagnosis of RAEB-1, demonstrate the presence of erythroblast with multinuclearity (**c**), micromegakaryocytes (**d**) and myeloblast (**e**). The periodic acid-Schiff (PAS) stain, on diagnosis of RAEB-2, was positive in the erythroid precursors in a globular pattern (**f**)

revealed increased number of erythrocytic precursors (59.4%) and myeloblast (11.0%). The erythroid precursors are dysplastic with megaloblastoid nuclei or multinucleated forms. The periodic acid-Schiff (PAS) stains were positive in the erythroid precursors in a globular pattern (Fig. 1f). The erythroblasts were positive for CD7, CD13, CD33, CD117, glycophorin A (GP-A) and transferring receptor (CD71), but negative with anti-MPO. A diagnosis of refractory anemia with excess blasts-2 was made according to the WHO classification. Although induction chemotherapy consisting of aclarubicin and low dose cytarabine was administered, the patient died due to hemoperitoneum.

To our knowledge, this is the first case report of HLH associated with MDS. Although a few reports have described MDS with hemophagocytosis, hemophagocytosis is observed in blast cells [3, 4] or megakaryocytes [5], and not in active histiocytes. Therefore, previous reports were not what we call HLH. HLH can also develop during the course of malignancy related to cancer treatment and

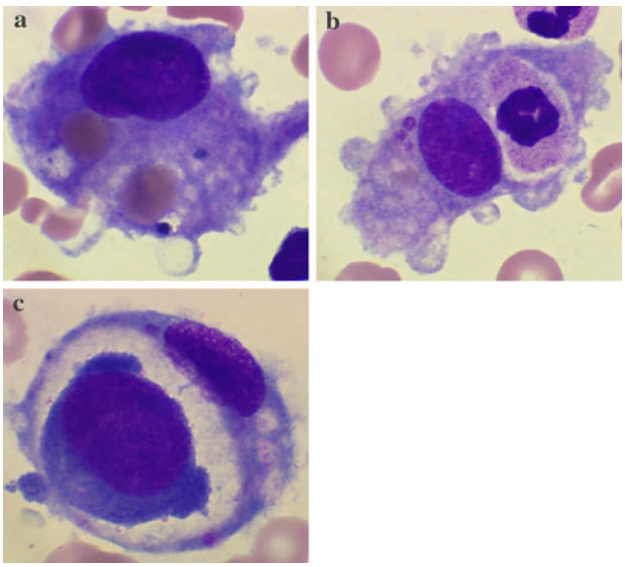

Fig. 2 The reactive histiocytes exhibit prominent phagocytosis of red cell (**a**), neutrophilic leukocyte and platelet (**b**), and erythroblast (**c**)

concomitant infections [6]. When this patient was diagnosed with MDS, five out of the eight HLH-2004 diagnosis criteria (fever, hemophagocytosis, splenomegaly, increased levels of ferritin and sIL-2R) were fulfilled. In addition, no evidence of infection, collagen disease or adverse effects of pharmacotherapy was identified. Therefore, we established a diagnosis of HLH associated with MDS.

The pathophysiology of HLH has become better defined in recent years. In primary HLH and EBV-HLH, uncontrolled lymphocyte activation induced by an abnormal immune response results in large quantities of inflammatory cytokines that promote macrophage infiltration in various tissues and can lead to tissue necrosis and organ failure [1]. The role of interferon-γ together with $CD8^+$ T cells in the development of HLH was recently demonstrated in a mouse model [7]. Patients with either FHL or secondary HLH present with severe impaired function of NK cells and cytotoxic T-lymphocyte [8, 9], although NK cell function was not impaired in this patient. The recruitment of $CD8^+$ T cells in BM was found to be related to antigen specificity in viral, autoimmune and neoplastic disease [10].

There is evidence of immune dysregulation in patients with MDS. Several studies have shown polyclonal expansion of $CD4^+$ T cells and oligoclonal or clonal expansion of $CD8^+$ T cells in the blood and bone marrow of patients with MDS [11]. In our patient, $CD8^+$ T cells in bone marrow were markedly increased, although no monoclonal rearrangement of TCR genes was detected by Southern blotting. Those abundant $CD8^+$ T cells might be involved in pathophysiology of MDS–HLH.

Further studies are required to establish the association between HLH and MDS.

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