J Clin Exp Hematopathol
Vol. 52, No. 2, Oct 2012

Case Study

Rapidly Progressing Fatal Adult Multi-Organ Langerhans Cell Histiocytosis Complicated with Fatty Liver Disease

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Langerhans cell histiocytosis (LCH) is a clonal neoplasm that shows diverse clinical manifestations and courses of disease progression. The etiology and pathophysiology of LCH remain uncertain. We describe the clinical course of a 23-year-old Japanese woman with multi-system LCH, who showed rapid progression after steroid reduction and developed multi-organ failure. Liver biopsy showed LCH infiltration with fatty degeneration. She was treated with cytarabine, vincristine, and prednisolone according to the Japan LCH study group 02 protocol, without any clinical improvement. Low expression of Ki67 and bcl-2 failed to explain the rapid clinical course. Panhypopituitarism and hypothalamic dysfunction may have caused nonalcoholic fatty liver disease and liver failure. This case indicates that some multi-system LCH patients with hypopituitarism and hypothalamic dysfunction show very rapid progression and are difficult to treat. 〔*J Clin Exp Hematopathol 52(2) : 121-126, 2012*〕

Keywords: Langerhans cell histiocytosis, hypopituitarism, hypothalamic dysfunction, nonalcoholic fatty liver disease

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a neoplastic disease of Langerhans-type cells, with the exception of smoking-related adult pulmonary LCH, which is identified by an assay of the human androgen-receptor gene locus[1,2] and BRAF mutation.[3] LCH occurs in about 5 people per million, and usually affects those younger than 10 years. Adult-onset LCH may reach 1-2 cases per million, and the mean age at LCH diagnosis is 30 years.[4,5] General symptoms are fever, weight loss, loss of appetite, asthenia, and night sweats. Diabetes insipidus (DI) is a hallmark of central nervous system involvement. LCH has a broad spectrum of clinical behaviors, from spontaneous regression to a fatal outcome, and the nature of LCH remains controversial. LCH cells have lost their ability to present antigens without stimulation by CD40. Histologically, LCH cells are characterized by their prominent cleaved nucleus with a pale cytoplasm, and are characteristically immunoreactive for CD1a, langerin (CD207), S-100 protein, and CD11. In addition, the cells are positive for vimentin, CD68, and HLA-DR. CD45 expression and the lysozyme content are low. Positivity for CD1a and/or langerin is the current standard for the diagnosis of LCH.[6,7]

LCH is divided into single-system LCH (SS-LCH) and multi-system LCH (MS-LCH), and MS-LCH is subdivided into a high-risk group, involving one or more risk organs, and a low-risk group, without involvement of risk organs. When LCH infiltrates into a risk organ, such as the liver, spleen, and bone marrow, the prognosis is poor. Liver dysfunction is the poorest prognostic factor.[8] According to a published report on 274 adult patients, the probability of survival 5 years after diagnosis was 92.3% overall, 100% for single-system disease, 87.8% for isolated pulmonary disease, and 91.7% for multi-system disease.[5] The treatment of adult-onset MS-LCH is multi-drug combination chemotherapy, depending on the involvement of risk organs and clinical course. In child cases, there have been three large-scale randomized control trials (RCT), and the treatment of the disease has been established to some extent.[9–11] On the other hand, in adult cases, optimal treatment has not been established, and the treatment strategy is employed referring to child cases.[4–5,8,12,13]

We herein present a case of adult-onset MS-LCH, which rapidly progressed to multi-organ failure after steroid reduction and showed no improvement despite combination chemotherapy.

Received : March 31, 2012
Revised : May 29, 2012
Accepted : June 25, 2012
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CASE REPORT

A 23-year-old Japanese woman had a one-year history of malaise, menoxenia, polyposia, and polyuria, and an 8-month history of intermittent fever, temporal headache, and hypothyroidism. Her body weight increased from 45 to 61 kg over one year. She had never smoked or drunk alcohol. No family history was present. She went to a local hospital with worsening malaise and headache. Magnetic resonance imaging of the brain with contrast demonstrated a 2-cm-diameter mass in the suprasellar area that appeared hyperintense on T_1-weighted images and isointense on T_2-weighted images (Fig. 1A). She was transferred to our hospital for further treatment. Laboratory tests showed panhypopituitarism, hypertriglyceridemia, and elevated liver enzymes (Table 1). Abdominal ultrasound or computed tomography (CT) scan was not performed at this time. An endoscopic biopsy of the suprasellar lesion showed the diffuse infiltration of histiocytes with negative staining for glial fibrillary acidic protein, placental alkaline phosphatase, and p53 accompanied by T and B cells. CD1a or S-100 protein staining was not performed at this time, so a conclusive diagnosis was not made, but lymphocytic hypophysitis was suspected. The patient had also been diagnosed with DI, and she was started on treatment with desmopressin acetate, prednisolone at 20 mg, hydrocortisone, levothyroxine sodium, and fibrate. Subsequently, the mass began to shrink, so the prednisolone was tapered and discontinued at 6 months (Fig. 1B).

Five months after the steroid therapy was discontinued, the patient started to have intermittent fever again, and the mass of the suprasellar lesion was found to have enlarged (Fig. 1C). Hydrocortisone was changed to prednisolone at 20 mg. Despite the initiation of steroid therapy, the mass enlarged and impairment of liver function progressed (Table 1). The patient was admitted to our hospital for a second time with exacerbation of liver dysfunction, dyspnea, and pain throughout the body five months later. A chest and abdominal CT scan with contrast showed diffuse multiple low-density areas in the liver, hepatosplenomegaly, multiple lung cysts, and left pleural effusion (Fig. 1D). LCH was considered as the most likely diagnosis due to the suprasellar mass with multiple lung cysts. Liver biopsy was performed on hospital day 3. The specimen showed histiocyte-like cells, which were immunoreactive for CD1a and S-100 protein without infiltration of eosinophilia or hemosiderosis (Fig. 2A-2B). Their nuclear atypia and pleomorphism were limited

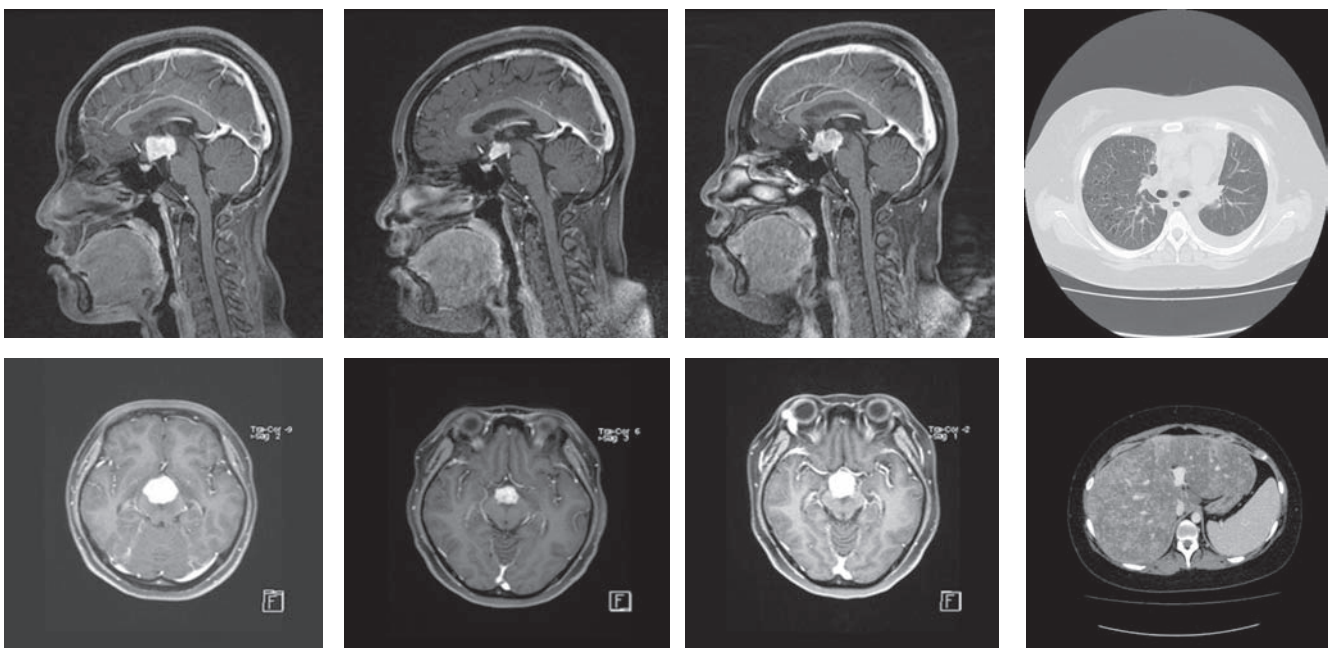

Fig. 1. Sagittal (*upper*) and transverse (*lower*) views of Gd-enhanced magnetic resonance images (*1A-1C*) during the clinical course and computed tomography scan of the chest and abdomen (*1D*). The suprasellar mass initially shrank after steroid therapy (*1B*), but began to regrow after steroid reduction (*1C*). Chest and abdominal CT scan showed multiple diffuse low-density areas in the liver, hepatosplenomegaly, multiple lung cysts, and left pleural effusion (*1D*).

Table 1. Laboratory data

Clinical data	First admission	End of steroid therapy	Second admission	
	16 mon before second admission	10 mon before second admission	On admission	Day 25
Hemoglobin (g/dL)	10.4	12.4	7.3	7.3
White-cell count (/mm^3)	5,000	6,700	4,900	100
Platelet count (/mm^3)	127,000	184,000	103,000	14,000
Prothrombin time (%)	92		68.5	54.9
Total bilirubin (mg/dL)	1.36	0.51	10.03	33.25
Direct bilirubin (mg/dL)	0.12	0.13	8.12	27.02
Total protein (g/dL)	6.1		5.3	4.9
Albumin (g/dL)	3.7	4.0	2.1	2.1
Alkaline phosphatase (U/L)	187	318	689	771
Aspartate aminotransferase (U/L)	35	94	63	138
Alanine aminotransferase (U/L)	41	131	63	285
γ-Glutamyltransferase (U/L)	10	94	229	250
Urea nitrogen (mg/dL)	13	10	12	79
Creatinine (mg/dL)	0.62	1.09	0.89	2.64
Sodium (mmol/L)	141	156	138	149
Potassium (mmol/L)	3.8	4.2	3.8	3.3
C-reactive protein (mg/L)	20.8	24.9	152.3	222.4
Lactate dehydrogenase (U/L)	333	497	404	382
Total cholesterol (mg/dL)	179	274		
Triglyceride (mg/dL)	147	534	157	178
HDL (mg/dL)	31			
Soluble interleukin-2 receptor (U/mL)	1,310		57,790	32,300

and mitotic activity was low, with approximately 1-2 mitoses/10 high-power fields. Therefore, LCH was diagnosed. In addition, almost 50% of the area of the liver specimen showed fatty degeneration. The biopsy sample of the suprasellar mass taken at the first admission was re-evaluated, and the infiltration of Langerhans cells was confirmed. The Ki-67 index of this patient was < 5% in the brain and 5-10% in the liver, and staining for Bcl-2 was negative (Fig. 2C-2H). Biopsies of the bone marrow and skin were negative for involvement of LCH.

The patient was transferred to our department for further treatment on hospital day 12 after confirmation of the diagnosis. She gained 15 kg in weight and weighed 98 kg during admission. She was comatose, with a score of 6 on the Glasgow Coma Scale. On examination, her face was round and full and her abdomen was obese with hepatomegaly palpable to the navel. There was no abdominal tenderness, distention, or guarding. There was edema extending to the hips bilaterally. Chest examination showed coarse inspiratory crackles in both lungs. The remainder of the examination was normal. Laboratory tests showed hepatic, kidney, and respiratory failure. She was treated in the intensive care unit and intubated on a vent, receiving pressors and continuous hemodiafiltration. Owing to multiple organ failure, reduced-dose induction therapy according to the Japan LCH study group (JLSG)-02 protocol was administered on hospital day 12 : cytarabine on d1-3 at 100 mg/body, and on d4-5 at 150 mg/day, vincristine on d1 at 1.5 mg/body, and prednisolone on d1 at 120 mg/body. Liver transaminases, lactate dehydrogenase, and soluble interleukin-2 receptor (sIL-2R) decreased after chemotherapy, but total bilirubin remained at a high level of around 30 mg/dL (Table 1).

On hospital day 14, pneumothorax occurred as previously reported and, despite drainage of the thoracic cavity, worsening of pulmonary and mediastinal emphysema was seen. On hospital day 26, as a result of septic shock and pulmonary hemorrhage, the patient died.

DISCUSSION

We described the clinical course and rapid progression of adult-onset MS-LCH after the discontinuation of steroid therapy. At first, the LCH cells responded to steroid therapy. However, after steroid discontinuance, the mass in the suprasellar area showed regrowth and the patient developed multiple organ failure. Despite multi-drug chemotherapy, there was no significant response and the patient expired due to other complications. One of the reasons for the difficulty of treatment is hepatic failure. LCH cells infiltrated the liver in accordance with Glisson cirrhosis, and almost 50% of the area of the liver biopsy showed fatty degeneration. The whole liver of this patient was hypodense on CT images, as previously reported.[13] The patient had never drunk alcohol, and laboratory tests ruled out viral hepatitis (hepatitis A, B, and C,

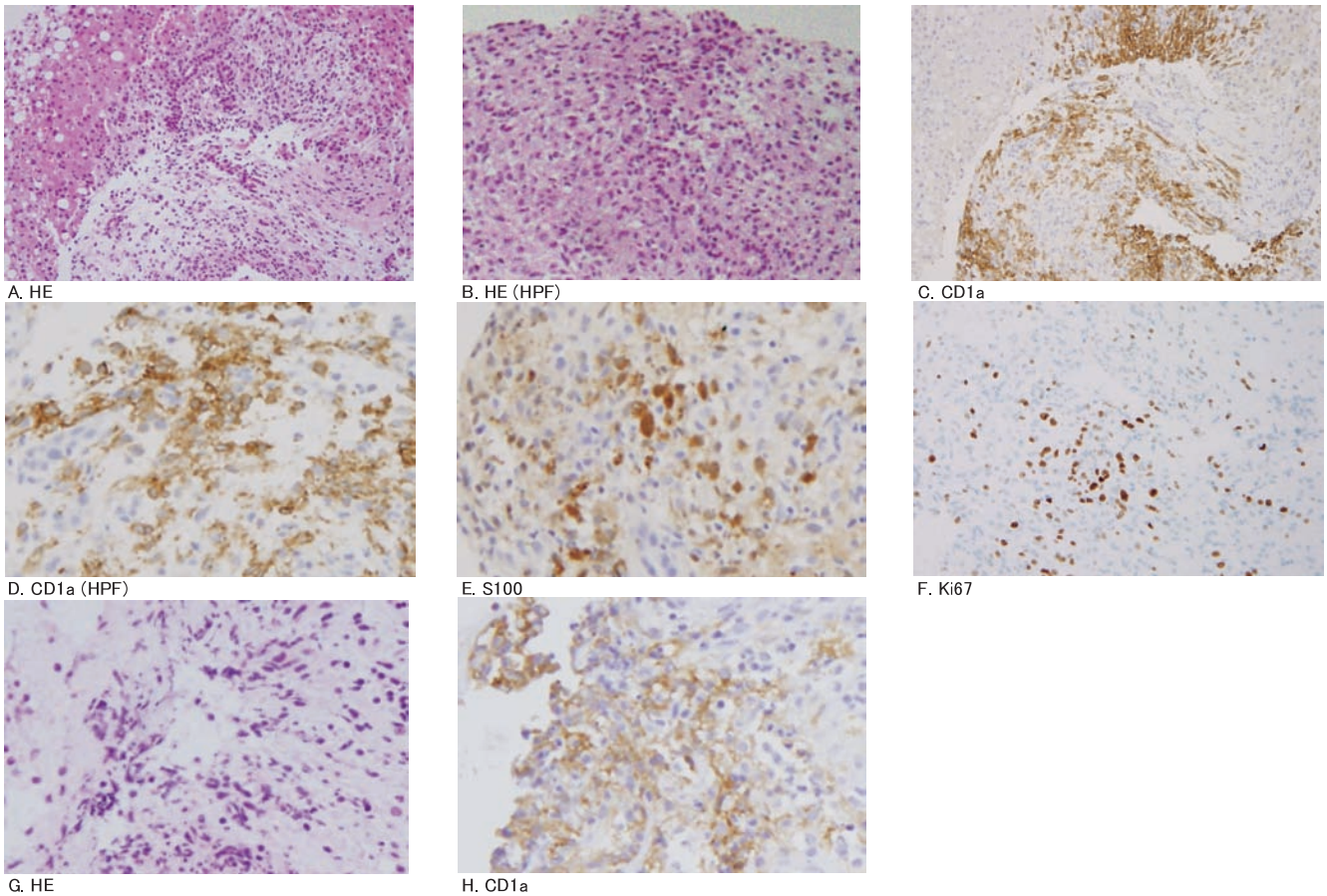

Fig. 2. Hematoxylin-eosin (HE) staining (*2A*, *2B*, *2G*), CD1a staining (*2C*, *2D*, *2H*), S-100 protein staining (*2E*), and the Ki-67 index (*2F*) of the liver, and suprasellar mass biopsy samples. Panels *2A-2F* show liver biopsy samples and Panels *2G-2H* show the suprasellar mass. The liver and suprasellar mass biopsy samples were immunoreactive for CD1a and S-100 protein. The Ki-67 index was 5-10% in the liver (Panel *2D*) HPF, high power field.

Epstein-Barr virus, and cytomegalovirus) and autoimmune-related diseases. Thus, nonalcoholic fatty liver disease (NAFLD) was considered, which caused the hepatic failure, in addition to LCH infiltration. Hypopituitarism and hypothalamic dysfunction are known as risk factors of NAFLD for the reason that they cause metabolic changes such as central obesity, hyperlipidemia, and insulin resistance, and result in fatty infiltration of the liver. LCH is often accompanied by them. Therefore, MS-LCH with hypopituitarism and hypothalamic dysfunction may be difficult to treat because of the coexistence of NAFLD.

The clinical course showed rapid worsening, like Langerhans cell sarcoma (LCS). LCS is a high-grade neoplasm with > 50% mortality from progressive disease. LCS is usually accompanied by nuclear pleomorphism and atypical mitosis. Chromatin is clumped and nucleoli are conspicuous. The immunophenotype is identical to that of LCH.[4] Lee reported on LCS arising from LCH.[17] However, regarding the biopsy samples, there were no characteristics of LCS ; therefore, our patient is considered to have had aggressive LCH.

High-level expression of Ki-67 and Bcl-2, the presence of MDM2, and the mRNA expression of c-myc and H-ras are detected in lesional LCH cells.[18] However, despite the presence of proliferation markers, the number of mitoses observed in LCH cells is usually low.[18] Ki-67,[19] Bcl-2,[19] and sIL-2R[20,21] are expressed more frequently in MS-LCH than in SS-LCH, although Bank reported no difference between them.[22] On the other hand, the frequency of Fas/Fas-L co-expression was found to be higher in single-system (69%) than in multi-system diseases.[23] The Ki-67 index ranged from 2 to 60% with a mean value of 10.5% for cytologically typical cases and 22.5% for cytologically malignant cases (LCS).[24] Ki-67 is correlated with the aggressiveness of LCH.[19] However, the relationship between the Ki-67 index and clinical outcome is uncertain. The Ki-67 index of this patient was < 5% in the brain and 5-10% in the liver (Fig. 2), and staining for Bcl-2 was negative. This result did not explain the clinical course.

A previous report showed that the sIL-2R serum level is a prognostic factor, correlated with the clinical stage, and the criterion value was 17,500 pg/mL.[20] In this case, the maximum sIL-2R serum level was 57,790 pg/mL and showed aggressiveness.

Although optimal treatment for child-onset LCH exists on the basis of a randomized control trial (RCT), treatment for adult-onset LCH remains to be established. The first international RCT for adult-onset LCH, LCH-A1, was conducted by the Histiocyte Society from 2004, which treated patients with vinblastine and prednisone. However, the LCH-A1 trial was discontinued because of the neurotoxicity of vinblastine. We treated the patient in this study according to the JLSG-02 protocol, consisting of cytarabine, vincristine, and prednisolone, but she died. Early diagnosis and multi-drug chemotherapy are essential for a favorable outcome.

MS-LCH usually progresses slowly, but some patients show rapid progression. At first, our case showed a favorable response to prednisone, but the rapid progression of adult-onset MS-LCH after steroid reduction. Adult-onset MS-LCH shows a diverse clinical course, and further clinical studies are necessary to establish stratification and optimal therapy. Our case is important due to the rapid progression and coexistence of NAFLD.

ACKNOWLEDGEMENT

The authors are indebted to Dr. Harumi Yano (Center for Clinical Infectious Diseases, Jichi Medical University) for critical review of the manuscript and Dr. Ichiro Murakami (Faculty of Medicine, Division of Molecular Pathology, Tottori University) for pathological advice.

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