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Hemophagocytic Lymphohistiocytosis during the Treatment of T-lymphoblastic Lymphoma

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Abstract: A 12-year-old Japanese boy presented with epigastric pain and swelling of the neck. Biopsy of the cervical lymph node and the bone marrow showed diffuse proliferation of lymphoblastic cells with precursor T-cell immunophenotypes. The patient was diagnosed with stage IV T-lymphoblastic lymphoma (T-LBL) and complete remission was successfully achieved after induction chemotherapy without any adverse events. At 10 months after diagnosis, he presented with an abrupt onset of transfusion-refractory thrombocytopenia during maintenance therapy. Bone marrow examinations revealed hypoplastic marrow with phagocytosis of the blood cells by multinucleated giant cells with foamy cytoplasm and a diagnosis of hemophagocytic lymphohistiocytosis (HLH) was confirmed. No evidence of T-LBL relapse was found by positron emission tomography. He progressed to severe bone marrow failure and underwent allogeneic stem cell transplantation (SCT) from his human leukocyte antigen (HLA)-matched brother. He achieved complete remission with partial hematological recovery. Unfortunately, the patient died from relapsed T-LBL at 6 months after SCT. The onset of HLH during childhood cancer therapy is extremely rare, but these conditions often develop chemoresistance resulting in a lethal outcome. Therefore, they may require more intensive myeloablative therapy with stem cell rescue.

Key Words: hemophagocytosis, lymphohistiocytosis, T-lymphoblastic lymphoma

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe, systemic inflammatory syndrome that can be fatal and is characterized by hyperactivation of T cells and macrophages. HLH consists of two groups: primary (or familial) HLH with specific genetic variants that directly cause HLH in infants of age less than 2 years, and secondary HLH associated with leukemia/lymphoma and the malignancies or triggered by infection (viral or bacterial) that can be seen at any age (1). Malignancy associated HLH is typically recognized at initial presentation of malignancy, mainly in patients with leukemia/lymphoma, but the onset of HLH during or after treatment of leukemia/lymphoma is very rare and an extremely unanticipated event (2, 3). We report here a case with unusual features of secondary HLH that developed during the maintenance chemotherapy for pediatric T-lymphoblastic lymphoma.

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Case Report

A 12-year-old Japanese boy presented with a one-month history of epigastric pain and non-tender swelling of the neck. Physical examinations showed bilateral cervical lymphadenopathy, splenomegaly, and an abdominal mass. Imaging studies indicated an anterior mediastinal mass, pleural effusion, and para-aortic multiple tumours without central nervous system involvement. The serum levels of soluble interleukin-2 receptors (sIL-2R) were high at 5,500 IU/mL (normal, 145-519) (Table 1). Biopsy of the cervical lymph node showed diffuse proliferation of lymphoblastic cells with the following immunophenotype: $CD2^+$/cytoplasmic $CD3^+$/$CD5^+$/$CD7^+$/$CD4^-$/$CD8^-$. Initial bone marrow examination showed infiltration of the marrow by blast cells. There was no hemophagocytosis in the marrow smear. The patient was diagnosed with stage IV T-lymphoblastic lymphoma (T-LBL) and was treated with induction

Table 1. Laboratory findngs of the patient

	unit	at diagnosis of T-LBL	at the onset of HLH
RBC	x $10^6/\mu L$	4.38	4.1
Hb	g/dL	13.1	12.4
Ht	%	37.6	37.1
WBC	x $10^3/\mu L$	8.57	1.7
neutrophils	x $10^3/\mu L$	3.15	1.2
lymphocytes	x $10^3/\mu L$	4.58	0.2
blast cells	x $10^3/\mu L$	0	0
PLT	x $10^3/\mu L$	170	65
PT	%	82.7	93.0
APTT	sec	31.1	33.6
Fib	mg/dL	403	457
FDP	μg/mL	5.0	7.8
D-dimer	μg/mL	1.97	1.29
BUN	mg/dL	12	7
Cre	mg/dL	0.60	0.65
UA	mg/dL	4.9	6.3
LDH	U/L	451	399
AST	U/L	43	22
ALT	U/L	97	29
T-Chol	mg/dL	88	167
TG	mg/dL	55	102
CRP	mg/dL	1.26	5.96
Ferritin	ng/mL	50	1,219
sIL-2R	U/mL	5,500	486

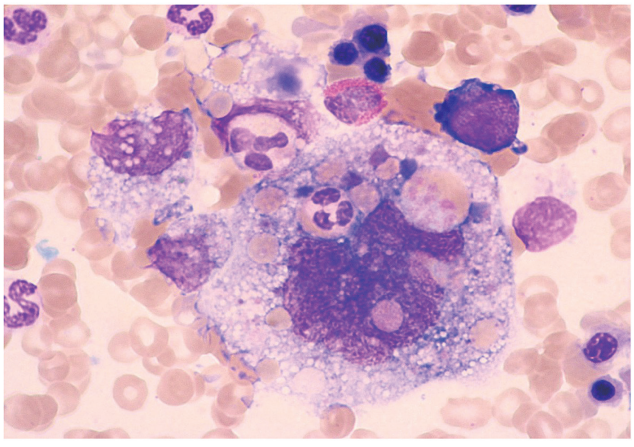

Figure 1. Bone marrow aspirate: a hemophagocytic macrophage (arrow) showing phagocytosis of leukocytes, erythrocytes, platelets, and other cellular debris by multinucleated giant cell with foamy cytoplasm (May-Grünwald-Giemsa stain, original magnification x1000).

chemotherapy that was comprised of prednisolone (PSL), cyclophosphamide (CPA), vincristine (VCR), daunorubicin, and *Escherichia coli*-asparaginase (L-Asp). After induction chemotherapy, a complete remission was successfully obtained without any adverse events.

At 10 months after diagnosis, he presented with an abrupt onset of transfusion-refractory thrombocytopenia during maintenance therapy with PSL, CPA, VCR, L-Asp, and mercaptopurine. Serum anti-platelet antibodies were negative. Serum sIL-2R levels (486 IU/mL) were within the normal range. Epstein-Barr virus and cytomegalovirus DNA in plasma were undetectable with the polymerase

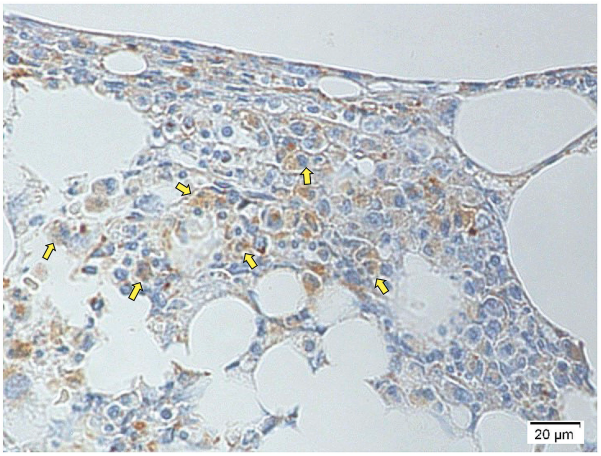

Figure 2. Bone marrow biopsy: increased numbers of $CD68^+$cells (CD68 stain for macrophages/histiocytes with hematoxylin stain). Arrows indicate $CD68^+$ hemophagocytic macrophages. A bar represents 20 μm.

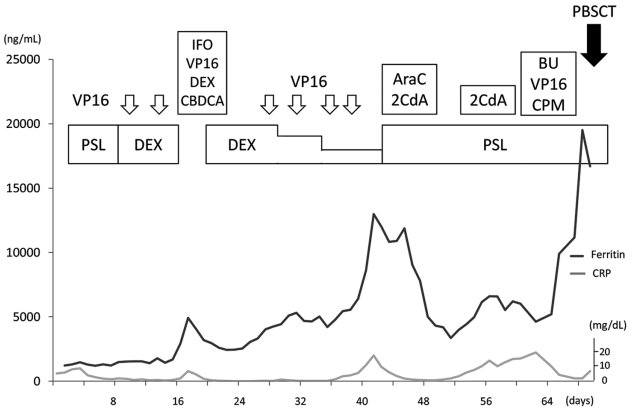

Figure 3. Combined use of chemotherapeutic agents for the treatment of HLH with allogeneic stem cell transplantation: Serum levels of ferritin and C-reactive protein (CRP) are shown as indicators of disease progression in HLH. *VP-16: etoposide; PSL: prednisolone; DEX: dexamethasone; IFO: ifosfamide; CBDCA: carboplatin; AraC: cytarabine; 2CdA: cladribine; BU: busulfan; CPM: cyclophosphamide; PBSCT: peripheral blood stem cell transplantation*

chain reaction. Repeated bone marrow examinations revealed hypoplastic marrow with phagocytosis of leukocytes, erythrocytes, platelets, and other cellular debris by multinucleated giant cells with foamy cytoplasm (hemophagocytic macrophages) (Figure 1), in addition to visually increased numbers of macrophages expressing the $CD68^+$ antigens (CD68 stain in Figure 2). A diagnosis of HLH was confirmed. No evidence of T-LBL relapse was found by 18F-fluorodeoxyglucose positron emission tomography (18FDP-PET). He did not respond to initial treatment with dexamethasone and etoposide, but partially responded to subsequent treatment with a combination of cytarabine and cladribine (Figure 3). Thereafter, he progressed to severe bone marrow failure and underwent allogeneic stem cell transplantation (SCT) from his human leukocyte antigen (HLA)-matched brother. He achieved complete remission with partial hematological recovery. The patient died from relapsed T-LBL at 6 months after SCT.

Discussion

Most of patients with HLH show persistent high-grade fever, pancytopenia, coagulation abnormality, liver dysfunction, and proliferation of hemophagocytic macrophages in the bone marrow, lymph nodes, spleen, and liver (1). In the present case, HLH developed during the maintenance chemotherapy with unusual features; sudden onset of transfusion-refractory thrombocytopenia, absence of fever, no lymphadenopathy nor lymph node accumulation on 18FDP-PET, and low levels of serum sIL-2R, while abundant hemophagocytic macrophages in the bone marrow. These conditions could be described as "clinically silent HLH", and therefore early diagnosis might be delayed by misinterpretation as chemotherapy-induced myelosuppression.

The onset of histiocytic disorders during childhood cancer therapy is extremely rare, but often has a lethal outcome (2, 3). The data from registry of the Berlin-Frankfurt-Munster (BFM) - acute lymphoblastic leukemia (ALL) trials from 1981-2001 showed that 4 out of 971 T-ALL patients developed HLH and none of them survived (2). The precise pathophysiology of HLH with this poor prognostic outcome must be clarified. In most cases, these conditions are resistant to conventional chemotherapy, and they therefore require more intensive myeloablative therapy with stem cell rescue (4).

Competing Interests

The authors have no competing interests.

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