

Case Report

Remission of Congenital Multi-system Type Langerhans Cell Histiocytosis with Chemotherapy

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Patients with multi-system (MS)-type langerhans cell histiocytosis (LCH) show poor outcomes, especially congenital MS LCH cases were shown in high mortality rate. We experienced a congenital case of MS LCH with high risk organs, who needed intensive respiratory support after birth. Even though intensive chemotherapy was discontinued, this patient's lung LCH lesions gradually became reduced and his respiratory condition recovered; therefore, we restarted and completed maintenance chemotherapy. The patient maintained complete remission for more than 4 years after the end of chemotherapy. Our case suggests that congenital MS LCH even with severe organ involvement can be treated successfully with chemotherapy.

Key words: Langerhans-cell histiocytosis, congenital, multisystem type

Langerhans cell histiocytosis (LCH) is a clonal disorder characterized by the proliferation of Langerhans cells in various organs, which results in several types of tissue damage. In general, LCH is classified as the single-system (SS)-type or multi-system (MS)-type based on the number of infiltrated organs. SS-type patients have unifocal or multifocal involvement in one organ, such as bones, skin, lymph nodes, or lungs. On the other hand, MS-type patients exhibit the involvement of two or more organs. They require chemotherapy and show a 5-year overall survival rate of 99-100% for those without risk organs such as the liver, spleen, or bone marrow [1-3]. The involvement of risk organs such as the hematopoietic system, liver, and/or spleen show a poor prognosis; furthermore, a poor response to initial chemotherapy results in fetal outcome [1-3]. The majority of congenital cases include the

skin region and show spontaneous remission; this type of LCH is called "congenital self-healing LCH" or "Hashimoto-Pritzker disease", but these cases are usually limited to skin involvement [4,5]. Congenital MS-type cases have rarely been reported, and the majority of them were fetal [6-8].

We present here a congenital case of MS LCH with risk organs who required intensive respiratory care because of bilateral multiple lung involvement. Even though induction chemotherapy was not completed, the lung disease gradually resolved; therefore, the patient re-started maintenance chemotherapy and maintained remission without relapse for more than 4 years after the end of chemotherapy. This case might suggest that congenital MS LCH even with critical organ involvement could be cured with chemotherapy.

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Case

A male infant was born at 38 weeks and 6 days' gestation after an uncomplicated pregnancy. He was born at 2,684 g with Apgar scores of 9 (1 min) and 10 (5 min). He had various types of dermatosis, such as ulcers, crust, and abscess at birth. His blood test showed no cytopenia and no elevation of liver function. The soluble IL-2 receptor and KL-6 levels were elevated (Table 1). A skin biopsy was performed, and a pathological examination showed a proliferation of aberrant cells, which had vesicles and kidney-shaped nuclei. Immunohistochemistry showed that these cells were positive for CD1a and S-100 protein, but negative for CD68. Therefore, the patient was given a diagnosis of LCH. Computed tomography (CT) showed disease involvement in the bilateral lungs, liver, spleen, cranial bones, thymus gland, and skin lesions noted above (Fig. 1). Because the LCH lesions infiltrated and damaged the lungs rapidly, the patient was transferred to another hospital for chemotherapy.

Chemotherapy was started according to the Japan LCH Study Group (JLSG)-02 induction A protocol (Fig. 2A) [3]. Prednisolone was switched to dexamethasone palmitate with the expectation of better migration to the LCH lesions. The dose of dexamethasone palmitate was determined according to the HLH-2004 protocol [9]. Three days after the start of the chemotherapy, pulmonary bulla and bleb from the LCH lung lesions caused pneumothorax, and artificial ventilation was required. Then, the patient suffered from pneumonia with neutropenia and his respiratory status became worse. Therefore, chemotherapy was discontinued (Fig. 2B). Despite the discontinuance of chemotherapy, his respiratory status gradually improved with a decrease in lung disease, and he was extubated after 2

months of intensive supportive care. He was admitted to our hospital to restart chemotherapy.

At the time of admission, his SpO₂ was 100% with ambient air, and his other vital signs were normal. On physical examination, he had many types of skin rashes and fine crackles at auscultation bilaterally. Laboratory data were normal. Plain chest CT showed multiple cystic lesions and no pneumothorax (Fig. 3A). We started chemotherapy according to the JLSG-02 maintenance C protocol. The maintenance C protocol comprised vin-

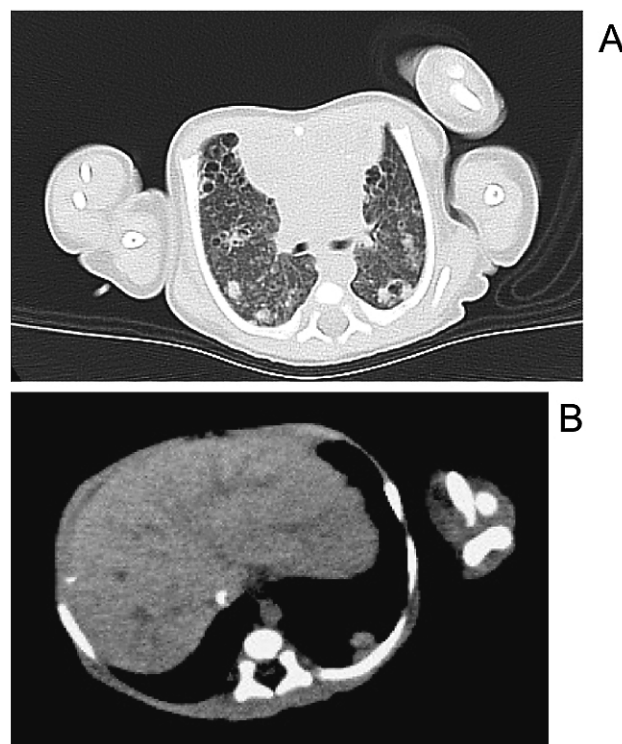


Fig. 1 Images of computed tomography (CT) at diagnosis. **A**, LCH lung lesions made multiple nodules and cysts; **B**, CT revealed hepatomegaly.

Table 1 blood examination data at initial diagnosis

WBC	6,600/ μ L	TP	5.8 g/dL	LDH	367 U/L
Neut	85.0 %	Alb	3.4 g/dL	UN	4 mg/dL
Ly	4.0 %	T-bil	12.2 mg/dL	Cre	0.48 mg/dL
Mo	11.0 %	ALP	464 U/L	ferritin	212.2 ng/mL
RBC	450×10^4 / μ L	AST	26 U/L	KL-6	550 U/mL
Hb	16.0 g/dL	ALT	9 U/L	sIL-2R	1,710 U/mL
Plt	26.1×10^4 / μ L	γ -GT	85 U/L	CRP	1.20 mg/dL

WBC, white blood cell; Neut, neutrophil; Ly, lymphocyte; Mo, monocyte; RBC, red blood cell; Hb, hemoglobin; Plt, platelet; TP, total protein; Alb, albumin; T-bil, total bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ -GT, γ -glutamyltransferase; LDH, lactate dehydrogenase; UN, urea nitrogen; Cre, creatinine; KL-6, glycoprotein Krebs von den Lungen-6; sIL-2R, soluble interleukin-2 receptor; CRP, C-reactive protein.

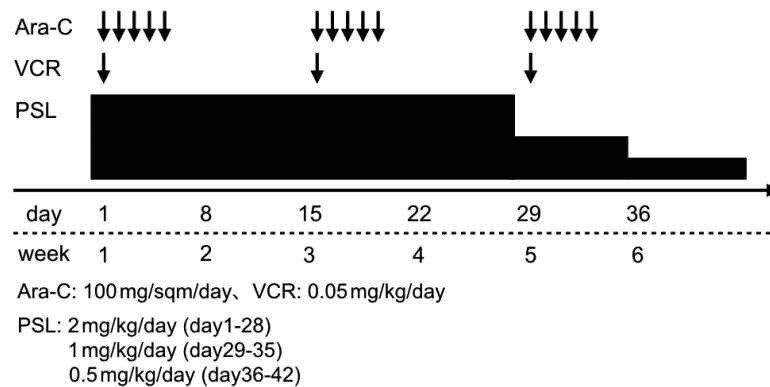


Fig. 2A Japan Langerhans Cell Histiocytosis Study Group (JLSG)-02 induction chemotherapy protocol A.

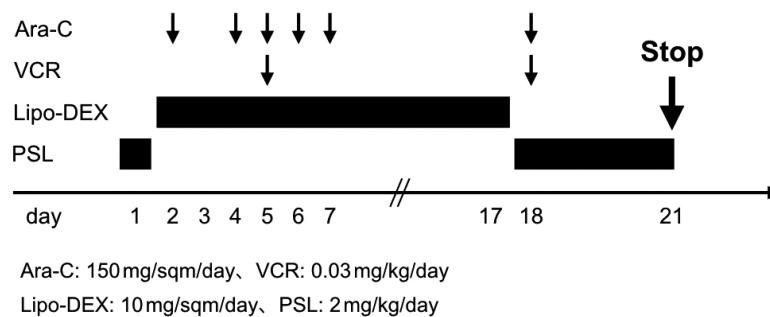


Fig. 2B Induction chemotherapy course for this case. Ara-C, cytarabine; VCR, vincristine; Lipo-DEX, dexamethasone palmitate; PSL, prednisolone.

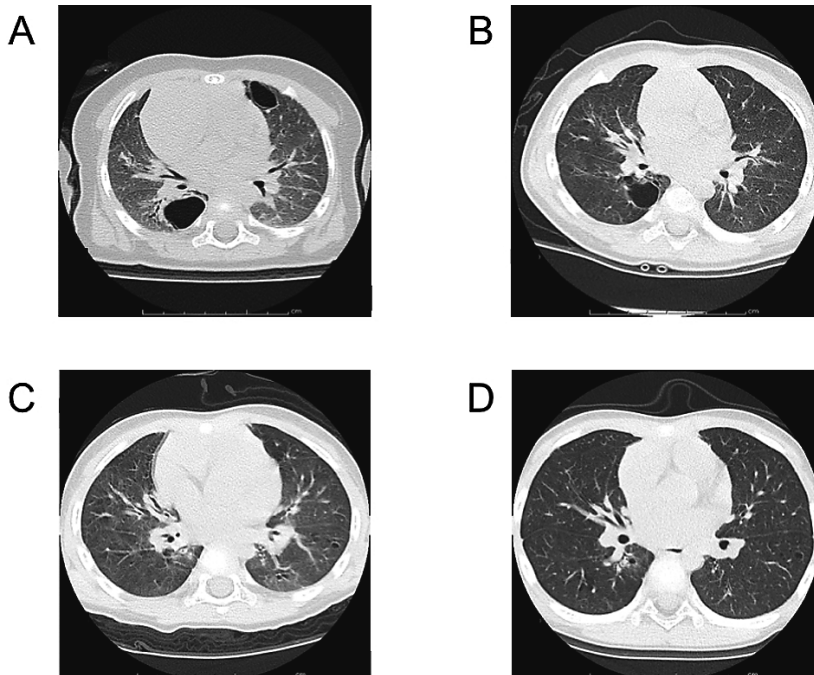


Fig. 3 A, CT shows multicystic lesions; B, C, D, LCH lung lesions gradually improved with supportive care.

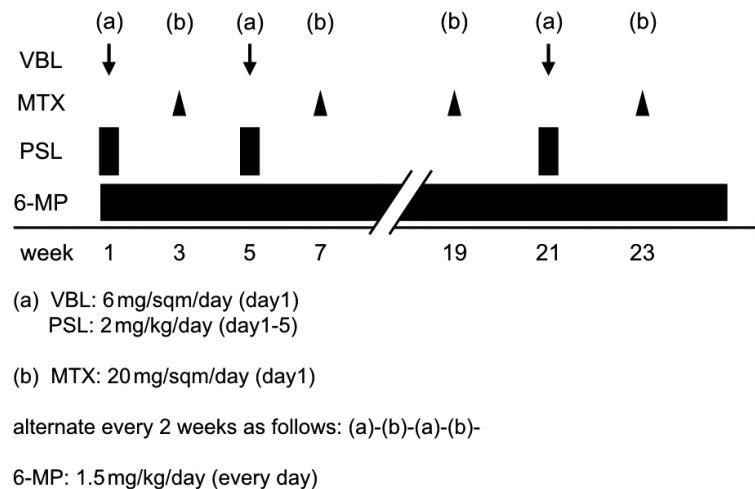


Fig. 4 Japan Langerhans Cell Histiocytosis Study Group (JLSG)-02 maintenance C protocol regimen. VBL, vinblastine; PSL, prednisolone; MTX, methotrexate; 6-MP, 6-mercaptopurine.

blastine, prednisolone, methotrexate and daily oral administration of 6-mercaptopurine. The maintenance C regimen lasts for 24 weeks (Fig. 4). He had no critical adverse events and finished approximately 6 months of maintenance chemotherapy. At the time of chemotherapy completion, lung cystic lesions remained, as shown by chest CT (Fig. 3B), and the other organ involvements were diminished.

The cystic lesions had spontaneously decreased 4 months after the end of maintenance therapy (Fig. 3C). At present, his lung cystic lesions have almost disappeared on CT at 4 years after the end of chemotherapy (Fig. 3D).

Discussion

Systemic chemotherapy for MS LCH improves the prognosis, but the mortality rate of patients with risk organ involvements remains high at 16-38% [1-3]. Recent studies have shown the importance of therapeutic intensification and prolongation to improve the outcome of MS LCH [2, 3].

Congenital MS LCH cases are rarely reported and are often fetal [6-8]. We suspected that chemotherapy could not be started because patient's condition would be worse in several unreported congenital MS LCH cases. Our congenital case also had several risk organ involvements and multiple lung lesions from birth. We started chemotherapy, but adverse respiratory events during induction chemotherapy led to the discontinua-

tion of chemotherapy at the early stage (Fig. 2B). Then, his lung lesions gradually regressed unexpectedly without any chemotherapy. After that, the improvement of the lung lesions continued under maintenance chemotherapy kept, and they appeared to have disappeared on chest CT.

LCH cases with spontaneous regression have been reported, but many of them were congenital skin-localized LCH [4, 5] or adult lung LCH related to smoking [10]. It is considered that MS LCH cases with risk organ inevitably need intensive chemotherapy, so our case presented an unusual clinical course. We suspected that the initial 3 days of induction chemotherapy with dexamethasone, cytarabine and vincristin was effective for this case and resulted in pneumothorax, and the patient needed artificial ventilation transiently. The recommended intensity of chemotherapy for congenital MS-LCH remains unknown, but mild chemotherapy such as steroid alone or supportive therapy alone would not be adequate to prevent disease progression. As a sequel to induction chemotherapy, maintenance chemotherapy was restarted, and remission has been maintained without relapse.

Recently, a recurrent *BRAF*-V600E gene mutation has been identified in LCH cases. The *BRAF*-V600E mutation is reported to be associated with high-risk clinical features, high risk of relapse, and poor response to chemotherapy [11]. In this case, we did not assess the *BRAF*-V600E mutation because initial samples were not available for *BRAF* mutation analysis. On

the other hand, one congenital benign LCH case was reported to have the *BRAF*-V600D mutation [12]. Further genetic study will be needed.

In conclusion, our case suggests that congenital MS LCH cases even with risk organ could be cured by chemotherapy. Further study of the prognostic factors and treatment intensity for congenital MS LCH is needed.

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