Original Article

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Clinical Outcomes of Langerhans Cell Histiocytosis: A Single-Center Experience

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Abstract:

Objective: To evaluate the clinical outcome of Langerhans cell histiocytosis (LCH) in countries with limited resources.

Material and Methods: A retrospective chart review of patients <15 years old, diagnosed with LCH and treated at Siriraj Hospital; from January 1, 2002 until December 31, 2016, was performed. The patients' demographic data, treatment protocol, and efficacy of treatment were collected and analyzed.

Results: LCH was diagnosed in 38 patients, with a median age of 1.9 years old; of whom, 24 had multisystem disease (MS) and 14 had single system disease (SS). In the MS group, 16 patients had risk of organ (RO) involvement, with hepatic involvement being most common. The prevalence of central diabetes insipidus was 21.0%. Reactivation was observed in 11 patients (28.9%). RO involvement of the hematopoietic system (p-value=0.016), spleen (p-value=0.031), and MS (p-value=0.001) were significantly associated with a poor response to induction therapy. RO involvement of the hematopoietic system (p-value=0.016), liver (p-value=0.0), and spleen (p-value=0.005), as well as MS (p-value=0.013) were significantly associated with reactivation risk. The 5-year event-free survival rate of patients with and without RO involvement were 9.2% and 88.3%, respectively. The 5-year overall survival rate of patients with and without RO involvement were 82.5% and 96.4%, respectively.

Conclusion: The prevalence of MS and RO involvement seemed high in this cohort; however, the outcomes were comparable to other Asian studies. Novel treatment for RO involvement may improve clinical outcomes.

Keywords: children, Langerhans cell histiocytosis, LCH, Thailand, treatment

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Introduction

Langerhans cell histiocytosis (LCH) is a clonal proliferative disease originating from myeloid-derived dendritic cells. The clinical features of LCH are heterogeneous, ranging from single localized lesions to systemic manifestations. Bones are the most common site of involvement (80.0% of cases), followed by skin (30.0%)[1]. The treatment of LCH depends on the site and extent of the disease. Patients with a single solitary lesion may require only surgical intervention, while those with systemic disease will require systemic chemotherapy[2]. Hematopoietic diseases are relatively uncommon; however, patients with hematopoietic involvement tend to have relatively poorer outcomes[3]. Although, the prognosis of LCH appears to be good, 10.0-20.0% of patients experience relapse or refractory diseases[2].

Data regarding the clinical features and outcomes of LCH are scarce, particularly from countries with limited resources. Thus, clinical studies of LCH focusing on these regions may better elucidate the possible outcomes in said countries.

Material and Methods

A retrospective chart review of patients <15 years old that were diagnosed with LCH; from January 1, 2002 until December 31, 2016, was performed. The patients' demographic and clinical data; including age at diagnosis, gender, and extent of disease, were collected and recorded. Toxicities were classified using the Common Terminology Criteria for Adverse Events v4.0. This study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (COA no. Si 721/2017).

LCH diagnosis was established based on histopathology and positivity of CD1a and/or CD207 (Langerin) or the presence of Birbeck granules. Laboratory tests as well as other investigations; including bone survey, bone scan, and chest x-ray (CXR), were perfromed to evaluate the extent of disease in all cases. Additionally, bone marrow studies, hormonal studies, magnetic resonance imaging for the brain and pituitary, and computerized tomography (CT) of chest and abdomen were carried out if involvement in these organs was clinically suspected.

LCH cases were classified as either single-system (SS) or multisystem disease (MS), in line with the extent of the disease. SS patients with a single bone lesion were treated with curettage and/or intralesional steroids; except those with skull involvement. Patients with MS or SS that had a solitary bone lesion involving the skull or multifocal bone lesions were treated with systemic chemotherapy. Patients with hepatic, splenic, or hematopoietic involvement were classified as having a risk of organ involvement (RO+). Due to the ongoing development of LCH protocols, patients were treated according to the corresponding protocol applied at the time; as per the evolving protocols described below.

All patients diagnosed prior to 2004, were initially treated with the LCH II protocol. This consisted of: vinblastine (VBL), prednisolone and etoposide during induction, followed by VBL, prednisolone, and 6-mercaptopurine (6-MP) in the maintenance phase, for a total treatment duration of 6 months[4]. Those diagnosed between 2004 and 2013, were treated as per the LCH III protocol[5]. Patients with MS and having RO+ were treated with the Arm B protocol from LCH III trial. This consisted of: VBL, prednisolone, and intermediate dose methotrexate (MTX) during induction, followed by VBL, prednisolone, oral MTX, and 6-MP in the maintenance phase; for a total treatment duration of 12 months. Those with MS, but without risk of organ involvement (RO-), and the others were treated with VBL and prednisolone during induction, and then received maintenance therapy with VBL and prednisolone, for a total treatment duration of 6-12 months; depending on treatment response. After 2014, since the data demonstrated superior efficacy of 1-year therapy and showed that there was no additional benefit of MTX[6], all patients were treated with a modified LCH III protocol. This consisted of VBL and prednisolone during

induction, followed by VBL, prednisolone, and 6-MP in the maintenance phase; additionally, the duration of treatment was prolonged to 1 year.

After a six-week induction, the clinical response was determined by physical examination, radiographic studies, and laboratory results. Responses were classified into different groups based on the reaction to the six-week induction treatment. Those whom had a complete response were deemed good responders (GR), while those who experienced partially-improved clinical symptoms and radiographic findings were classed as partial responders (PR). Patients that had neither a clinical response nor disease progression were classified as non-responders (NR). Those with disease progression were classified as progressive disease (PD). Patients with relapse or refractory diseases were treated as per the Japan Langerhans Cell Histiocytosis Study Group-96 protocol (JLCHSG-96 protocol): Arm A for RO- and others and Arm B for RO+[7]. Arm A consists of a 6-week induction therapy with vincristine (VCR), prednisolone, and cytosine arabinoside (Ara-C), followed by 6 months of maintenance therapy with VCR, Ara-C, MTX, and prednisolone. Arm B consists of VCR, cyclophosphamide (CTX), adriamycin (ADR), and prednisolone for 6 weeks during the induction period, followed by the maintenance phase with VCR, ADR, MTX, CTX, and prednisolone for 6 months.

Patients that had refractory bone disease were treated with pamidronate: as previously described[8]. Allogeneic stem cell transplantation (SCT) was considered in patients with refractory systemic disease, if they had an HLA-identical matched sibling. Those that were unable to perform allogeneic SCT were treated with other salvage regimens: as per the physicians' discretion.

Statistical analysis

Data management and analysis were performed using statistical package for the social sciences (SPSS) Statistics v12.0 for Windows (SPSS, Inc., Chicago, IL, USA). Data are presented as median and range. The Kaplan-Meier method was performed to evaluate event-free survival (EFS) and overall survival (OS); an event was defined as disease reactivation or death. The correlations between the clinical factors and prognosis were evaluated using the chi-square test, two-sample t-test, and binary logistic regression. A p-value<0.05 was regarded as being statistically significant.

Results

Thirty-eight patients, comprising of 20 girls and 18 boys, were diagnosed with LCH during the study period. The median age at diagnosis was 1.9 years old (range 1 day-14.4 years). Table 1 demonstrates the clinical presentations and abnormal physical findings of the LCH patients. The clinical classifications are given in Figure 1.

Table 1 Clinical manifestations and physical examination of the patients (n=38)

Parameter	Number of patients (%)
Clinical manifestation	
Subcutaneous mass	21 (55.3)
Rash	13 (34.2)
Bone pain	10 (26.3)
Fever	9 (23.7)
Polyuria	7 (18.4)
Lymphadenopathy	7 (18.4)
Abdominal enlargement	6 (15.8)
Exophthalmos	6 (15.8)
Otitis media	6 (15.8)
Anemia	4 (10.5)
Blurred vision	2 (5.2)
Dyspnea	1 (2.6)
Physical examination	
Subcutaneous mass	21 (55.3)
Skin rash	14 (36.8)
Hepatomegaly	13 (34.2)
Splenomegaly	7 (18.4)
Lymphadenopathy	7 (18.4)
Exophthalmos	6 (15.8)
Otitis media	6 (15.8)
Pallor	3 (7.9)
Poor vision	2 (5.2)

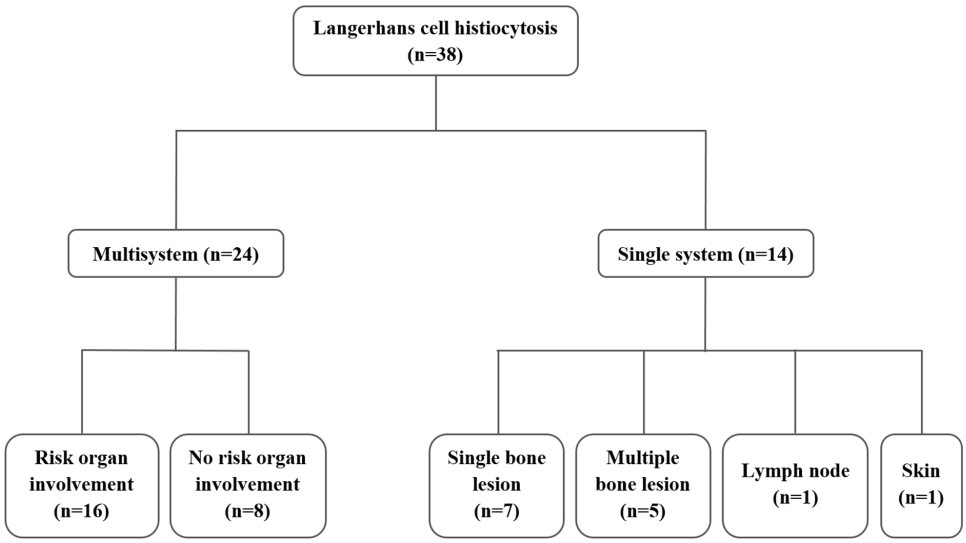

Figure 1 Clinical classifications of the patients (n=38)

There were 16 RO+ patients, among whom the liver was the most common organ involvement (81.3%), followed by the hematopoietic system (62.5%) and spleen (43.8%), respectively. Pulmonary involvement diagnosed by a CXR and CT was found in 2 patients. Abnormal bone survey results were found in 20 patients (52.6%); skull was the most common site (47.3%), followed by long bone (28.9%) and pelvis (7.8%). Eight patients (21.0%) had endocrinopathy, all of them had central diabetes insipidus, and 2 of those 8 had panhypopituitarism. All but one patient with endocrinopathy had an abnormal radiographic lesion of the skull.

Among the 7 patients with a single bone lesion, 4 of them had a lesion of the extremities and were treated with surgical curettage, while 3 with skull involvement in the mastoid and orbital region were designated as having a central nervous system risk lesion and were treated with chemotherapy, as indicated in the modified LCH III protocol. The other 2 SS patients (1 lymph node, 1 skin) were treated with surgical excision only.

There were 32 patients treated with chemotherapy; 9 with LCH II, 14 with LCH III, and 9 with the modified LCH III protocol. After 6 weeks of induction therapy, 90.6% of the patients responded to treatment; PR was the most common result (46.9%), followed by GR (43.8%), PD (6.2%), and NR (3.1%). Any treatment response less than PR were associated with initial hematological involvement (p-value=0.016), splenic involvement (p-value=0.031), and MS (p-value=0.001). However this was not associated with the hepatic involvement (p-value=0.165) or pulmonary involvement (p-value=1.0). Patients with SS disease attained a good response significantly more than those with MS disease (p-value=0.001).

Eleven patients (28.9%) experienced disease reactivation, with a median duration of 1.6 years after diagnosis (range 0.3-3.4 years). Three patients experienced disease reactivation during treatment, while eight patients had disease reactivation after therapy was completed. The most common sites of relapse were the bone (72.7%), risk organs (45.0%), and endocrine system (36.4%). RO+; including hematologic (p-value=0.016), hepatic (p-value=0.0), and splenic involvement (p-value=0.005), as well as MS (p-value=0.013), was significantly associated

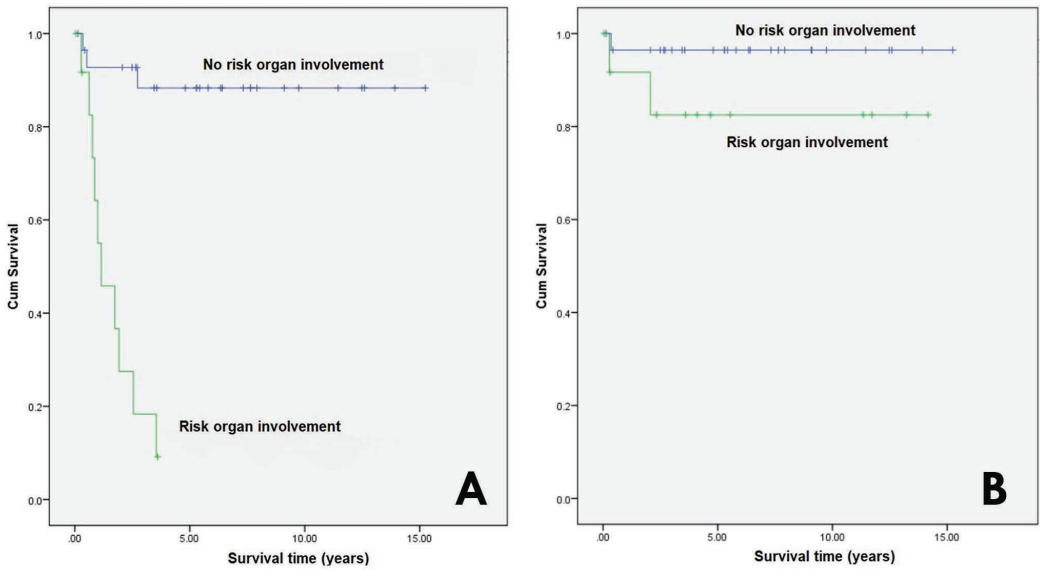

Figure 2 Event-free survival (A) and overall survival (B) of patients with and without risk organ involvement

with a reactivation risk, whereas, pulmonary involvement was not (p-value=0.297). Treatment for reactivation varied, as 8 patients with MS were treated with the JLCHSG-96 protocol, while 3 with a single bone lesion were treated with pamidronate. None of the patients received SCT or another salvage regimen. All the patients with a single bone lesion attained complete remission and survived; except for one whom is still receiving hydroxyurea for disease reactivation. The 5-year EFS and OS were 64.7% and 92.3%, respectively. There was a statistically significant difference in the 5-year EFS between the RO- and RO+ group (88.3% versus 9.2%, p-value=0.0), but not for the 5-year OS (96.4% versus 82.5%, p-value=0.136), as shown in Figure 2.

Four patients in the cohort passed away, three of whom died due to the disease. These three were RO+, and all had initially failed to respond to induction therapy. The remaining deceased patient was RO- whom developed nodular sclerosis Hodgkin lymphoma 5 years after the diagnosis of LCH, and subsequently underwent autologous SCT. He later attained remission, but finally succumbed to transplantation-related interstitial lung disease and myelodysplastic syndrome.

Discussion

Although most studies have revealed a male preponderance to LCH[9-12]; particularly in Asia, this study did not demonstrate any gender preference, which is in line with a previous study[13]. The median age at diagnosis in this study was comparable to the results from Chinese[14] and Turkish studies[15], but younger than in Korea[10] and some other regions[12,16]. Concordant with other research[17], SS accounted for 36.8% of all cases. Notably, the prevalence of RO+ seemed higher in this study's results compared to other Asian studies[14,17].

Approximately 10.0-50.0% of LCH cases initially have central diabetes insipidus[18]. The concurrent abnormality of other hypothalamic-pituitary axis hormones was observed in about 20.0% of these cases, most of whom were adolescents; additionally growth hormone deficiency was common[19]. This study, however, found that 25.0% of LCH patients with central diabetes insipidus at

the initial diagnosis had panhypopituitarism. This highlights the importance of testing for other pituitary hormones in people with central diabetes insipidus in order to prevent further complications from panhypopituitarism.

The extent of the disease and RO+ seems to be the most significant predictor of the response to treatment in the first 6 weeks of iinduction as well as in regards to the reactivation risk. This study's results are similar to those from other research studies, which have demonstrated that RO+ is associated with adverse outcomes[5,7]. In this study, 3 RO+ patients that did not respond to treatment died of the disease, while the other 13 RO+ patients survived. The heterogeneity of genetic mutations in regards to the disease may account for differences in treatment responses, translating into disease severity[20].

The use of bisphosphonate has demonstrated efficacy in LCH with bone involvement[21]. induction as cohort, 3 patients who experienced reactivation of bone disease were able to attain a second remission without further reactivation. Osteonecrosis of the jaw is a major concern in those receiving bisphosphonat; particularly in people with poor oral hygiene and malignancy. However, the incidence of jaw osteonecrosis in children is rare[22], and there was no such instance in this study. Taken together, bisphosphonate may be considered as a potential salvage therapy for bone disease reactivation.

Although, RO+ patients had worse prognoses than RO- patients, most were able to attain remission after receiving salvage therapy. Despite having a poor 5-year EFS of 9.2%, the patients with RO+ in this study still had a high 5-year OS rate of 82.5%, comparable to the results in other research[14,23]. Nevertheless, RO+ patients that do not respond to salvage treatment have grave prognoses, and may require effective second-line therapie; such as a cladribine-containing regimen or a BRAF inhibitor, as exigent treatment. Unfortunately, such medications are generally unaffordable for many families, so this may pose a major hindrance in countries with limited resources and access.

Long-term survivors of LCH may be at risk for solid and hematologic secondary malignancies[24]. The association between LCH and Hodgkin lymphoma has been reported in several papers, with most having LCH concurrently or after Hodgkin lymphoma[25-28]. However, the diagnosis of LCH in our case preceded Hodgkin lymphoma, which was previously addressed in only a few case reports[29,30]. The harboring of a BRAF/ERK pathway mutation may account for triggering other hematologic malignancies in LCH[24]. Therefore, long-term follow-up with surveillance for second malignancies is indispensable in LCH patients.

There are some limitations of this study that should be noted. First, data may be absent: as this was a retrospective study. Second, as we are both a tertiary medical and referral center, some refractory LCH patients were referred by pediatric hematologists and thus, our cases may not represent the majority in Thailand.

Conclusion

LCH appears to have a high heterogeneity of manifestations and outcomes. Bisphosphonate is effective for those with bone involvement. Meanwhile, patients who are RO+ may require intensive treatment, especially if they are unresponsive to standard induction therapy. Long-term follow-up, particularly vigilant observation of potential second malignancies, is critical.

Conflict of interest

All the authors declare that they have no personal or professional conflicts of interest and received no financial support from companies that produce and/or distribute the medications, devices, or materials described in this report.

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