Characteristics and Treatment Outcomes of Pediatric Langerhans Cell Histiocytosis with Thymic Involvement

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Objective To evaluate the characteristics and treatment outcomes of patients with pediatric Langerhans cell histiocytosis (LCH) with thymic involvement.

Study design We retrospectively described the clinical, biological, and imaging characteristics of a series of 19 patients with pediatric LCH with thymic involvement in our center between September 2016 and December 2019. We further analyzed the treatment response and outcomes of patients treated with chemotherapy or targeted therapy.

Results Thymic involvement was found in 4.4% of a 433-consecutive pediatric LCH cohort; all LCH–thymic involvement presented with multisystem disease. Patients with thymic involvement were typically younger, harboring more lung and thyroid involvement and less bone involvement than those without thymic involvement. Most patients with thymic involvement had alteration of immunocompetence with decreased numbers of T-lymphocyte subsets and immunoglobulin G levels. Overall, 47.1% of patients demonstrated a response after 6 weeks of induction therapy, and 92.3% of the patients who did not respond to the first-line treatment had resolution of thymus after the second-line and/or targeted therapy. The progression/relapse rate showed no difference between patients who shifted to second-line therapy and those to dabrafenib (33.3% vs 25%, $P = 1.000$). The survival for patients with thymic involvement did not differ from those without thymic involvement. More patients treated with second-line chemotherapy had severe adverse events than those given dabrafenib (88.9% vs 0, $P < .001$).

Conclusions Thymic involvement was observed rarely in LCH and had specific clinical characteristics. Chemotherapy could resolve most thymic lesions, and BRAF inhibitors might provide a promising treatment option with less toxicity for infants with BRAF-V600E mutation. *(J Pediatr 2022; ■:1-9)*.

Trial registration http://www.chictr.org.cn, identifier: ChiCTR2000030457 (BCH-LCH 2014 study); ChiCTR 2000032844 (dabrafenib study).

Langerhans cell histiocytosis (LCH) is a rare disease characterized by accumulation of CD1a-positive ($CD1a^+$)/CD207 $(Langerin)^+$ histiocytes with inflammatory lesions in various organ systems.[1,2] Since the identification of recurrent mutations in the mitogen-activated protein kinase pathway, LCH has been considered a myeloid neoplastic disorder.[3-5] LCH can affect patients of all ages but predominantly affects young children.[6,7] The clinical presentations and outcomes of LCH are variable, ranging from a solitary spontaneously regressing lesion to explosive multisystem disease with life-threatening organ dysfunction or permanent sequelae.[8,9] The commonly affected systems include bones, skin, lung, lymph nodes, pituitary, etc. The liver, spleen, and hematologic system are considered risk organs because patients with such organs involvement are at high risk for poor outcomes.[10,11]

The thymus is a vital organ essential for the development of T lymphocytes, which orchestrate adaptive immune responses.[12,13] The thymus has been described as one of the uncommon organs involved in LCH, typically as part of systemic LCH in children.[14-16] In one study, thymic involvement of LCH occurred in younger children with a median age of 0.7 years and displayed a more aggressive and extended disease, requiring systemic therapy.[14] The response of thymic lesions to chemotherapy or targeted therapy and treatment outcomes has not been fully clarified. The present study retrospectively evaluated the clinical, biologic, and imaging characteristics and analyzed the treatment outcomes of a series of pediatric patients with LCH and thymic involvement.

AE	Adverse event
BRAF	B-type Raf proto-oncogene
CD	Cluster of differentiation
CT	Computed tomography
IgG	Immunoglobulin G
LCH	Langerhans cell histiocytosis

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Methods

Nineteen pediatric patients (<18 years) diagnosed as having LCH with thymic involvement in our center from September 2016 to December 2019 were enrolled in this study. The diagnosis of LCH was confirmed by histologic examination with positive CD1a and/or CD207 (Langerin) immunohistochemical staining of the lesional cells.[10] Presence of thymic involvement required either typical imaging presentation of the thymus on thoracic computed tomography (CT) or ultrasound scan, as has been previously described (18 cases),[14-18] or a definitive diagnosis of LCH with thymic involvement by histological examination (7 cases). This study was approved by the Beijing Children's Hospital institutional review board and was conducted in accordance with The Declaration of Helsinki. Informed consents were obtained from guardians of the patients.

Therapeutic Regimen

Patients were treated with a systemic chemotherapy regimen BCH-LCH 2014 (http://www.chictr.org.cn, identifier: ChiCTR2000030457), based on the LCH-III and Histiocyte Society-LCH salvage treatment.[11,19,20] To summarize, first-line therapy was a vindesine–steroid combination therapy (vindesine: 3 mg/m^2/day; prednisone: 40 mg/m^2/day), beginning with one or two 6-week courses of initial induction therapy followed by maintenance therapy (vindesine: 3 mg/m^2/day; prednisone: 40 mg/m^2/day; 6-mercaptopurine: 50 mg/m^2/day for patients with multisystem LCH). The overall duration of the first-line therapy was 12 months. Patients with poor response to initial treatment or who relapsed were shifted to the second-line treatment, composed of four 5-day courses of cytarabine (150 mg/m^2/day), cladribine (9 mg/m^2/day), vindesine (3 mg/m^2/day), and dexamethasone (6 mg/m^2/day), followed by another four 5-day courses of cytarabine, vindesine and dexamethasone, and maintenance therapy.

From January 2019, patients with refractory or relapsed multisystem LCH disease were given the BRAF inhibitor dabrafenib (http://www.chictr.org.cn, identifier: ChiCTR2000032844). Dabrafenib was administered orally (2 mg/kg twice a day) for 12 months, adjusted according to disease assessment. Patients were then treated with maintenance chemotherapy, including mercaptopurine, vindesine, and prednisone for 6 months.[21]

Assessment Criteria

Patients were stratified into single-system and multisystem LCH, based on the extent of involvement at diagnosis; the latter was defined as the involvement of 2 or more organs/systems with or without risk organs.[10] Treatment response was evaluated according to the International LCH Study Group Criteria.[10,11] Nonactive disease, active disease–better, and active disease–intermediate were defined as complete resolution, continuous regression of disease, or unchanged disease. Active disease–worse was assigned in case of disease progression or the appearance of new lesions. Patients who responded to therapy were defined as those who had nonactive disease or active disease/better response. Relapse was defined as the reappearance of signs and symptoms of active disease after either complete disease resolution or after a period of disease control that persisted for >3 months on maintenance therapy.[22]

Statistical Analyses

Between-group differences were compared by the Mann–Whitney *U* test for quantitative variables and the Fisher exact test for qualitative variables. Survival rates were estimated with the Kaplan–Meier method, and subgroups were compared with the log-rank test. Progression-free survival was calculated from the date of diagnosis or initial treatment until one of the following events: progression, relapse, or death, whichever came first. The patients without event were censored at the date of the last contact. Overall survival was defined as the time from the diagnostic date to death or the last follow-up. All tests were performed using SPSS 25.0 software (IBM Corp).

Results

Characteristics of Patients with LCH and Thymic Involvement

In total, 433 consecutive pediatric patients with newly diagnosed LCH were enrolled in our center from September 2016 to December 2019; 244 (56.4%) patients were classified as having single-system LCH, 117 (27.0%) patients had multisystem risk organ–negative LCH, and 72 (16.6%) had multisystem risk organ–positive LCH. Nineteen (4.4%) were diagnosed with LCH–thymic involvement; all presented with multisystem disease, with 8 having at least 1 risk organ involved. There were 8 (42.1%) boys and 11 (57.9%) girls with thymic involvement. The age of these patients at diagnosis ranged from 0.1 to 11.2 years, with a median age of 0.6 years, and 63% were aged <1 year.

When we compared clinical features between patients with multisystem LCH with or without thymic involvement (**Table I**), patients with thymic involvement were typically younger than those without thymic involvement ($P = .020$). Furthermore, patients with thymic involvement had greater frequencies of lung (73.3%) and thyroid (26.3%) involvement (P values were .001 and .028, respectively). Patients with thymic involvement exhibited less bone involvement than those without thymic involvement (47.4% vs 87.6%, $P < .001$). Other organ involvement, such as risk organs, skin, etc, showed no significant difference between the 2 groups and no correlation with thymic involvement (all $P < .05$). Of note, the positivity of BRAF-V600E mutation in lesional tissue did not differ between patients with multisystem LCH with and without thymic involvement (56.3% vs 67.8%, $P = .403$).

Clinical Manifestation and Biologic Measures

The initial symptoms leading to LCH diagnosis in patients with thymic involvement were rash (8/19, 42.1%), cough (4/19,

Table I. Comparison of clinical characteristics in patients with multisystem LCH with or without thymic involvement in this study

Clinical characteristics	Multisystem LCH	Multisystem LCH without thymic involvement	Multisystem LCH with thymic involvement	*P* value
No.	189	170	19	
Sex, No. (%)				
Male	111 (58.7%)	103 (60.6%)	8 (42.1%)	.144
Female	78 (41.3%)	67 (39.4%)	11 (57.9%)	
Age at diagnosis, y, No. (%)				
≥1	134 (70.9%)	127 (74.7%)	7 (36.8%)	.002
<1	55 (29.1%)	43 (25.3%)	12 (63.2%)	
Median (range)	1.8 (0.1-14.9)	1.9 (0.1-14.9)	0.6 (0.1-11.2)	.020
Bone involvement, No. (%)				
No	31 (16.4%)	21 (12.4%)	10 (52.6%)	<.001
Yes	158 (83.6%)	149 (87.6%)	9 (47.4%)	
Skin involvement, No. (%)				
No	88 (46.6%)	82 (48.2%)	6 (31.6%)	.226
Yes	101 (53.4%)	88 (51.8%)	13 (68.4%)	
Risk organ involvement, No. (%)				
No	117 (61.9%)	106 (62.4%)	11 (57.9%)	.804
Yes	72 (38.1%)	64 (37.6%)	8 (42.1%)	
Lung involvement, No. (%)				
No	122 (64.6%)	117 (68.8%)	5 (26.3%)	.001
Yes	67 (35.4%)	53 (31.2%)	14 (73.7%)	
Thyroid involvement, No. (%)				
No	170 (89.9%)	156 (91.8%)	14 (73.7%)	.028
Yes	19 (10.1%)	14 (8.2%)	5 (26.3%)	
Lymph node involvement, No. (%)				
No	143 (75.7%)	132 (77.6%)	11 (57.9%)	.087
Yes	46 (24.3%)	38 (22.4%)	8 (42.1%)	
Ear involvement, No. (%)				
No	147 (77.8%)	134 (78.8%)	13 (68.4%)	.381
Yes	42 (22.2%)	36 (21.2%)	6 (31.6%)	
Eye involvement, No. (%)				
No	166 (87.8%)	148 (87.1%)	18 (94.7%)	.478
Yes	23 (12.2%)	22 (12.9%)	1 (5.3%)	
Pituitary involvement, No. (%)				
No	153 (81.0%)	136 (80.0%)	17 (89.5%)	.537
Yes	36 (19.0%)	34 (20.0%)	2 (10.5%)	
Mucosa involvement, No. (%)				
No	177 (93.7%)	161 (94.7%)	16 (84.2%)	.106
Yes	12 (6.3%)	9 (5.3%)	3 (15.8%)	
BRAF-V600E in lesion tissues, No. (%)*				
Total available samples, No. (%)	134	118	16	
Negative	45 (33.6%)	38 (32.2%)	7 (43.8%)	.403
Positive	89 (66.4%)	80 (67.8%)	9 (56.3%)	

*BRAF-V600E mutation in biopsies of lesion tissue was determined in 135 patients with multisystem LCH.

21.1%), fever (3/19, 15.8%), bone pain (2/19, 10.5%), and mass (2/19, 10.5%), respectively. Most patients had an initial presentation due to multiple organs or systems involved. Only 2 patients were investigated initially for a mediastinal mass and were diagnosed as LCH with thymic involvement; the other 17 cases had thymic involvement discovered during the pretreatment clinical evaluation of LCH. Only 1 infant had specific symptoms of superior vein cava syndrome and respiratory distress related to thymic involvement at the onset of LCH. Seven patients had a cough, 2 had asthma, and wheeze, and all of them had lungs involved; therefore, it is difficult to ascertain whether these symptoms were caused by lung involvement or thymic involvement. A detailed clinical presentation of LCH patients with thymic involvement is shown in **Table II** (available at www.jpeds.com).

Notably, 16 (84.2%) of the patients with LCH with thymic involvement had decreased numbers of T lymphocytes at diagnosis (lower than the reference value for peripheral blood lymphocyte subsets of healthy children in China).[23] In contrast, only 33.1% (56/169) of the patients with multisystem LCH without thymic involvement had a decline of T cells ($P < .001$; **Figure 1**, A). Twelve patients with LCH with thymic involvement had reduction of both $CD4^+$ and $CD8^+$ T lymphocytes, one had only low $CD4^+$, and 3 had only $CD8^+$ decreased. Reduced $CD4^+$ or $CD8^+$ T lymphocytes were more prevalent in patients with thymic involvement than those without thymic involvement (P values were .005 and <.001, respectively; **Figure 1**, B and C). Moreover, 11 (57.9%) patients with thymic involvement presented with an elevated $CD4^+/CD8^+$ ratio, which was more prevalent than patients without thymic involvement ($P = .005$, **Figure 1**, D). In total, 47.4% (9/19) of patients with LCH with thymic involvement had a drop in the levels of IgG (less than reference value 7 g/L), whereas 20.7% of patients with multisystem LCH without thymic involvement had reduced IgG ($P < .001$, **Figure 1**, E).

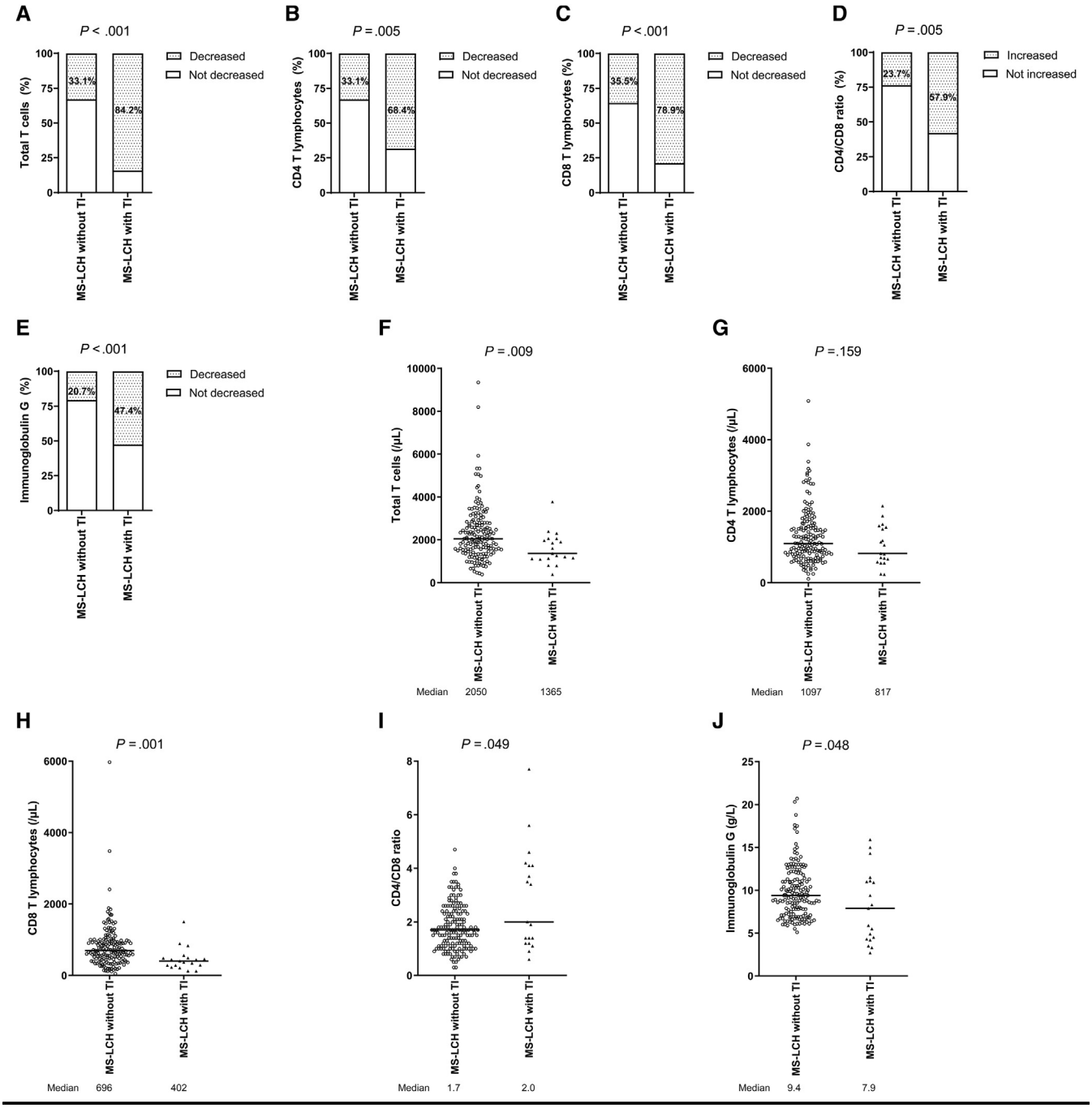

Figure 1. Comparison of T-lymphocyte subsets and IgG in patients with multisystem LCH with or without thymic involvement. **A-E,** The proportion of decreased T-lymphocyte subsets and IgG levels; and **F-J,** absolute numbers of T-lymphocyte subsets and IgG levels. *MS*, multisystem; *TI*, thymic involvement.

Furthermore, by comparing absolute numbers of T lymphocyte subsets, the numbers of total T cells, $CD8^+$ T lymphocytes, and IgG levels were significantly lower in patients with LCH and thymic involvement than in patients without thymic involvement (*P* values were .009, .001, and .048, respectively; Figure 1, F, H, J). The numbers of $CD4^+$ T lymphocytes were not deceased in patients with thymic involvement (*P* = .159, Figure 1, G), but the $CD4^+/CD8^+$ ratios were significantly increased compared with patients without thymic involvement (*P* = .049, Figure 1, I). Details of the T-lymphocyte subsets are shown in Table III (available at www.jpeds.com).

Imaging Presentation of Thymus

All 19 patients with thymic involvement had abnormal imaging in thoracic CT and/or thymic ultrasound scan at diagnosis. Moreover, the diagnosis of LCH–thymic involvement was confirmed by histologic examination of a biopsy of the thymus

in 7 patients. Immunohistochemical stains showed that both CD1a and CD207 were positive (**Figure 2**; available at www.jpeds.com). Six (85.7%) of the 7 patients presented with an enlarged mass in the anterior mediastinum on CT scan, 3 of whom were diagnosed as an enlarged thymus. Two also showed tracheal compression (**Figure 3**, A), one had punctuated calcifications in the thymus (**Figure 3**, C), and another patient displayed nodular contour of the thymus. Ultrasonography scans in these 6 patients showed increased volume of the thymus with uneven, decreased internal echoes. In addition, 1 patient with thymic involvement presented with diffusely thickened pleura extending to the anterior mediastinum with unclear borders on CT (**Figure 3**, E) and ultrasonography scan. The images of thymic lesions were significantly improved after treatment of LCH (**Figure 3**, B, D, and F).

In 12 patients without histologic confirmation, similar imaging presentations were found on CT and/or ultrasonography scan. Notably, 2 cases had no obvious abnormality of thymus or mediastinum on CT imaging, whereas B-

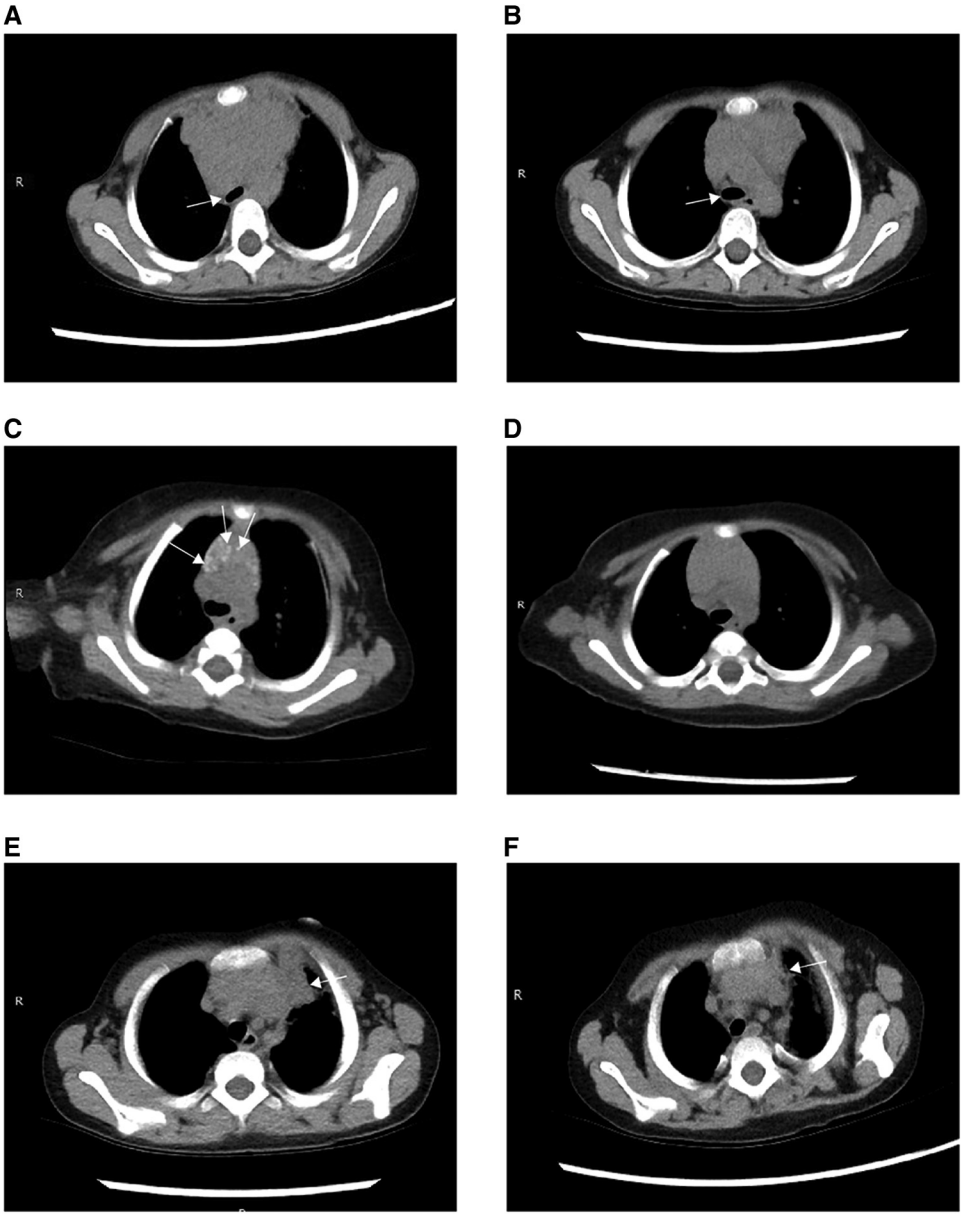

Figure 3. Imaging presentation of thymus on thoracic CT of patients with LCH with thymic involvement. **A,** Presence of an enlarged mass in the anterior mediastinum and tracheal compression (*arrow*) in patient P9. **B,** Reduction of thymus size and tracheal compression (*arrow*) after 6 weeks of induction treatment in patient P9. **C,** Presence of calcifications in the thymus of patient P17 (*arrows*). **D,** Reduced calcifications in the thymus of patient P17 after 3 months of dabrafenib administration in patient P17. **E,** Presence of the thickening pleura diffusely extends to the anterior mediastinum with unclear boundaries in patient P18 (*arrow*). **F,** Reduction of thickening pleura after six week of induction treatment in patient P18 (*arrow*).

ultrasound scan revealed the thymic involvement due to the presence of ectopic thymic tissue in the thyroid. Summary of imaging features of thymic involvement on CT and ultrasonography scan in patients with LCH at diagnosis are shown in **Table IV** (available at www.jpeds.com).

Treatment Response and Survival

As shown in **Figure 4** (available at www.jpeds.com), 17 patients with LCH with thymic involvement were treated initially with induction therapy based on the vindesine–prednisone combination. After the 6-week course of induction treatment, 8 (47.1%) patients were evaluated as active disease–better, 6 (35.3%) patients were active disease–intermediate, and 3 (17.6%) were active disease–worse, according to the evaluation criteria of the International LCH Study Group. Eight (47.1%) patients showed improvement of thymic lesions at week 6. Furthermore, in 8 patients with concurrent risk organs and thymus involvement, the response rates (nonactive disease or active disease-better) were 12.5% (1/8) for risk organs, 50.0% (4/8) for thymus, and 62.5% (5/8) for other organs or systems. Another patient with severe pneumonia and respiratory distress was not given any chemotherapy and died 2.7 months after admission. One patient was directly treated with dabrafenib due to her young age and poor vascular condition. She was treated with 12 months of dabrafenib, followed by one-half of a year of maintenance chemotherapy. Thymic involvement and other lesions were significantly improved after 6 months of the administration, and she achieved nonactive disease status after discontinuation.

Two of the 17 patients treated with the first-line therapy had resolution of LCH disease, including the thymus lesion. Another 2 patients had an active disease–better response at week 6 of induction therapy and then gave up treatment and were lost to follow-up. Thirteen of the patients had either progression, relapse, or no improvement of risk organs and were shifted to either salvage or targeted therapy: 9 patients received the second-line therapy including cladribine and cytarabine; 4 patients with BRAF-V600E mutation were given the BRAF inhibitor dabrafenib. In the 9 patients treated with the second-line treatment, 3 patients experienced thymus progression or relapse. In detail, 1 risk organ–positive patient experienced thymus progression after 3 courses of second-line therapy. He was treated with dabrafenib, to which he initially responded but then relapsed after stopping dabrafenib. Two patients who had thymus progression or relapse during the second-line treatment had disease resolution after a shift to dabrafenib treatment and achieved nonactive disease status in the thymus. Another 6 patients achieved nonactive disease status after second-line therapy, and they all had resolution of their thymic disease.

In the 4 patients who shifted from first-line therapy to targeted therapy, dabrafenib was administrated 12 months, followed by one-half a year of chemotherapy. Patients had improvement of the thymus after 1-3 months of dabrafenib administration and achieved nonactive status of the thymus at 9-12 months. All 4 patients have stopped taking dabrafenib. Two had complete drug discontinuation, and one of them had a bone relapse 4 months later, whereas the other had disease resolution. Two other patients underwent maintenance chemotherapy and at last follow-up they both had LCH disease resolution. Longer follow-up is required to determine long-term outcomes.

Overall, 92.3% (12/13) of the patients who did not respond to first-line therapy had resolution of the thymus after second-line therapy and/or targeted therapy, and only one risk organ–positive patient experienced multiple episodes of progression or recurrence. There were no significant differences in treatment outcomes between patients who were shifted from first-line treatment to second-line chemotherapy and those switched to dabrafenib (progression/relapse rate: 3/9, 33.3% vs 1/4, 25%, $P = 1.000$). Details of treatment response and outcomes of patients with LCH with thymic involvement are shown in **Table V** (available at www.jpeds.com).

With a median follow-up of 19.8 months (range 1.6-44.3 months), the estimated 3-year overall survival of patients with thymic involvement was 94.4 ± 5.4%, similar to the patients with multisystem LCH without thymic involvement (98.2% ± 1.0%, $P = .290$; **Figure 5**, A). Eight (42.1%) patients experienced progression or relapse, with the sites being liver (4), thymus (4), bone (1), and oral mucosa (1). The 3-year progression-free survival did not significant differ between the patients with multisystem LCH with and without thymic involvement (49.4% ± 13.5% vs 45.7% ± 4.4%, $P = .876$; **Figure 5**, B). Furthermore, there was no significant difference between the patients with and without thymic involvement in multisystem risk organ–negative or risk organ–positive patients (**Figure 5**, C and D).

No patients had a severe infection or other adverse events (AEs) during the first-line therapy. However, most patients (8/9, 88.9%) treated with second-line chemotherapy had myelosuppression and profound pancytopenia (Common Terminology Criteria for Adverse Events grade 3-4), complicated by severe infection and fever. In contrast, the 8 patients given dabrafenib had no AE above grade 3 ($P < .001$). Five AEs of grade 1-2 occurred in 50% (4/8) of patients during dabrafenib administration, which were skin rashes (3), headache (1), and decreased appetite (1).

Discussion

This study retrospectively analyzed the characteristics and treatment outcomes of patients with pediatric LCH with thymic involvement. Patients with LCH with thymic involvement had special clinical, biologic, and imaging features compared with patients without thymic involvement. Moreover, most patients with thymic involvement achieved disease resolution with chemotherapy or targeted therapy.

Thymic involvement is observed rarely in LCH and probably underestimated.[14-17] Our data showed that thymic involvement occurred in 4.4% of a large consecutive Chinese pediatric LCH cohort, which was slightly greater than the French cohort.[14] Most of the patients with thymic involvement in this study were infants aged <1 year, similar to the previous studies.[14-16]

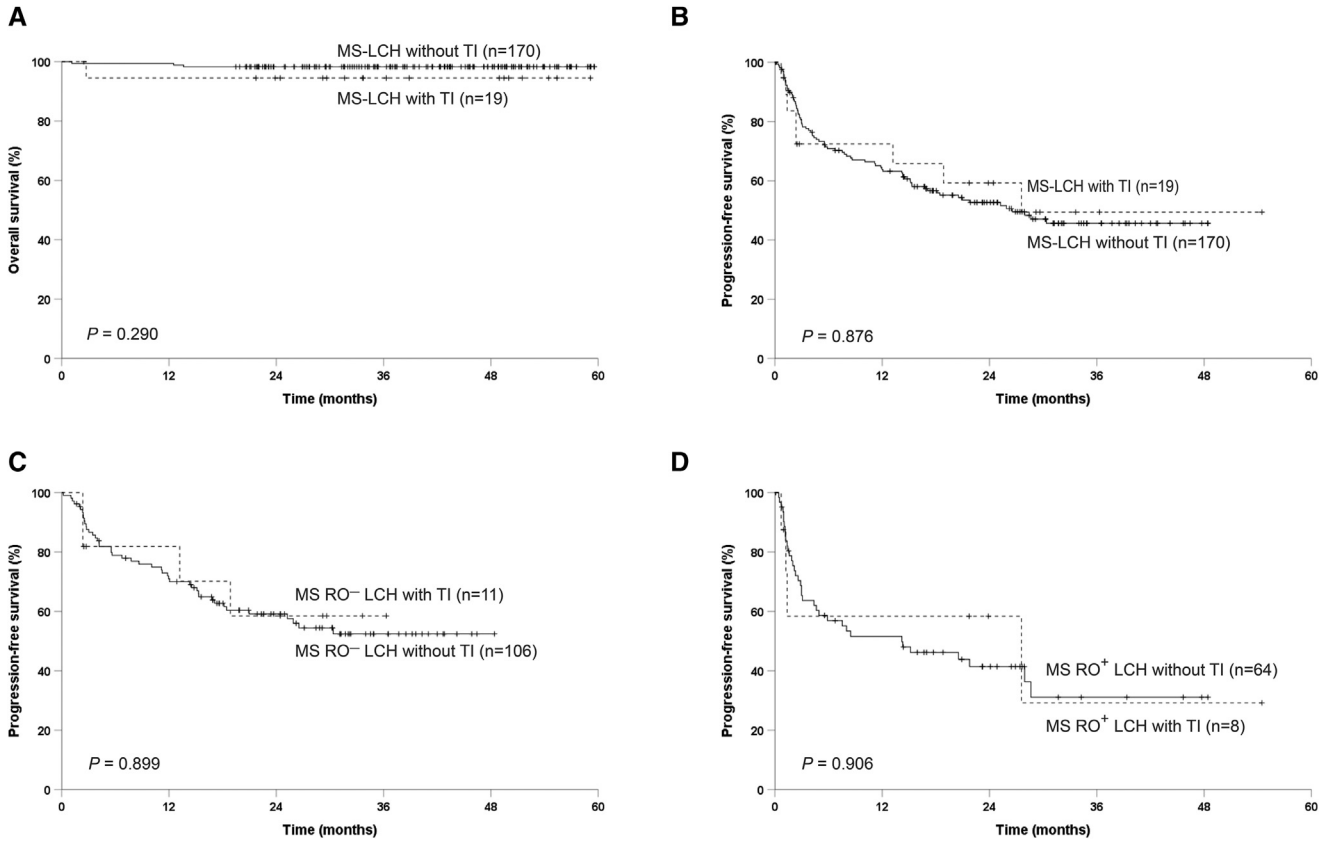

Figure 5. Comparison of survival rates for patients with LCH with or without thymic involvement. **A,** Overall survival for patients with multisystem LCH. **B,** Progression-free survival for patients with multisystem LCH. **C,** Progression-free survivals for multisystem risk organ negative-LCH patients. **D,** Progression-free survivals for multisystem risk organ positive-LCH patients. *RO*, risk organ.

Because all patients with thymic involvement had multisystem involvement, the clinical characteristics of patients with thymic involvement were compared with those patients with multisystem LCH without thymic involvement. Patients with thymic involvement had greater frequencies of lung and thyroid involvement, which might be due to these organs' close proximity. The reason for less bone involvement remains unclear. Herein, we found no relationship between thymic involvement and risk organs involvement. Specific symptoms related to thymic involvement in patients with LCH were rare, most often occurring in infants. Therefore, for infants with LCH with lung or thyroid involvement, or symptoms such as tracheal compression and dyspnea, it is necessary to confirm the LCH involvement of thymus.

The thymus is an organ that produces functionally competent T lymphocytes, and $CD8^+$ T cells are chiefly generated in the thymus through the process of positive selection, which has a central role in immune defense against viral infection, intracellular pathogens, and malignant tumors.[24-26] We found that most patients with LCH with thymic involvement had alteration of immunocompetence with decreased T lymphocytes and IgG levels at diagnosis, indicating the impairment of function with the thymus. Of note, approximately one-half of patients had a noticeable increased $CD4^+/CD8^+$ ratio, indicating a significant decrease in $CD8^+$ T lymphocytes.

Histologic examination and immunohistochemical assay remain the gold standard for diagnosing LCH with thymic involvement, and there were variable histopathologic patterns of thymic involvement, with either a medullary restricted pattern or more diffuse gland involvement.[27] However, biopsy for histologic confirmation is limited in clinical practice because it is an invasive and potentially dangerous procedure. The imaging findings in this study confirmed the previously reported morphologic description,[14-16] suggesting that thoracic CT and ultrasonography scan are useful techniques to evaluate thymic involvement. The combination of these 2 examinations might be helpful both in improving the diagnosis of thymic involvement and also in monitoring treatment response of the thymus.

Because all patients with thymic involvement presented with multisystem disease, they were treated with systemic therapy. Thymic lesions improved in approximately one-half of the patients after 6 weeks of induction treatment, which was similar to the response in other organs and better than risk organs. Most patients who did not respond to first-line therapy had resolution of the thymic disease after second-line and/or targeted therapy. Our data showed that salvage therapy including cytarabine and

cladribine could effectively control active LCH with thymic involvement but was associated with high toxicity and required extensive supportive care. Patients with LCH with thymic involvement were usually younger than 1 year with impaired immunocompetence, and severe grade 3-4 infections are potentially life-threatening. BRAF inhibitors have demonstrated dramatic effectiveness in treating patients with BRAF-mutant LCH over recent years.[21,28,29] Our findings also showed that dabrafenib could control LCH disease and thymic involvement effectively with less toxicity. Therefore, targeted therapy might provide a promising treatment option for infants with BRAF-V600E mutant-LCH-thymic involvement.

Despite the improvements in overall survival, disease reactivations/relapse occurred in approximately one-third to one-half of patients with LCH, which remains an obstacle for improving long-term prognosis.[30,31] Only 1 patient died in this study cohort, but approximately one-half of the patients with thymic involvement had progression or relapse. Unlike the most common bone recurrence in LCH, thymic recurrence is common in patients with thymic involvement. Although the progression-free survival was not significantly different in the patients with and without thymic involvement in multisystem risk organ–negative or risk organ–positive patients, and the thymus was not considered a high-risk organ, monitoring for thymic recurrence should be part of clinical management.

In conclusion, thoracic CT and ultrasonography scan were useful techniques to diagnose and evaluate LCH with thymic involvement. First- or second-line chemotherapy could resolve most thymic lesions, and the BRAF inhibitor dabrafenib might provide a promising treatment option with less toxicity for infants with BRAF-V600E–positive LCH with thymic involvement. Achieving sustained resolution of LCH disease and thymic involvement remains a challenge, and further prospective studies with larger sample sizes and extended follow-up will be required. ■

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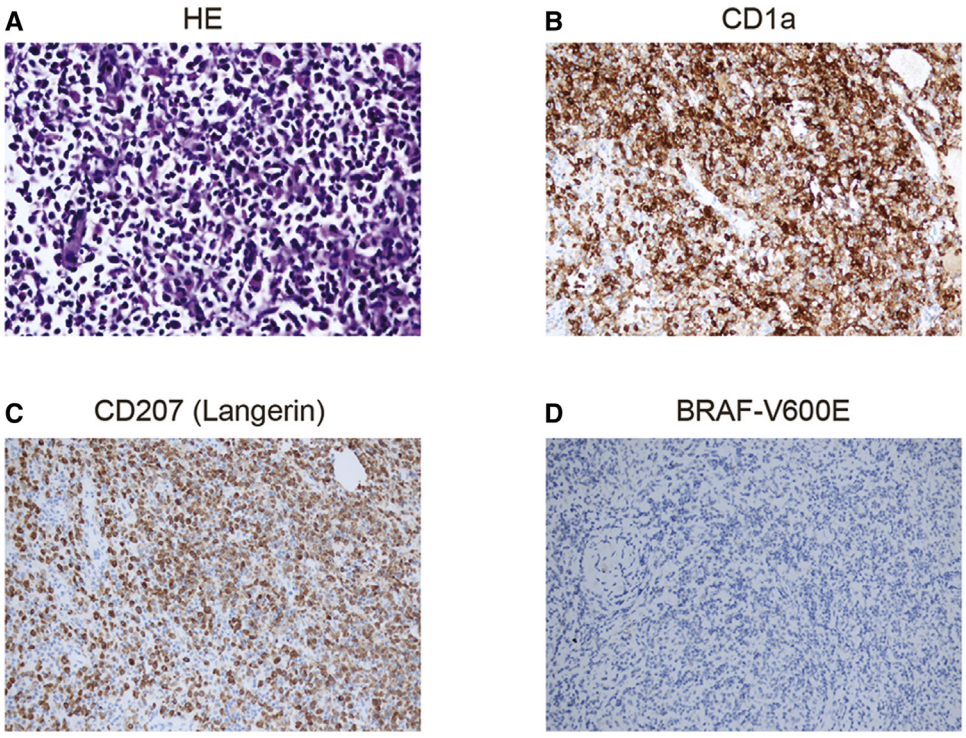

Figure 2. Histologic examination and immunohistochemical stains of a biopsy of the thymus in the patients with LCH with thymic involvement. **A,** HE; **B,** CD1a; **C,** CD207 (Langerin); **D,** BRAF-V600E. *HE*, hematoxylin and eosin.

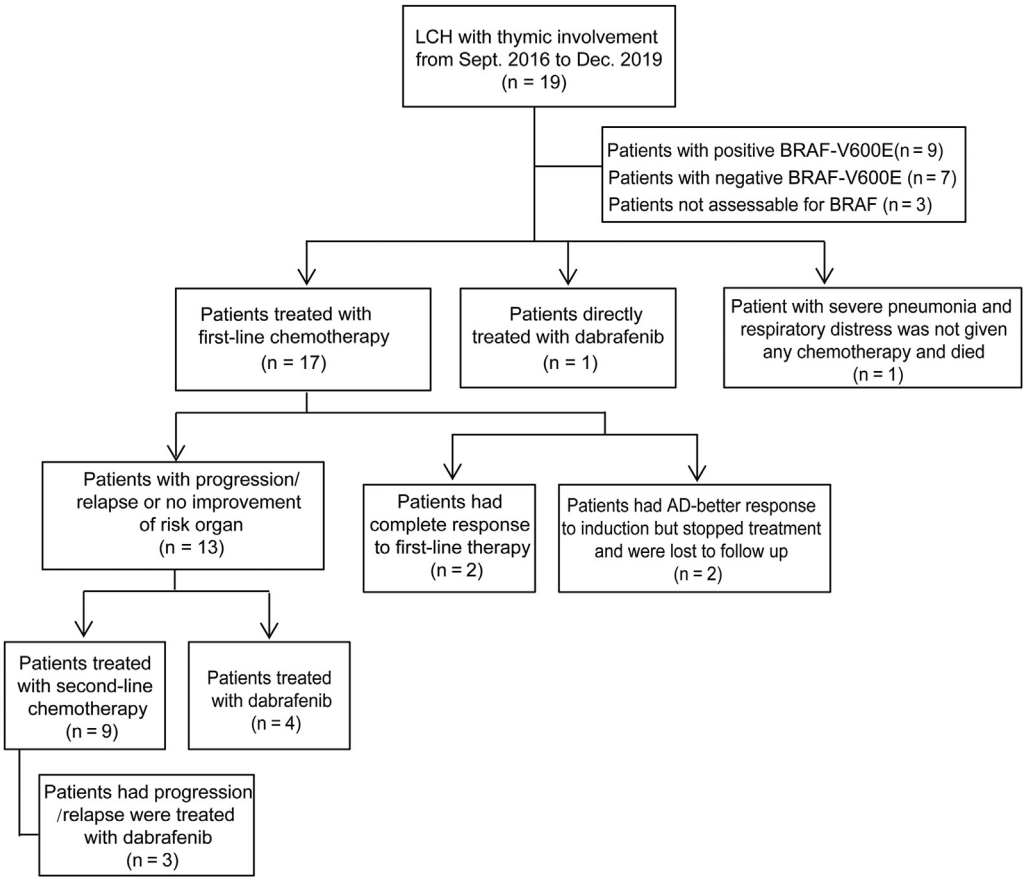

Figure 4. Flow diagram of treatment in the patients with LCH with thymic involvement. *AD*, active disease.

Table II. Clinical presentation of patients with LCH with thymic involvement

No. patients	Age at diagnosis, y	Sex	Clinical symptoms	Involvement sites	Clinical classification*	BRAF-V600E mutation
P1	0.86	Female	Fever	Thymus, liver, lung, lymph nodes	Multisystem risk organ positive	Positive
P2	0.16	Female	Right frontal mass	Thymus, liver, spleen, lung, skin, pituitary, ear, bones	Multisystem risk organ positive	Negative
P3	0.30	Male	Rash, cough with asthma and wheezing	Thymus, liver, lung, skin, lymph nodes, ear	Multisystem risk organ positive	Positive
P4	0.60	Male	Fever, cough	Thymus, lung	Multisystem risk organ negative	Positive
P5	0.54	Female	Fever	Thymus, liver, spleen, lung, skin, lymph nodes, ear, bones	Multisystem risk organ positive	Negative
P6	0.67	Male	Rash, cough	Thymus, liver, lung, skin, ear	Multisystem risk organ positive	NA
P7	0.58	Female	Fever, cough, respiratory distress	Thymus, spleen, lung, skin	Multisystem risk organ negative	NA
P8	0.52	Female	Rash, cough with asthma and wheezing	Thymus, liver, spleen, lung, skin, lymph nodes, ear, bones, thyroid	Multisystem risk organ positive	Positive
P9	4.00	Male	Fever, cough	Thymus, lung, skin	Multisystem risk organ negative	Negative
P10	1.20	Female	Fever	Thymus, lung, lymph nodes	Multisystem risk organ negative	Negative
P11	0.50	Female	Rash, purulent secretion in external auditory canal	Thymus, lung, skin, lymph nodes, oral mucosa, ear	Multisystem risk organ negative	Positive
P12	0.10	Female	Rash	Thymus, lung, skin, thyroid	Multisystem risk organ negative	Negative
P13	6.00	Male	Bone pain	Thymus, bone	Multisystem risk organ negative	Negative
P14	2.10	Female	Bone pain	Thymus, skin, bones, thyroid	Multisystem risk organ negative	Positive
P15	10.30	Male	Neck mass	Thymus, pituitary, thyroid, lymph nodes, bones	Multisystem risk organ negative	NA
P16	11.25	Female	Rash, angular mass, recurrent oral ulcer	Thymus, bones, oral mucosa, ear, eye, skin	Multisystem risk organ negative	Negative
P17	0.20	Male	Rash, fever	Thymus, skin, lung, thyroid, bones, gums	Multisystem risk organ negative	Positive
P18	4.40	Male	Cough	Thymus, liver, spleen, lung, pleura	Multisystem risk organ positive	Positive
P19	0.50	Female	Rash, purulent secretion in external auditory canal	Thymus, liver, spleen, lung, skin, bones, ear, lymph nodes	Multisystem risk organ positive	Positive

NA, not available.
*Rick organ positive indicates multisystem LCH with risk organ involved; risk organ negative indicates multisystem LCH without risk organ involved.

Table III. The numbers of total T lymphocytes and their subsets in pediatric patients with LCH and thymic involvement

No. patients	Total T cells, /μL	Normal range, /μL	CD4 T lymphocytes, /μL	Normal range, /μL	CD8 T lymphocytes, /μL	Normal range, /μL	CD4/CD8 ratio	Normal range	IgG, g/L
P1	2388	2488-5422	1869	1433-3874	441	710-1843	4.2	0.7-2.8	4.5
P2	1851	2766-4068	1635	1890-2988	211	658-1276	7.7	1.62-3.77	5.5
P3	1210	2179-4424	686	1461-3018	486	556-1687	1.4	0.7-2.8	3.3
P4	1132	2187-6352	549	1125-3768	490	686-2278	1.1	0.7-2.8	4.9
P5	1089	2488-5422	551	1433-3874	445	710-1843	1.2	0.7-2.8	11.0
P6	2056	2187-6352	1552	1125-3768	458	686-2278	3.4	0.7-2.8	11.5
P7	1365	2488-5422	1051	1433-3874	285	710-1843	3.7	1.1-2.0	2.7
P8	1604	2488-5422	1178	1433-3874	290	710-1843	4.1	0.7-2.8	5.9
P9	2059	1424-2664	817	686-1358	891	518-1125	0.9	0.7-2.8	15.9
P10	1262	1775-3953	659	948-2477	562	531-1521	1.2	1.05-2.53	11.1
P11	1962	2766-4068	1590	1890-2988	284	658-1276	5.6	1.62-3.77	3.5
P12	1899	2421-4577	1498	1744-3226	369	609-1348	4.1	1.97-3.32	4.3
P13	789	1424-2664	240	686-1358	402	518-1125	0.6	0.87-1.94	7.9
P14	1153	1775-3953	803	948-2477	229	531-1521	3.5	1.05-2.53	10.9
P15	387	1325-2276	232	531-1110	123	480-1112	1.9	0.81-1.66	8.3
P16	1117	1297-2480	700	621-1258	345	509-1150	2.0	0.92-1.73	15.0
P17	804	2179-4424	577	1461-3018	126	556-1687	4.6	1.47-3.23	4.2
P18	2306	1794-4247	1137	902-2253	834	580-1735	1.4	0.90-2.13	9.4
P19	3772	2766-4068	2146	1890-2988	1501	658-1276	1.4	1.62-3.77	14.3

Table IV. Imaging features of thymic involvement in patients with LCH at diagnosis

Examination methods	Imaging features	Number of patients, No. (%)
CT	Mass in the anterior mediastinum	13 (68.4)
	Enlargement of thymus	9 (47.4)
	Tracheal compression	3 (15.8)
	Punctuated calcification	6 (31.6)
	Nodosity enhancement	1 (5.3)
	Diffuse pleural thickening	1 (5.3)
Ultrasound scan	Enlargement of thymus	14 (73.7)
	Decreased internal echoes in thymus	13 (68.4)
	Thymus calcification	6 (31.6)
	Diffuse pleural swelling	1 (5.3)
	Ectopic to thyroid	2 (10.5)

Table V. Treatment response and outcome of patients with LCH with thymic involvement

No. of patients	Therapy	Treatment response at week 6 of induction therapy (overall)	Thymic response at week 6	Outcome
P1	First-line therapy + second-line therapy + dabrafenib	Active disease–worse	Active disease–intermediate	Liver progressed at week 7 of induction therapy; thymus progressed after 3 courses of the second-line therapy; thymus relapsed 2.5 years after dabrafenib discontinuation
P2	First-line therapy	Active disease–better	Active disease–better	Gave up treatment and lost to follow-up at week 6 of induction therapy
P3	First-line therapy	Active disease–intermediate	Active disease–intermediate	Nonactive disease
P4	First-line therapy + second-line therapy + dabrafenib	Active disease–intermediate	Active disease–intermediate	Thymus relapsed 5 months after discontinuation of second-line therapy; nonactive disease now
P5	First-line therapy + second-line therapy + dabrafenib	Active disease–worse	Active disease–intermediate	Liver and bone progressed at week 6 of induction therapy; thymus progressed after four courses of the second-line therapy; current overall status is active disease-better, nonactive disease for thymic involvement
P6	First-line therapy + second-line therapy	Active disease–worse	Active disease–intermediate	Liver and lung progressed at week 6 of induction therapy; current overall status is active disease–better, nonactive disease for thymic involvement
P7	No chemotherapy or dabrafenib	NA	NA	Died of severe pneumonia and respiratory distress 2.7 months after admission
P8	First-line therapy + dabrafenib	Active disease–intermediate	Active disease–better	T4 relapsed 4 months after dabrafenib discontinuation; nonactive disease for thymic involvement
P9	First-line therapy + second-line therapy	Active disease–better	Active disease–better	Current overall status is active disease–better, nonactive disease for thymic involvement
P10	First-line therapy + second-line therapy	Active disease–better	Active disease–intermediate	Thymus progressed at week 11 of induction therapy; nonactive disease now
P11	First-line therapy	Active disease–better	Active disease–better	Gave up treatment and lost to follow-up at week 6 of induction therapy
P12	Dabrafenib	NA	NA	Current overall status is active disease–better, nonactive disease for thymic involvement
P13	First-line therapy	Active disease–better	Active disease–better	Nonactive disease now
P14	First-line therapy + second-line therapy	Active disease–better	Active disease–better	Liver progressed at week 11 of induction therapy; current overall status is active disease–better, nonactive disease for thymic involvement
P15	First-line therapy + second-line therapy	Active disease–intermediate	Active disease–intermediate	Current overall status is active disease–better, nonactive disease for thymic involvement
P16	First-line therapy + second-line therapy	Active disease–better	Active disease–intermediate	Thymic involvement and oral mucosa relapsed 1 year after the first-line therapy; current overall status is active disease–better, nonactive disease for thymic involvement
P17	First-line therapy + dabrafenib	Active disease–better	active disease–intermediate	Nonactive disease now
P18	First-line therapy + dabrafenib	Active disease–intermediate	active disease–better	Current overall status is active disease–better, nonactive disease for thymic involvement
P19	First-line therapy + dabrafenib	Active disease–intermediate	active disease–better	Current overall status is active disease–better, nonactive disease for thymic involvement

NA, not available.