

Case Report

## A Case of Refractory Langerhans Cell Histiocytosis Complicated with Hemophagocytic Lymphohistiocytosis Rescued by Cord Blood Transplantation with Reduced-intensity Conditioning

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We diagnosed a female infant with Langerhans cell histiocytosis (LCH) who was refractory to conventional chemotherapy. She showed refractory inflammation that was complicated with hemophagocytic lymphohistiocytosis (HLH) during LCH chemotherapy; therefore, we changed the protocol to HLH2004 (dexamethasone, cyclosporine A and VP16). However, there were no signs of hematological recovery. We therefore performed cord blood transplantation with reduced-intensity conditioning, and she achieved complete remission for over 2 years. As salvage therapy for refractory LCH, hematopoietic stem cell transplantation may be a good therapeutic choice, especially when LCH is complicated with HLH.

**Key words:** langerhans cell histiocytosis (LCH), hemophagocytic lymphohistiocytosis (HLH), hematopoietic stem cell transplantation (HSCT), reduced-intensity conditioning (RIC), refractory

Langerhans cell histiocytosis (LCH) is a rare disease with various clinical presentations from localized to disseminated features. Patients with multisystem LCH who are very young at onset with risk organ involvement, or whose disease is refractory to conventional chemotherapy, have shown poor outcomes [1,2]. For these high-risk patients, 2-CdA or clofarabine is administered as a rescue therapy [3,4]; the alternative approach is allogeneic stem cell transplantation (HSCT). Several reports have suggested that HSCT with reduced-intensity conditioning (RIC) improved the outcome of LCH patients [5-9].

Hemophagocytic lymphohistiocytosis (HLH) is also a rare complication of LCH. Although there have been only a few reports on LCH patients complicated with

HLH, the prognosis seems to be very poor when HLH occurs in refractory LCH patients [10].

We report the case of an infant with multisystem LCH complicated with HLH who was refractory to chemotherapy, but was successfully treated by cord blood transplantation (CBT) with RIC. The benefits of CBT with the RIC regimen are discussed.

### Case Report

A one-year-old girl exhibited a recurrent fever refractory to antibiotics with left cervical lymphadenopathy as well as a skin rash on her head lasting five months. She was admitted to our hospital for further examination and treatment. At admission, she had a high fever with tachypnea and tachycardia. Physical

Table 1 Blood examination on admission

WBC	5,410 / $\mu$ l	TP	4.4 g/dl
Neu	41 %	Alb	2.1 g/dl
Hb	5.9 g/dl	T.Bil	0.59 mg/dl
Plt	22.5 $\times 10^4$ / $\mu$ l	D.Bil	0.09 mg/dl
		AST	9 U/l
Fibbg	649 mg/dl	ALT	2 U/l
PT-INR	1.27	ALP	197 U/l
AT3	62 %	$\gamma$ GTP	9 U/l
FDP	10.1 $\mu$ g/ml	CHE	45 U/l
		LD	168 U/l
sIL2-R	5,410 U/ml	UN	6.4 mg/dl
Type 4 collagen	4.2 ng/dl	CRTN	0.19 mg/dl
Hyaluronic acid	94.8 ng/dl		
AFP	2.5 ng/dl	T.Cho	127 mg/dl
		TG	131 mg/dl
		ferritin	169.1 ng/dl
		CRP	10.7 mg/dl

Blood test of the patient on admission. Abnormal data represented by **thick letters**. It showed severe anemia, coagulopathy, elevation of CRP, and hypoalbuminemia. Soluble IL-2 receptor and liver fibrotic marker levels were elevated.

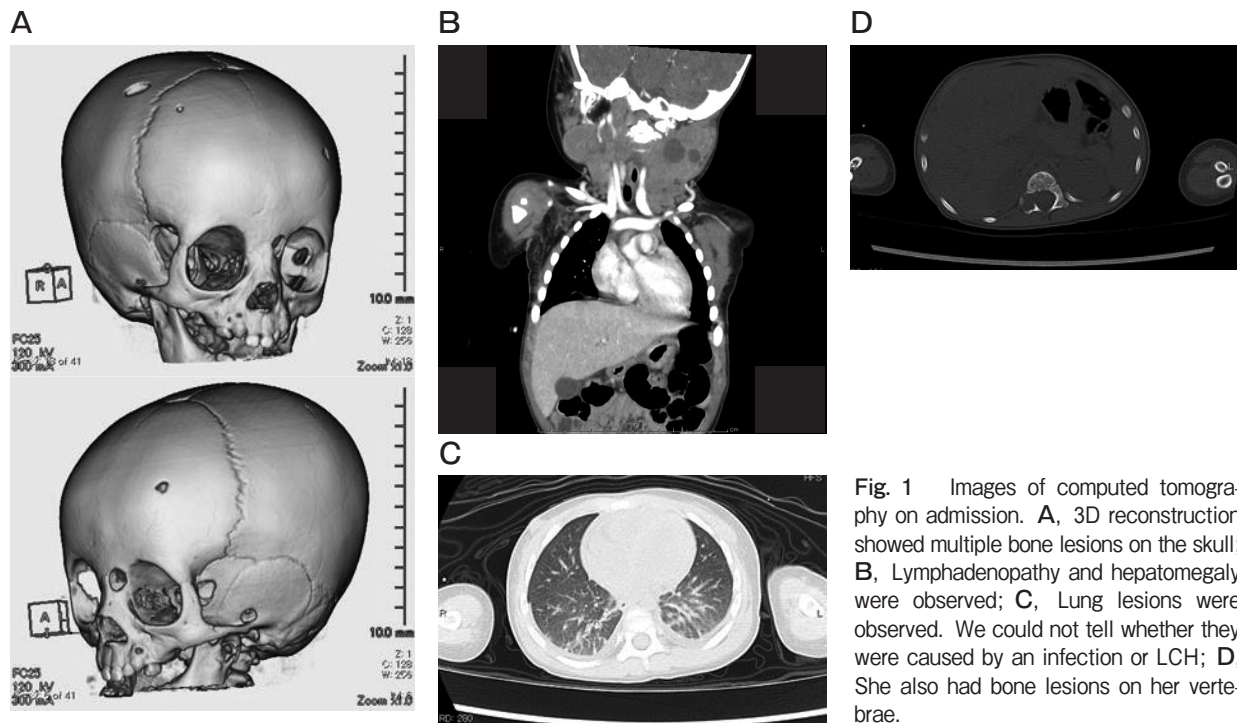
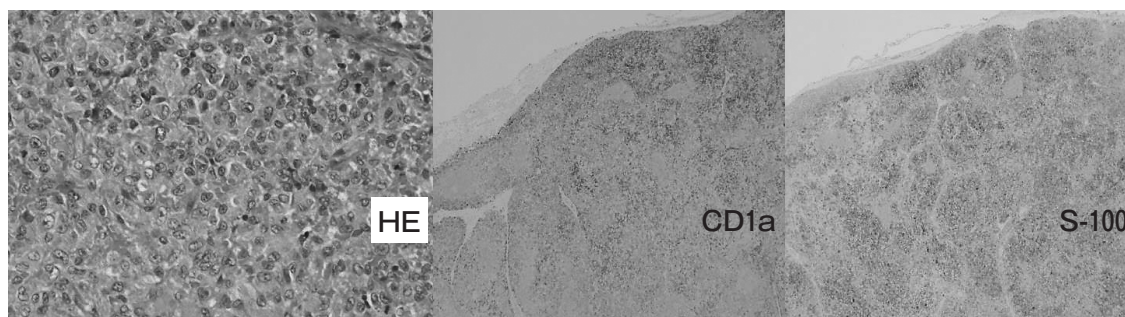


Fig. 1 Images of computed tomography on admission. **A**, 3D reconstruction showed multiple bone lesions on the skull; **B**, Lymphadenopathy and hepatomegaly were observed; **C**, Lung lesions were observed. We could not tell whether they were caused by an infection or LCH; **D**, She also had bone lesions on her vertebrae.

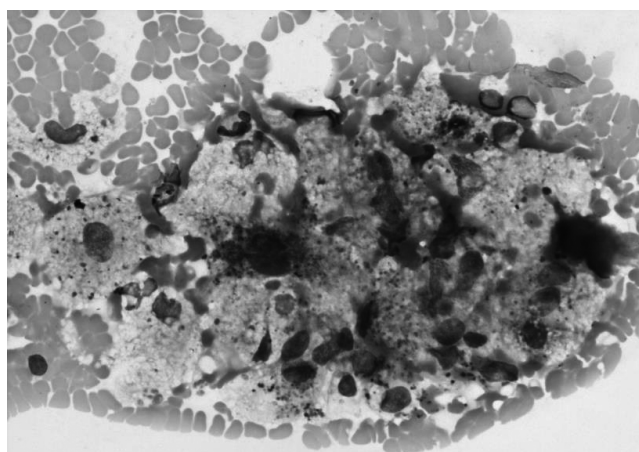
examination revealed bilateral massive cervical lymphadenopathy, hepatomegaly, skin rash of bilateral postauricular lesions and inguens. Her blood test showed severe anemia, coagulopathy, elevation of

C-reactive protein, and hypoalbuminemia. Soluble IL-2 receptor and liver fibrotic marker levels were elevated (Table 1). Computed tomography showed massive cervical lymphadenopathy, hepatomegaly, and

### A. Patho-histologic examination of cervical lymph node



### B. Bone marrow aspiration; May-Grunwald Giemsa staining (onset of HLH)



**Fig. 2** **A.** Patho-histologic examination of the cervical lymph node on admission. The normal lymphatic tissue was replaced with a proliferation of polymorphic and dysplastic abnormal cells stained positively with S100 and CD1a. **B.** Bone marrow aspiration at the onset of hemophagocytic lymphohistiocytosis. May-Grunwald Giemsa staining was performed.

infiltration of the lower lung area (Fig.1). Multiple punched-out bone lesions were observed on the temporal bone, orbit, vertebra, and pelvis. Bone marrow aspiration resulted in a dry tap. Abnormal cells with rich cytoplasm were observed on the smear sample, but there was no sign of hemophagocytosis. Patho-histologic examination of a cervical lymph node revealed a proliferation of polymorphic and dysplastic abnormal cells stained positively with S100 and CD1a, which had replaced the normal lymphatic tissue. From these results, the patient was diagnosed with LCH (Fig.2A).

We started administration of prednisolone (PSL) and chemotherapy following the Japan LCH Study Group (JLSG)-02 induction A protocol [1]. She returned to an afebrile state, and the lymphadenopathy was gradually reduced; however, the skin rash and hepatomegaly were still present. After 3 weeks, she

developed recurrent fever with pancytopenia, elevation of serum ferritin, biliary enzyme, and progressive coagulopathy (Table 2). Bone marrow aspiration revealed massive hemophagocytosis and hypocellular marrow (Fig.2B). Epstein-Barr virus and cytomegalovirus were negative on RT-PCR. We diagnosed her with secondary HLH following LCH, and changed the protocol to HLH2004 (dexamethasone, cyclosporine A and VP16) [11]. After 1 month, her peripheral ferritin level was around 800 ng/ml, and neutropenia continued. She achieved an afebrile state only with the use of acetaminophen for pain control. Hemophagocytosis was observed in her bone marrow, and there was no sign of normal hematopoiesis; therefore, we considered performing HSCT (Fig.3). She had no HLA-matched related donor, and received 8/8 HLA-matched cord blood transplantation (CBT) with RIC. We chose fludarabine (Flu; 180 mg/sqm) and mel-

Table 2 blood examination at the onset of HLH

WBC	<b>960</b> / $\mu$ l	TP	3.7 g/dl
Neu	4 %	Alb	2.0 g/dl
Hb	<b>6.9</b> g/dl	T.Bil	1.31 mg/dl
Plt	<b>13.3</b> $\times 10^4$ / $\mu$ l	D.Bil	0.49 mg/dl
		AST	5 U/l
Fibg	<b>919</b> mg/dl	ALT	2 U/l
PT-INR	1.25	ALP	U/l
AT3	<b>81</b> %	$\gamma$ GTP	9 U/l
FDP	<b>5.3</b> $\mu$ g/ml	CHE	18 U/l
		LD	80 U/l
sIL2-R	<b>2,492</b> U/ml	UN	7.9 mg/dl
EBV-PCR	0 Copies/ $\mu$ gDNA	CRTN	0.14 mg/dl
CMV-PCR	0 Copies/ $\mu$ gDNA	T.Cho	mg/dl
		TG	188 mg/dl
		ferritin	897.5 ng/dl
		CRP	13.2 mg/dl

Blood test of the patient on admission. Abnormal data represented by **thick letters**. It showed rapidly progressed anemia and neutropenia, elevation of CRP, ferritin, and soluble IL-2 receptor. It also showed hypoalbuminemia. No evidence of reactivation of EBV nor CMV.

phalan (L-PAM; 140 mg/sqm) as the conditioning regimen. We also intensified the conditioning with antithymocyte globulin (ATG; 2.5 mg/kg) and low-dose cyclophosphamide (CY; 100 mg/sqm) as immunosuppressants. Successful engraftment was confirmed by bone marrow examination on day 33, and short tandem repeat revealed over 95% donor type. After neutrophil engraftment, we gradually reduced PSL dosage, and there was no sign of refractory fever or hemophagocytosis. Stage 1 skin rash was the only symptom of graft-versus host disease. Neither virus reactivation nor fungal infection was observed. She was discharged 3 months after CBT, and no recurrence of LCH or HLH has been observed during a follow-up of more than 2 years.

## Discussion

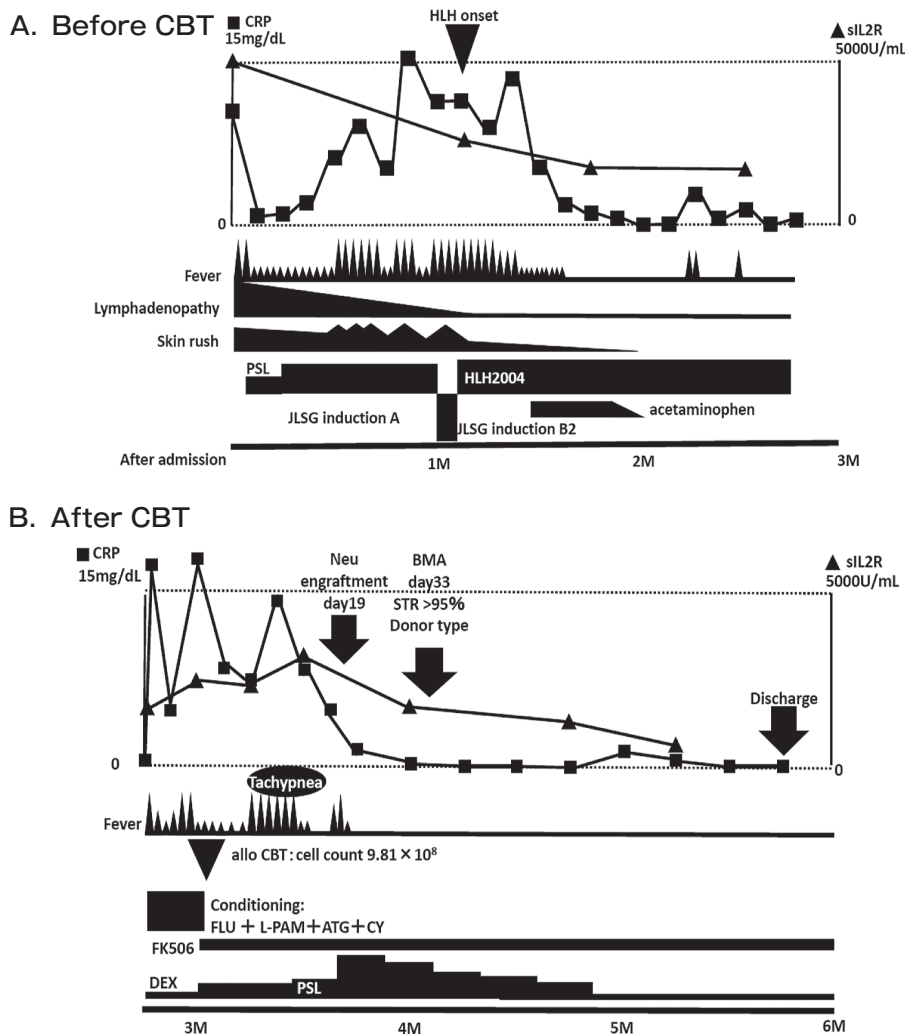
LCH is a rare clonal disorder characterized by the proliferation and accumulation of clonal CD1a-positive immature dendritic cells, accompanied by the infiltration of various inflammatory cells [1,2]. The clinical presentation of LCH is highly variable, ranging from benign localized to disseminated aggressive disease, which may be fatal. Patients under 2 years of age at onset who have involvement of one or more 'risk organs' including the hematopoietic system, liver, spleen, and lung, or are refractory to conventional che-

motherapy have a poor outcome with a survival rate of less than 30% at 2 years [5].

Macrophage activation and secondary HLH are rarely reported in association with LCH. Blaise *et al.* reviewed 30 LCH cases that had pathological signs of macrophage activation [10]. They concluded that multisystem LCH and young age are factors for macrophage activation. Of the 7 patients who had fully developed HLH, 4 died. Therefore, the complication of HLH might increase the mortality rate of high-risk LCH [10].

In our patient, high risk organs such as the liver, bone marrow, and lung were involved. She also had suffered inflammation, her disease was refractory to conventional chemotherapy, and finally she developed HLH during the clinical course. After one month of HLH 2004 therapy, she could not achieve remission of LCH or HLH. She had hypertension and hyperglycemia as complications of the diseases and therapies, suggesting the progression of endothelial disorder. We expected that her prognosis would be very poor; therefore, we planned salvage HSCT as soon as possible.

Several studies have described the application of HSCT for refractory LCH. In those reports, myeloablative conditioning appears to be related with high treatment-related-mortality rate [5,9]. However, other reports have suggested that HSCT with RIC could be a promising salvage therapy for refractory LCH [5-9]. Kudo *et al.* reported that HSCT with a Flu+L-PAM



**Fig. 3** Clinical course after admission. **A.** Before transplantation. **B.** After transplantation. CBT, cord blood transplantation; PSL, prednisolone; JLSG, Japan Langerhans Cell Histiocytosis Study Group; HLH, hemophagocytic lymphohistiocytosis; sIL2R, soluble IL-2 receptor; DEX, dexamethasone; Neu, neutrocyte; BMA, bone marrow aspiration; STR, short tandem repeat; FLU, fludaurine; L-PAM, melphalan; ATG, antithymocyte globulin; CY, cyclophosphamide.

regimen was safely and successfully performed in 15 refractory LCH patients [7]. We chose cord blood stem cell transplantation; therefore, we intensified the conditioning with ATG and low-dose CY as an immunosuppressant to avoid engraftment failure. Fortunately, our patient had no severe complications with HSCT, showed successful engraftment, and has been in complete remission for over 2 years.

In conclusion, immune system recovery by HSCT with RIC may be a treatment option for refractory LCH with HLH. HSCT with RIC as a possible salvage therapy for refractory LCH should be considered.

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