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ORIGINAL ARTICLE

Langerhans cell histiocytosis with multifocal bone lesions: comparative clinical features between single and multi-systems

Shinsaku Imashuku · Naoko Kinugawa · Akinobu Matsuzaki · Toshiyuki Kitoh · Kentaro Ohki · Yoko Shioda · Yukiko Tsunematsu · Toshihiko Imamura · Akira Morimoto · Japan LCH Study Group

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Abstract Langerhans cell histiocytosis (LCH) can be a single system or multi-system disease. Both disease types can be associated with multi-focal bone lesions, but their bone involvement patterns have not been compared systematically. Of the new pediatric LCH cases enrolled into the JLSG-02 study during 2002–2007, 67 cases of single system multifocal bone (SMFB) LCH and 97 cases of multi-system bone (MSB) LCH were analyzed to determine if the bone involvement patterns differ in these two types, and whether these differences correlate with outcome. Statistical analysis was performed with Mann–Whitney *U* test, Fisher's exact test, and other measures. Onset ages were higher for SMFB ($P < 0.001$), but the two types did not differ in the number of bone lesions per patient. The skull was most frequently affected in both types, followed by the spine. Lesions in the temporal bone ($P = 0.002$), ear-petrous bone ($P < 0.001$), orbita ($P = 0.003$), and zygomatic bone ($P = 0.016$) were significantly more common in MSB. The two types did not differ in response to treatment, but MSB was associated with a significantly higher incidence of diabetes insipidus (DI) ($P < 0.001$). Novel measures are required in preventing the development of DI in MSB-type LCH patients with "risk" bone lesions.

Keywords Langerhans cell histiocytosis · Bone lesions · Diabetes insipidus · Late sequelae · Outcome

S. Imashuku (✉)
Division of Pediatrics, Takasago-seibu Hospital, 1-10-41 Nakasuji, Takasago, Hyogo 676-0812, Japan
e-mail: shinim95@mbox.kyoto-inet.or.jp

N. Kinugawa
Showa University, Tokyo, Japan

A. Matsuzaki
Kyushu University, Fukuoka, Japan

T. Kitoh
Aichi Medical University, Nagakute, Japan

K. Ohki
Chiba University, Chiba, Japan

Y. Shioda · Y. Tsunematsu
National Center for Child Health and Development, Tokyo, Japan

T. Imamura
Kyoto Prefectural University of Medicine, Kyoto, Japan

A. Morimoto
Jichi Medical University, Shimotsuke, Japan

Abbreviations for chemotherapeutic agents and employed dosages

Ara-C	Cytarabine (100 mg/m^2/day, drip)
VCR	Vincristine (0.05 mg/kg/day, IV)
PSL	Prednisolone (max; 2 mg/kg/day, PO)
ADR	Doxorubicin (35 mg/m^2/day, IV)
CPM	Cyclophosphamide (10 mg/kg/day, IV)
CSA	Cyclosporine A (3 mg/kg/day, drip)
MTX	Methotrexate (1–3 mg/kg/day, IV or 20 mg/m^2/day, PO)
6MP	6-Mercaptopurine (1.5 mg/kg/day, PO)
VBL	Vinblastine (6 mg/m^2/day, IV)

1 Introduction

Langerhans cell histiocytosis (LCH) develops as a single system or multi-system disease. In terms of disease sites,

bone is the most commonly involved organ. Single (unifocal) bone lesions, which are found more commonly in single system disease than in multi-focal bone disease, generally have a benign prognosis [1–3]. Therefore, in pediatric practice, more attention is focused on multifocal bone disease, whether it occurs in the context of single system LCH disease [designated here as single system multi-focal bone (SMFB) disease] or multi-system LCH disease that also involves the skin or other organs [designated here as multi-system bone (MSB) disease]. How SMFB should be treated has been the subject of extensive investigation in the past [2]. However, as detailed below, it appears that the SMFB and MSB types of LCH have thus far not been systematically compared in terms of their bone involvement and response to treatment.

While several large series of patients with bone LCH have been studied in the past [3–5], it remains unclear where the bone lesions in single system or in multi-system LCH occur, how they respond to therapy, and if and where they recur. Our literature survey also suggests that there has been little comparison of bone lesion-associated single system and multi-system LCH cases in terms of their clinical features and outcome. Previously, Ghanem et al. [6] classified LCH-associated bone lesions into three groups depending on whether there was a solitary bone lesion (Group I), multiple bone lesions with no systemic involvement (Group II), and multiple bone lesions with systemic involvement (Group III). Stuurman et al. [2] classified bone-associated LCH disease in a similar manner. The SMFB and MSB diseases are the equivalents of Group II and Group III diseases, respectively. The previous studies examining both Group II and Group III patients were unable to compare these two disease types because they were not treated in a similar manner [2, 6]. However, since we developed our Japan LCH Study Group (JLSG)-96 therapeutic protocol, we have treated SMFB (designated previously as SS-m) and multi-system (designated previously as MS) LCH cases in a similar manner. This makes it possible to compare these diseases more directly, and we showed that when treated according to the JLSG-96 protocol, these two types of LCH do not differ significantly in terms of overall 5-year survival rates (100% and 94.4% ± 3.2% survival, respectively) [7].

On the basis of our JLSG-96 therapeutic results, we have modified the protocol, which is now referred to as the JLSG-02 protocol. In this new protocol, systemic chemotherapy is similarly given to both SMFB and MSB cases. To investigate how bone lesions affect the outcome of these two types of LCH, we performed a prospective study by the Japan LCH Study Group, which compared the bone involvement patterns of 164 pediatric cases with either SMFB or MSB disease.

2 Patients and methods

The JLSG study was approved by the institutional review board of the Kyoto Prefectural University of Medicine, where the registration center is located. The study was performed in accordance with institutional ethical standards and the tenets of the Helsinki Declaration. The JLSG-02 study protocol requests that for all registered cases, the anatomical sites of all LCH lesions should be recorded. The lesion detection methods, a combination of physical findings, bone survey, and imaging (CT, MRI or PET) with proven histology, are at the discretion of physician-in charge at each institute. Single system unifocal bone LCH was excluded from the registry. In total, 202 new pediatric (age <18 years) LCH cases with multiple lesions (in bone and/or other organs) registered in the JLSG-02 study protocol during 2002–2007 were eligible for analysis. Of these, we analyzed the data of 164 cases that had multifocal bone involvement (81.2%). The remaining 38 cases (18.8%) did not have any bone involvement. Of the 164 eligible cases, 67 had SMFB disease and 97 had MSB disease (Table 1). We deemed a patient to have multi-focal bone lesions if there was more than one lytic lesion in the bone, even if all lesions were present in just one anatomical location (e.g., the temporal skull). Similarly, if the thoracic spine was involved, we considered the bone lesions to be multifocal if more than one thoracic vertebrae were involved. In the MSB cases, the bone lesions were associated with lesions in non-bone sites such as the skin, lymph nodes, and hematopoietic system (Table 2).

The details of the JLSG-96 protocol study, which is the predecessor of the JLSG-02 protocol (available at http://www.jlsg.jp), have been reported previously [7]. The structure of the revised JLSG-02 protocol is shown in Fig. 1. All eligible patients receive 6 weeks of induction A treatment (Ara-C/VCR/PSL). At the 6-week evaluation, patients showing a good response (GR) or a partial response (PR) start the 24-week maintenance A treatment (VCR/MTX/6MP/PSL). Patients who show no response (NR) or progressive disease (PD) immediately receive B1 (ADR/CPM/VCR/PSL) or B2 (ADR/CPM/VCR/PSL/CSA) treatment. This is followed by the maintenance B treatment (ADR/CPM/VCR/PSL). Patients not responding to B1/B2 treatment are removed from the protocol. At the end, all cases receive 18 weeks of maintenance C treatment (VBL/MTX/6MP/PSL). Total duration of therapy was approximately 12 months. The evaluation criteria at 6 weeks of treatment, the response criteria at 3 years, and the "reactivation" or "event" criteria are the same as those defined previously [7]. In such criteria, both bone lesions and organ involvement were evaluated; GR/PR at 6 weeks indicates improvement of organ involvement associated with healing bone lesions, while reactivation was defined

Table 1 Incidence and distribution of bone lesions in bone-involving Langerhans cell histiocytosis (LCH) in pediatric patients; comparison between single system multi-focal bone (SMFB) and multi-system bone (MSB) diseases

	SMFB	MSB	*P*
Patients (*n*)	67	97	
Age (years: median; range)	3.33 (0.33–14.3)	1.54 (0.1–17.1)	<0.001
Age (years); distribution			
<2	21	59	
>2	46	38	<0.001
Sex (M/F)	43/24	50/47	0.113
Number of bone lesions per patient; distribution			
1	0	14	
2–4	53	58	
>5	14	25	0.200
Skull	(78)[b]	(175)[b]	
Parietal	21	32	0.866
Frontal	15	27	0.471
Occipital	11	19	0.684
Temporal[a]	13/10	30/28	0.002
Sphenoid	4	14	0.127
Ear-petrous bone[a]	4/0	15/10	<0.001
Facial bone[a]	(9)[b]	(52)[b]	
Orbita	4/0	9/14	0.003
Zygomatic bone	1/0	4/8	0.016
Maxilla	1/0	2/2	0.649
Mandible	2/1	6/7	0.066
Spine	(41)[b]	(41)[b]	
Cervical vertebrae	9	7	0.284
Thoracic vertebrae	14	14	0.298
Lumbar vertebrae	15	15	0.306
Sacrum	3	5	>0.999
Upper torso[a]	(23)[b]	(31)[b]	
Clavicle	1/1	3/3	0.474
Scapla	0/2	4/3	0.312
Ribs	11/8	14/4	0.183
Pelvic bone[a]	(22)[b]	(28)[b]	
Os ischii	1/3	1/1	0.227
Os ilium	11/5	12/13	0.856
Os pubis	0/2	1/0	0.568
Lower extremities[a]	(29)[b]	(36)[b]	
Femur head	3/4	2/1	0.093
Femur	8/9	13/13	0.859
Tibia	1/2	2/3	>0.999
Fibula	1/1	1/1	>0.999
Not specified[a]	2/3	4/7	0.594

[a] Laterality (right/left) was classified. Total numbers were employed for statistical analysis

[b] Numbers in parenthesis indicate total lesions in each site

Table 2 Distribution of non-bone organ involvement in MSB diseases

	n	%
Total	97	
Skin	56	57.7
Lymph node	38	39.2
Soft tissue[a]	20	20.8
Liver	20	20.6
Spleen	18	18.6
Thymus	15	15.5
Lungs	10	10.3
Bone marrow	8	8.2
Mucous membrane	5	5.2
Thyroid	2	2.1
Not specified	8	8.2

[a] Soft tissue lesions were noted; 7 in the orbita, 6 in the temporal to peri-auricular area, 3 in the parieto-occipital area, 3 in the chest, and one in the eye lid

as the development of a new bone lesion (at previous or new site) or new organ involvement. Particularly, the bone lesion evaluation was made by X-ray and images combined with physical and laboratory findings. Diagnosis of diabetes insipidus and neurodegenerative disease was made, as previously described [8, 9].

Statistical analysis was performed with the Mann–Whitney *U* test, Fisher's exact test, chi-square test, and Kaplan–Meier method with Wilcoxon test. *P* values less than 0.05 were considered to be significant.

3 Results

As summarized in Table 1, the SMFB cohort had a significantly higher median age at onset (3.33 years) than the MSB cohort (1.54 years; $P < 0.001$). The two cohorts did not differ in terms of the number of bone lesions per patient, although 14 of the 97 MSB (14.4%) had single bone lesions. In terms of where the bone lesions were located, the skull was the most frequently affected site in both disease types (78 sites in SMFB and 175 sites in MSB), followed by the spine (41 sites each) and the lower leg bones. Facial bone lesions occurred much more frequently in the MSB cohort (52 sites). No right or left laterality was noted in any bone lesions. MSB disease significantly more likely involved bone lesions in the temporal bone ($P = 0.002$), ear-petrous bone ($P < 0.001$), orbita ($P = 0.003$), and zygomatic bone ($P = 0.016$) than SMFB disease. The incidence of bone lesions at other sites did not differ between the two disease types. Of the 14

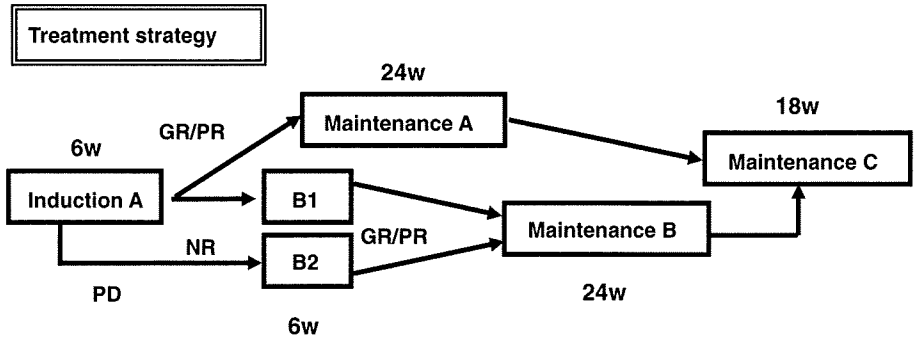

Fig. 1 Schematic depiction of the JLSG-02 protocol. Induction A treatment consists of Ara-C (day 1–5, 15–19, 29–33)/VCR (day 1, 15, 29)/PSL (day 1–28, then taper in 2 weeks). At the 6-week evaluation, patients showing a GR or a PR start the 24-week maintenance. Maintenance A treatment consists of alternative (**a**) and (**b**) regimens q2 weeks; the (**a**) regimen consists of VCR (day 1)/AraC (day 1)/PSL (day 1–4), while the (**b**) regimen consists of MTX (IV, day 1)/PSL (day 1–3) for 6 months. Patients who show NR or PD to Induction A immediately receive B1 protocol, which consists of ADR (day 1, 15, 29)/CPM (day 1–5, 15–19, 29–33)/VCR (day 1, 15, 29)/PSL (day 1–5, 15–19, 29–33) or B2 protocol, which includes additional CSA (day 1–14) to B1 protocol. This is followed by the maintenance B treatment, which consists of cycling (**a**), (**b**) and (**c**) q2 weeks; the (**a**) regimen consists of ADR(day 1)/VCR(day1)/PSL(day1–5), (**b**) regimen MTX(IV, day1)/PSL(day1–3) and (**c**) regimen CPM(day1)/VCR(day1)/PSL(day1–5). Patients not responding to B1/B2 treatment are removed from the protocol. At the end, all cases receive 18 weeks of maintenance C treatment, which consists of daily 6MP and alternative (**a**) and (**b**) regimens q2 wks; the regimen (**a**) consists of VBL(day 1)/PSL (day 1–5) and the (**b**) regimen consists of MTX (PO, day 1)

single bone MSB cases, 8 had skull/facial bone disease including one orbita and the remaining had peripheral bone disease. In terms of the non-bone lesions of the MSB cases, the lesions were most often in the skin, followed by lymph nodes and soft tissue (Table 2).

To compare the responses of the two cohorts 6 weeks after initiating induction A treatment, we analyzed the available data, namely, those of 63 SMFB and 92 MSB cases (Table 3). Both groups responded equally well (SMFB 85.1% vs. MSB 84.5%; $P > 0.999$). During the longer follow-up period (median 34 mo, range from <1 to 78 months) of these patients, reactivation was detected in 14/64 SMFB cases (22%) and 23/92 MSB cases (25%); ($P = 0.652$). Of these cases with reactivation, bone-alone reactivation was noted in 10/14 SMFB cases (71%) and 10/23 MSB cases (44%), ($P = 0.098$). Thus, the two diseases do not differ significantly in terms of reactivation. In addition, even if the incidence of all bone-involved reactivations was compared, no difference was noted between the two groups ($P = 0.265$). The 3-year overall survival (OS) and 3-year event-free survival (EFS) were calculated by Kaplan–Meier analysis. The OSs of the SMFB and MSB groups were 100% and 97.6 ± 1.7% ($P = 0.240$), respectively, while their EFSs were 66.3 ± 6.7% and 57.7 ± 6.4% ($P = 0.248$), respectively (Fig. 2). The MSB cases were significantly more likely to develop diabetes insipidus (DI) as a late sequela, and of the 19 DI cases, 18 were associated with MSB and one with SMFB ($P < 0.001$). DI was already noted at diagnosis in 12, while the remaining seven developed it during or after treatment. The bone lesions in 11 of the DI cases were in the temporal, ear-petrous, orbita, or zygomatic bones. Another four cases had lesions in other parts of the skull or facial bones. Thus, 15 of the 19 DI cases had skull and/or facial bone involvement, whereas four did not ($P < 0.001$). The one DI case with SMFB had occipital bone lesions as well as multiple spine and rib lesions. On the other hand, neurodegenerative disease was found in one case each in the SMFB and MSB group.

4 Discussion

This report focuses specifically on the LCH bone lesions of the multifocal LCH cases that were registered for the JLSG-02 protocol. Another report describing how JLSG-02 compares to JLSG-96 in terms of the therapeutic results of the entire cohort (and with longer follow-up times) is currently being prepared as a separate paper. Our recent literature survey has shown that of the studies discussing the management of bone LCH, most mix patients with single bone (monostotic) disease with patients with multiple bone (polyostotic) disease [10–13]; many also do not separate the pediatric patients from the adult patients [4, 5]. Thus, the bone involvement of pediatric cases with SMFB- and MSB-type LCH has not been analyzed systematically. In general, however, these studies show that LCH-associated bone lesions typically involve the flat bones, with lesions of the skull, pelvis, and ribs accounting for more than half of all lesions. In particular, the skull is the most frequently affected bone site in children and adults [3–5], while about 30% of the lesions occur in the long bones [14]. It seems that the bone involvement patterns of children and adults differ [5], since flat bones, including the

Table 3 Comparative outcome between SMFB and MSB diseases

Outcome/type	SMFB	MSB	*P*
Cases analyzed	67	97	
Treatment response at 6 weeks			
GR/PR	57 (85.1%)	82 (84.5%)	>0.999
NR/PD	6	10	
Not available	4	5	
3 year OS-Kaplan–Meier analysis	100	97.6 ± 1.7	0.240
3 year EFS-Kaplan–Meier analysis	66.3 ± 6.7	57.7 ± 6.4	0.248
Total reactivation rate	14/64[a]	23/92[a]	0.652
Reactivation at bone alone (total bone-involved reactivation cases)	10/14 (11/14)	10/23 (14/23)	0.098 (0.265)
Other organ(s) alone	1	4	
Not specified	2	5	
CNS disease			
DI at onset	0	12	
DI during/after chemotherapy	1	6	
Total DI as sequelae	1	18	<0.001
Neurodegenerative disease	1	1	>0.999

[a] Data missing in 3 SMFB and 5 MSB cases

GR good response, *PR* partial response, *NR* no response, *PD* progressive disease, *OS* overall survival, *EFS* event-free survival, *CNS* central nervous system, *DI* diabetes insipidus

jaw, are involved more frequently in adults [15]; ribs are also commonly affected sites in adults but not in children [5, 16]. In terms of spinal LCH, Garg et al. [17] studied a series of 26 pediatric cases and found that the lesions predominated in the cervical spine ($P \leq 0.02$). Sixteen of these 26 patients (62%) were found to have multifocal bone disease. These observations are all consistent with the distribution of the bone lesions in our cases (Table 1).

With regard to bone LCH disease types, single bone disease, multiple bone disease, and multi-system disease were 121, 34, and 97 cases, respectively, in the DAL-HX83/90 studies [3], 48, 40 and 34 cases, by Jubran et al. [13], and 22, 12, and 28 cases, respectively, in the report by Willis et al. [10]. In our study here, excluding single bone disease, we found multifocal SMFB (67 cases) and MSB (97 cases) in the study of 164 bone LCH patients. In addition, we clarified that the majority (85.6%) of our MSB cases had multiple bone lesions, which characteristically involved risk bones. Even the single bone MSB cases (remaining 14.4%) had skull/facial bone involvement in 8/14 (57.1%). By contrast, Stuurman et al. [2] reported that of the 25 multi-system disease with bone involvement, 16 (64%) had multifocal and the remaining 9 (36%) had single bone lesions, differing from our bone involvement pattern in MSB. It remains to be determined if there exists any distinct bone LCH involvement patterns among various ethnic groups. Also, whenever bone LCH is diagnosed, it is imperative to determine if it belongs to single system or multi-system disease, single or multiple bone lesions or if it involves "risk" bones.

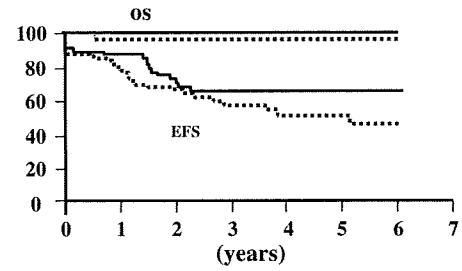

Fig. 2 Overall survival (OS) and event-free survival (EFS), in SMFB (*straight line*) and MSB (*dotted line*). There are no significant differences at 3-year survival between the two groups (see Table 3)

In terms of treatment, patients with SMFB and MSB are usually treated with chemotherapy. Other therapeutic measures, such as NSAIDS and bisphosphonates, have also been proposed to be suitable for SMFB, but not for MSB, in terms of alleviating pain and accelerating the healing of bone lesions [1]. However, our data presented here show that SMFB and MSB cases do not differ significantly in terms of their response to treatment with chemotherapy alone. We thus think that policies targeting SMFB cases (and excluding MSB cases) for treatment with NSAIDs and biphosphonates may need to be re-evaluated and assessed by future studies. On the other hand, our observations show that the outcome of MSB and SMFB patients is not the same because MSB patients have a significantly higher incidence of DI ($P < 0.001$). Similarly, when Stuurman et al. [2] compared the outcomes of 24 single system multifocal bone disease and 25 multi-system disease, they found that the

latter patients not only had higher reactivation rates (70 vs. 24%), but they also had a higher incidence of DI (55 vs. 13%). We also noted previously that patients with multi-system disease that started at a younger age had a high incidence of neurodegenerative CNS disease later [9]. Only a few such cases were detected in our cohort here, but this may reflect the short follow-up period.

Regarding the late sequelae of LCH, DI in pediatric LCH is well known to be associated with multi-system disease [10], the involvement of risk organs such as craniofacial lesions (in particular in the ear, eye, and oral regions) [8], and reactivation [5, 18]. A late effect study by the Histiocyte Society also showed that DI is associated with skull ($P = 0.003$), ear ($P < 0.0001$), and orbital lesions ($P = 0.005$), while neurological problems are associated with ear ($P < 0.0001$), facial bone ($P = 0.005$), and orbital ($P = 0.005$) lesions [19]. Our findings here showed that MSB patients were significantly more likely to have lesions in the temporal bone ($P = 0.002$), ear-petrous bone ($P < 0.001$), orbital ($P = 0.003$), and zygomatic bone ($P = 0.016$). Eleven of our 19 DI cases had these bone lesions; if other skull and/or facial bone lesions are also included, 15 DI cases in total had risk organ lesions. Another interesting finding was that of the 19 DI cases, twelve already had DI at onset, while the remaining seven developed it later, either during or after treatment for LCH. Thus, of the whole cohort, 7.3% had DI at onset and 4.3% developed it later. This is slightly different from the observations made previously by Grois et al., who found that 6% of LCH cases had DI at onset while another 9% developed DI later [20]. Stuurman et al. noted that of the 126 bone LCH patients, 7% had DI at diagnosis while 8% developed it later [2]. These observations suggest that it is imperative that LCH cases be diagnosed rapidly, before they develop DI, in order to reduce the incidence of DI particularly in LCH patients with MSB.

In addition, novel therapies is needed to prophylactically treat those MSB cases that are at a higher risk of developing DI, namely, those with lesions in "risk" bones such as temporal, ear-petrous, facial and orbital bones, or other skull/facial lesions. Also, LCH reactivation is significantly associated with an increased likelihood of a poor outcome and late sequelae [2, 5, 18, 21]. Thus, useful measures that can prevent reactivation should be routinely used in the treatment of SMFB and MSB.

In summary, we found that temporal skull and/or facial bones were more frequently affected in MSB pediatric patients, who also tended to be younger than the SMFB pediatric LCH patients. The fact that the SMFB and MSB patients responded equally well to the JLSG-02 protocol therapy, and that DI developed after or during treatment at a lower rate than has been reported previously in another patient series [2, 20], may reflect the usefulness of the current protocol for both types of pediatric multifocal bone-associated LCH and in the prophylaxis of CNS complications.

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