Radiological Features of Thymic Langerhans Cell Histiocytosis

Karoly Lakatos,1 Heidrun Herbrüggen,2 Ulrike Pötschger,2 Helmut Prosch,3 and Milen Minkov2,4*

TI was reported in 18/1,264 (0.4%) LCH patients. All nine patients with TI at initial LCH presentation were below 2 years of age and had multisystem LCH (9/242, 4%). Images (sonography, CT, MRI) for central review were available in 15 cases. Characteristic findings of TI were thymus enlargement (67%), few to many cysts (80%), and few to many calcifications (100%). Sonographic and MRI findings were in excellent agreement. We recommend adding sonography of the thymus to the standard for initial clinical evaluation of LCH patients below the age of 2 years. Pediatr Blood Cancer 2013;60:E143–E145.

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Key words: histiocytosis X; imaging; sonography; thymus

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease characterized by proliferation of clonal dendritic cells [1,2]. It may affect virtually any organ and its clinical manifestations range from a single bone lesion to multisystem disease. Single cases and small series [3–7] document thymus involvement (TI) by LCH but its frequency is still unknown. This article presents results of a retrospective search for TI in a LCH database with a particular focus on radiological findings.

PATIENTS AND METHODS

The cohort included 1,264 patients with LCH enrolled into the consecutive international studies LCH-I, LCH-II, and LCH-III by 62 institutions of the German Society for Pediatric Hematology and Oncology (GPOH) between 1992 and 2009. Inclusion criteria were biopsy-proven LCH, age <18 years, no earlier treatment for LCH and written informed consent. All patients had standardized initial evaluation including chest radiography. As routine thymus imaging was not part of the patient evaluation, the database was screened for incidental reporting of TI. Images of the thymus were collected and centrally reviewed by two experienced radiologists with emphasis on thymus size, texture, cysts, and calcifications. Thymus size was assessed at maximum transverse width [8]. Calcifications were semi-quantitatively categorized as: + + + + + + + + (several dot-like); ++ + + + + + + + + + + (many, extensive, coarse). Cysts were classified as: + + + + + + + + + + (10) or ++ + + + + (10).

Eighteen patients with TI were identified, 15 of them had sufficient clinical information and images available for review. One patient (case 3) has been previously published for his instructive clinical course [9]. We looked for association between TI and age and disease extent for the 15 patients only. Three histology reports from thymus biopsy were available. Two of them confirmed active LCH lesions and one (fine-needle biopsy) revealing unspecific inflammatory changes.

RESULTS

Prevalence of TI

Eighteen patients (18/1,264; 1.4%) were reported to have TI. The population characteristics of the 15 patients with TI and available clinical and imaging information are summarized in a Supplementary Table. TI was diagnosed at initial LCH presentation (n = 9) or developed later (n = 6). TI at initial disease presentation was seen exclusively in patients with multisystem LCH (9/397, 2% vs. 9/867 SS-LCH; P < 0.001). All nine patients were below 2 years of age at LCH presentation (9/242, 4% vs. 0/155: P < 0.015). Among those who developed TI later, only one had an initial disease presentation single-system LCH (isolated skin disease). At the time TI was detected all patients had active disease in at least one additional organ, and thus were classified as MS-LCH. The clinical course of LCH in the 15 patients with available clinical information is presented in a Supplementary Figure.

Imaging Findings

The findings based on the first available thymus images are presented in Table 1. Ten patients (67%) had an enlarged thymus. Few or many cysts with a diameter of up to 7 mm were present in 12 patients (80%). Few, some or many calcifications were present in 15 patients (100%).

SONOGRAPHY

Affected thymus appeared inhomogeneous with some to many calcifications (Fig. 1A) and few to many hypoechogenic cysts up to 4–5 mm in diameter.

CT

Affected thymus appeared inhomogeneous containing hypodense (cysts) and hyperdense (calcifications) areas as compared to muscle density. Calcifications (Fig. 1B) varied from few to many. In five of seven cases very well defined, round to oval cysts with a

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Conflict of interest: Nothing to declare.

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### TABLE I. Initial Radiological Findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at LCH diagnosis (mo)</th>
<th>LCH diagnosis to first TI image (months)</th>
<th>Imaging technique</th>
<th>Size* (cm)</th>
<th>Cysts a</th>
<th>Calcifications a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0</td>
<td>CT</td>
<td>9.4 (4.9)</td>
<td>None</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>13</td>
<td>CT</td>
<td>7.6 (5.0)</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>3</td>
<td>0.25</td>
<td>3</td>
<td>CT</td>
<td>5.0 (4.9)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>0</td>
<td>MRI</td>
<td>3.7 (4.9)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>0</td>
<td>CT</td>
<td>4.5 (4.9)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>0</td>
<td>CT</td>
<td>7.6 (4.9)</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>7</td>
<td>21</td>
<td>0</td>
<td>US</td>
<td>8.0 (4.9)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>0</td>
<td>MRI</td>
<td>7.7 (4.9)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>4</td>
<td>MRI</td>
<td>8.4 (4.9)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>0</td>
<td>MRI</td>
<td>4.0 (4.9)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
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<td>0</td>
<td>MRI</td>
<td>4.0 (4.9)</td>
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<tr>
<td>12</td>
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<td>2</td>
<td>MRI</td>
<td>5.3 (4.9)</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>13</td>
<td>2.5</td>
<td>1</td>
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<tr>
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<td>15</td>
<td>MRI</td>
<td>5.5 (4.9)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>17</td>
<td>0</td>
<td>MRI</td>
<td>2.9 (4.9)</td>
<td>none</td>
<td>-</td>
</tr>
</tbody>
</table>

*aSize: Maximum transverse width, age appropriate references [10] provided in brackets.

*aCysts: ++ few (<10); +++ many (>10); n.a.: not assessable.

*aCalcifications: ++ few (single dot-like); +++ some (multiple); +++ many (extensive, coarse).

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Diameter between 3 and 7 mm were present. Cysts were not evaluable in two cases due to poor image quality.

#### MRI

Affected thymus appeared inhomogeneous with hypointense areas on T1-weighted MRI images (Fig. 1C), corresponding to either cysts or calcifications. On T2-weighted images (Fig. 1D), cysts appeared hypointense, while calcifications were hypointense or without signal. Images after contrast application were available in six patients, all revealing an extensive contrast uptake. Thymus was evaluated by more than one technique in seven patients and the findings were quite consistent. Of particular interest is the excellent agreement between sonography and MRI (Table I).

Follow-up images were available in a few patients. Imaging time points and treatment varied considerably, thus precluding conclusions about TI dynamics. Complete reversal of TI (normalization of thymus size and complete disappearance of calcifications and cysts) was documented in six cases on follow-up images performed between 0.6 and 4.5 years after diagnosis of TI.

#### DISCUSSION

TI in LCH has been unequivocally documented in a number of case reports [6,7,10,11] but its frequency is still unknown. The articles of Newton et al. and Junewick et al. [5,12] suggest that it may be more common than previously recognized. Overall TI frequency of 1.4% in our cohort is most probably underestimated. According to a recent retrospective study [13], TI frequency is obviously age-related (6.5% among infants with LCH). In our series...

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**Fig. 1.** A: Sonography; thymus enlargement, calcifications and cysts; B: Computed tomography; enlarged thymus with smooth contours and punctate calcifications; C: T1W MRI image showing enlarged thymus hypointense areas representing small cysts and dot-like calcifications; D: T2W MRI image of the same patient revealing hyperintense (cystic) areas and dot-like hypointense areas corresponding to calcifications; solid arrows show calcifications; dotted arrows show cysts.

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TI at initial LCH presentation was reported exclusively in MS-LCH patients younger than 2 years (9/242, 4%). Summarizing our experience and literature data, we conclude that TI is most common in young children with MS-LCH.

Current guidelines for evaluation of patients with LCH do not require routine thymus imaging. TI can be easily overlooked on the mandatory chest radiograph, as (i) in routine examination thymus size is subjectively assessed; (ii) a large thymus is not unusual in healthy infants; and (iii) as shown by our data the size of an affected thymus is not always impressive. Asymptomatic thymic mass was suspected on mandatory chest X-ray or was revealed by a chest CT performed for other reasons (e.g., suspected pulmonary or osseous LCH lesions) in both our series and the literature. This may be the explanation for the striking association of thymic and pulmonary LCH reported by Heller et al. [14]. A thymic mass may however be symptomatic. The most common presentations reported in the literature are jugular or supraclavicular mass, cough, chest pain, impaired respiration, and superior vena cava syndrome [7,10,11,13,15,16]. The rare cases of a bulky mediastinal mass causing compression of large vessels and/or the lower airways may have crucial impact on both differential diagnosis and clinical management [9,16].

On chest radiographs TI presents as unspecific mediastinal enlargement [5,10,11,14–18]. Sonography, CT and MRI allow for assessment of thymus size and texture, and hence for recognition of cysts and calcifications. Previous reports [6,7,10,11] and the two biopsies in our series document a correlation between pathology and radiological findings. Thus, the presence of calcifications and/or cysts in normal or enlarged thymus in the setting of LCH confirmed by biopsy of another organ can be considered diagnostic for TI.

In the literature, CT assessed thymus in LCH patients or MRI performed for other reasons (e.g., respiratory symptoms or pulmonary involvement suggested by radiography [5,10,11,14–18]). However, both imaging modalities are hardly to justify in young children, as they require sedation for optimal quality and CT is additionally associated with radiation load. Sonography was only exceptionally used for this indication [18]. It showed good visualization quality and an excellent agreement with MRI in our cohort. In addition, ultrasound has the advantage of being easily available, radiation-free, and not requiring sedation. Based on our findings we recommend sonography for thymus assessment in LCH patients below the age of 2 years.

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REFERENCES