Langerhans Cell Histiocytosis with Multisystem Organ Dysfunction

A Clinical Experience of 11 Patients

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Abstract  Objective: To clarify the clinical characteristics, treatment and outcome of Langerhans cell histiocytosis (LCH) with multisystem organ dysfunction.  Design: Retrospective chart review of children with multisystem LCH between 1983 and 1994.  Setting: Collaborative study with 6 affiliated hospitals of Childhood Cancer Conference of Osaka.  Results: Eleven patients had evidence of dysfunction of the liver, lungs and/or bone marrow. Their median age at diagnosis was 10 months (range: 0.8-14 months). Treatment consisted initially of a combination of prednisolone and vinblastine or etoposide, which eventually failed to yield a good response. Subsequently, several chemotherapeutic drugs including cyclophosphamide, doxorubicin, vincristine, cytarabine, 6-mercaptopurine, methotrexate, cyclosporin, interferon-α, interleukin-2 などが使用されて、11例中4例が死亡し、死因は3例が肺浸潤による呼吸不全、1例が真菌感染であった。3年生存率は61.3±15.2%で、生存中の7例は、原疾患に起因する病変に経り返す骨髄増殖（3例）、肺症（2例）、白血病（1例）、腎症（2例）を有しており、無治療で観察中の例はわずか2例であった。臓器不全を伴う年少児のLCHで、特に初発時に肺病変を伴っている例は生命予後不良である、発症頻度の少ない疾患であり、適切な治療法の確立には多施設での共同研究が望まれる。

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survivors, 5 have been treated for disease-related late consequences. They have suffered from recurrent bone tumors \( (n=3) \), diabetes insipidus \( (n=2) \), leukoencephalopathy \( (n=1) \), and persistent splenomegaly \( (n=2) \). No secondary malignancy was noted. Conclusions: Patients with LCH with organ dysfunction, particularly when accompanied by pulmonary involvement, have the poorest prognosis. At present, the long-term disease-free survival rate is low.

Key words: Langerhans cell histiocytosis, organ dysfunction

I. Introduction

Langerhans cell histiocytosis (LCH) is one of the histiocytoses of unknown etiology. This syndrome was formerly grouped as "histiocytosis X", which, in 1953, Lichtenstein integrated with a group of diseases known as Hand-Schüller-Christian disease, eosinophilic granuloma, and Letterer-Siwe disease. The clinical spectrum of LCH varies from a single bone lesion to systemic multiple organ dysfunction. Therefore, therapy needs to be arranged according to the clinical staging and pathophysiology. Actually, however, therapy for LCH in children has not yet been established. Factors which make it difficult to establish an effective therapy for LCH are as follows: (1) the incidence of LCH is very low; (2) the disease has been regarded not as a malignant entity but essentially as a reactive lesion, and (3) its clinical features are very diverse ranging from spontaneous regression to rapid aggravation leading to death and a chronic course with recurrences over a long period of time. LCH with multisystem organ dysfunction in patients under 2 years of age is said to have the poorest prognosis, but the actual state remains obscure.

The purpose of this report is to describe the clinical experience with LCH in six institutions and to stress the importance of multi-institutional trials to establish the most effective therapeutic regimen for the patients with multisystem organ dysfunction.

II. Subjects and Methods

During the last 12-year period from January 1983 to September 1994, questionnaires were sent to members of Childhood Cancer Conference of Osaka at 28 hospitals. Out of 41 patients diagnosed with LCH, the 11 patients (27%) with multisystem organ dysfunction were studied. The diagnosis of LCH was confirmed by pathological examination of biopsy specimens taken from the skin, bone, lymph nodes or bone marrow. S-100 protein positivity was found in 8 patients, CD1a-positive cells in 2, and Birbeck granules by electron microscopy were demonstrated in 3. As to the clinical staging, patients with multisystem involvement and accompanying failure of the liver, lungs or bone marrow were selected according to Mahmoud's classification. In judging organ dysfunction, the criteria proposed by Lahey were used, and roentgenographic findings (alveolar or interstitial infiltration) were appended to pulmonary signs.

The therapeutic responses were defined as follows. "Complete response" is the lack of symptoms of LCH, normal physical and radiologic findings, and the absence of new lesions. "Partial response" is a more than 50% reduction in organ involvement in either extent of the disease or number of organs involved and resolution of any organ dysfunction. "No response" is a less than 50% reduction in organ involvement or the persistence of organ dysfunction attributable to LCH. "Progressive disease" is the involvement of additional organs or greater than 50% progression of the disease in two or more organs, any new organ dysfunction, or worsening of any existing dysfunction.

III. Results

Table 1 shows a summary of the patients at the time of diagnosis. The age at diagnosis was under 1 year and 2 months in all the patients. Symptoms and their incidence were fever and skin lesion (100%), hepatosplenomegaly (81.8%), pancytopenia (63.6%), respiratory symptoms (54.5%), swelling of lymph nodes (36.4%), and bone lesions (36.4%). There were 6 patients at stage III and 5 patients at stage IV according to the classification of clinical staging by Osband et al., and 10 of 11 patients had 5 points or more on Lahey's score. As for the serum immunoglobulin level, the median value was 1,020 mg/dl (range: 466 - 1,240). Subsets of lymphocytes were examined in 7 patients, and the CD4/CD8 ratio in 4 patients showed a high value of 4.0 or more. By contrast, no patient showed a low value less than 1.0. Cytokines were examined in only 3 patients. Elevation of sIL-2R and IL-6...
was noted in 2 patients, and tumor necrosis factor (3 patients) and IL-1 (1 patient) were within normal limits. Interferon-γ was variable in one patient, as is characteristic of the disease.

The initial treatment consisted of two regimens: prednisolone (PSL) and etoposide (VP-16), and PSL and vinblastine (VBL). Satisfactory results were not obtained in any patient with either regimen of the initial treatment and subsequently various medications were attempted. Two patients underwent blood purification therapy including plasmapheresis and exchange transfusion on aggravation of symptoms. These two patients are presently in partial remission. Combination chemotherapy including cyclophosphamide (CPA), doxorubicin, vincristine (VCR), and PSL (CHOP therapy) was given to two patients, and cytosine arabinoside (AraC), VCR, and PSL to two. These four patients showed no response to the former and a partial response to the latter. Besides, CPA (5 patients), methotrexate (4), 6-mercaptopurine (2), dexamethasone (DEX) (1) and methylprednisolone pulse therapy (4), cyclosporin (CSA) (6), interferon-α (1) and IL-2 (1) were administered. Subsidence of fever and cutaneous involvement with a switchover from PSL to DEX was noted in one patient and a partial response was obtained with CSA administration in one. The effectiveness of these retrieval treatments in either patient, however, was difficult to evaluate because more than one agent was administered and also the number of subjects studied was small. A survival curve for the 11 patients is shown in Fig. 1. Four patients died 19 days to 2 years and 6 months after the diagnosis. The cause of death was respiratory failure in 3 out of 4 patients and mycotic infection in 1. The three patients who died because of respiratory failure showed pulmonary involvement at the onset of the disease. Seven patients are alive, but none have attained complete remission yet, and five of them are still receiving some treatment. During a follow-up period of 1 year to 6 years and 6 months after the diagnosis, recurrent bone tumors in 3 patients, diabetes insipidus in 2, and leukoencephalopathy and quadriplegia in 1 have been noted. Splenomegaly persists in two patients, who are followed up without any treatment. It remains unknown whether leukoencephalopathy is due to

### Table 1 Clinical features, initial treatment and outcome of 11 patients with multisystem LCH

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age(months) /Sex</th>
<th>Sites involved</th>
<th>Initial treatment</th>
<th>Response</th>
<th>Retrieval treatment</th>
<th>Survival (cause of death or current status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/F</td>
<td>LN, Bone, Liver, Spleen, Lung, BM</td>
<td>+ + + + + + PSL</td>
<td>Partial</td>
<td>CPA, MTX, VP-16, mPSL</td>
<td>2y6m (respiratory failure)</td>
</tr>
<tr>
<td>2</td>
<td>5/M</td>
<td>− − − − − − − + + − − VP-16 + PSL</td>
<td>Partial</td>
<td>CHOP, VBL + PSL, CSA, IL-2, MTX, mPSL</td>
<td>2y7m (sepsis)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8/M</td>
<td>− + + + + + + + + + + + + + PSL</td>
<td>Partial</td>
<td>VP-16, CPA, MTX, mPSL</td>
<td>7y + (leukoencephalopathy)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7/F</td>
<td>− − + + + + − − VP-16 + PSL</td>
<td>Partial</td>
<td>VP-16, CSA</td>
<td>6y3m+ (DI, bone tumor)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10/F</td>
<td>+ + + + + + + + + + VP-16 + PSL</td>
<td>Progressive</td>
<td>CSA</td>
<td>19d (pulmonary infiltration)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>12/F</td>
<td>+ + + + + + + + + + + + VP-16 + PSL</td>
<td>None</td>
<td>VBL, CSA, IFN-α</td>
<td>4y2m+(splenomegaly)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>11/F</td>
<td>− + + + + + + + + + + VP-16 + PSL</td>
<td>None</td>
<td>CHOP, MTX, CPA</td>
<td>3y9m+(bone tumor)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.8/M</td>
<td>+ + − − − − − − − VP-16 + PSL</td>
<td>None</td>
<td>CA + VCR + PSL, 6MP</td>
<td>2y8m+ (bone tumor)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>12/M</td>
<td>− − + + + + + + + + + + PSL</td>
<td>None</td>
<td>VP-16, CPA, DEX, 6MP, PBL</td>
<td>2y7m + (splenomegaly)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10/M</td>
<td>− + + + + + + + + + − − VP-16 + PSL</td>
<td>None</td>
<td>VBL, CSA</td>
<td>1y1m (pneumonia)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>14/F</td>
<td>− + + + + + + + + + + + + + VP-16 + PSL</td>
<td>None</td>
<td>VBL, mPSL</td>
<td>1y3m+ (DI)</td>
<td></td>
</tr>
</tbody>
</table>


![Fig. 1](image-url)
the medication or the primary disease. Other chemotherapy-related late effects including secondary malignancy have not occurred yet in the survivors.

IV. Discussion

Infantile LCH, particularly disseminated LCH which is accompanied by pulmonary involvement or in which the lesion extends to several organs excluding bone or soft tissue, carries a grave prognosis. The survival rate for the 11 patients was 61.3%±15.2% during a median observation period of 3 years and 9 months, there being not much difference from the patients reported in the past.

When the deceased patients were compared with the survivors in terms of the infiltrated organs at the onset of the disease, pulmonary involvement was found in 3 of the 4 deceased, representing a high percentage compared with the survivors (3 out of 7). As to the liver and bone marrow involvements, no difference was seen between the survived and dead patients. The incidence of bone lesions tended to be rather low in disseminated LCH on the whole. Of the organic impairments, therefore, the pulmonary involvement in particular appeared to affect the prognosis.

As to the initial treatment, no characteristic difference was seen between the cases of death and survival. Regarding the retrieval treatment, deceased patients showed no distinct difference from the survivors; they attained partial remission but had recurrence, showed resistance to various medications and eventually died. As such, a long-term therapeutic plan, both maintenance and intensification therapy, is needed.

Recently, the institution of chemotherapy for multisystem LCH has become a main current. On the other hand, it is also a fact that there have been opinions showing hesitation and/or opposition to the use of cytotoxic drugs or multi-drug combination chemotherapy particularly for young children, since LCH has been believed to be a reactive disease. As to the etiology of this disease, there have been some recent reports that confirmed clonal proliferation. There is, however, still room for debate as to how potent the chemotherapy should be. In our study, death is due not to secondary immunodeficiency but no Langerhans cell infiltration in 3 out of 4 patients. Consequently, there is a need to study the issue of intensity and duration of multi-drug combination chemotherapy of this disease.

The incidence of infantile LCH in Japan is 0.15 per 100,000 infants or the estimated number of cases per year is 34 according to the survey of Imashuku et al. Because of the small number of patients with LCH worldwide, no established therapeutic guideline is available, and the results of prospective protocol studies have been reported by only a few groups. Egeler et al administered a 4-day course of Ara-C, VCR, and PSL at intervals of 3 to 6 weeks for 52 weeks to 8 children with disseminated LCH and found the 6-year survival rate to be 62.5%.

In our patients, the same therapy was given to two patients who failed to attain remission with other therapies and the results were relatively satisfactory. Their protocol is worth studying to determine whether it is effective as the initial treatment or whether it should be incorporated in the therapeutic program as a maintenance therapy. By the Italian group, combination chemotherapy using VCR, CPA, ADM, and PSL was administered for a total of 9 courses, and the survival rate in 12 months was 45.5%. In a German multi-center clinical trial, a protocol using VP-16, VBL, and PSL as a starter followed by 36 weeks of maintenance therapy was studied; the 8-year survival rate was reported to be 61.9%. The Histiocyte Society has proposed an international study since 1991, and a randomized study with m-PSL pulse therapy combined with either VP-16 or VBL is ongoing. According to this Society, however, patients unresponsive to the initial treatment are those who are under 2 years of age and with multi-system disease accompanied by multiple organ dysfunction; such high-risk LCH cases can be the subjects of an experimental approach and therefore pose a problem to be solved in the future.

Another issue found by the present study is that the event-free survival rate is very low. There are therapy-related consequences and disease-related consequences. In our study, the latter poses a more immediate problem. As to the long-term prognosis of LCH, particularly high-risk LCH, there have been few reports. Regarding VP-16, the risk of developing secondary malignancy has been reported, but this agent should be incorporated into the therapeutic regimen for high-risk LCH after considering the benefit/risk ratio. In no study has it ever been confirmed that long-term prognosis improves depending on the therapeutic regimen or therapeutic period. As to diabetes insipidus, however, such a possibility has been suggested by some studies.
The results of this study indicate the following: 1) patients with poor prognosis had characteristic clinical features such as pulmonary involvement at the onset in the disseminated LCH with organ dysfunction, 2) conventional therapy, including PSL, VBL or VP-16, was not enough to have an initial favorable response, and 3) the consequences and quality of life in the survivors were unsatisfactory. It may be necessary to make free use of plasma exchange and combination chemotherapy (plus bone marrow transplantation) in some circumstances as in the case of malignant blood disease. Clinical investigators should be encouraged to take part in prospective multi-institutional trials. There is a need to define clinical staging and risk factors as in the group study of leukemia or neuroblastoma and to propose a protocol to achieve a better outcome in patients with LCH.

References