Lymphomatoid Papulosis in Children

A Retrospective Cohort Study of 35 Cases

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Background: Lymphomatoid papulosis (LyP) is a rare entity, considered to be part of the spectrum of the CD30+ cutaneous lymphoproliferative disorders. About 10% to 20% of the adult LyP patients will develop an associated lymphoid malignancy. Only a few cases of LyP have been described in children, and the risk of associated lymphoid malignancies in these patients is not known.

Objectives: To study the association between childhood onset of LyP and other malignancies and to determine the clinical characteristics in this subgroup of patients.

Design: Retrospective cohort study.

Setting: Referral center at a university hospital. Retrospective registry for patients with LyP of childhood onset (≤18 years).

Patients: Thirty-five patients with childhood-onset LyP (19 boys and 16 girls) were interviewed by telephone using a standardized questionnaire. The median duration of follow-up was 9.0 years. All included patients were confirmed by histologic examination.

Results: The age distribution was significantly different, with boys having an earlier onset of LyP (P = .03). Of the 35 LyP patients, 3 (9%) developed a malignant lymphoma; all were diagnosed as having non-Hodgkin lymphoma. Compared with the general population, patients with childhood-onset LyP have a significantly increased risk of developing non-Hodgkin lymphoma (relative risk, 226.2; 95% confidence interval, 73.4-697.0). More than two thirds of the patients reported being atopic, which is significantly more than the expected prevalence of atopy (relative risk, 3.1; 95% confidence interval, 2.2-4.3).

Conclusions: Lymphomatoid papulosis presents similarly in children and adults, including the risk of lymphoid malignancies. Therefore, all LyP patients should be closely monitored throughout their lives.

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LYMPHOMATOID PAPULOSIS (LyP) was described by Maclaulay1 in 1968 as “a clinically benign condition with the histopathology of a malignant lymphoma.” It is a rare skin disease within the spectrum of the CD30+ cutaneous lymphoproliferative disorders.2 The cause of LyP is unknown. There is no sex predilection, and LyP can affect individuals of any age, although it has been reported only rarely in children.3-17 The clinical presentation and histopathological features of LyP in children are comparable to those in adults, with recurrent crops of reddish brown papules and/or nodules primarily involving the trunk and extremities.3,4 Typically, recurrent episodes of LyP lesions will last an average of 2 to 8 weeks, followed by spontaneous resolution with frequent secondary scarring. The histologic types of LyP can resemble Hodgkin disease (HD) (type A), mycosis fungoides (type B), or anaplastic large-cell lymphoma (type C) (Figure 1).3

The eruption is in general not associated with systemic illness.3 However, about 5% to 20% of adult LyP patients will develop a malignant lymphoma, most commonly mycosis fungoides, HD, and cutaneous and systemic CD30+ anaplastic large cell non-Hodgkin lymphomas (NHLs).18-22 The overall 5-year survival of LyP patients is excellent (100%).18,19 To our knowledge, the possible association of childhood onset of LyP and lymphoid malignancies has not been systematically assessed.

We, therefore, established a retrospective registry for LyP with childhood onset at the Beth Israel Deaconess Medical Center, with the primary objective of evaluating the long-term risk of developing lymphoid malignancies in childhood.
cases of LyP. We also sought to identify genetic and environmental risk factors for the development of LyP. The present study details the demographic variables, the clinical characteristics, and the risk of associated malignancies of the 35 enrolled patients with childhood LyP.

METHODS

First, patients with LyP with an onset at 18 years or younger were selected from the files of the Cutaneous Oncology Clinic at Beth Israel Deaconess Medical Center and the consultation files of 1 of us (M.E.K.) between September 1, 1980, and June 1, 2002. The diagnosis of LyP was confirmed by a pathology report of a certified pathologist or dermatopathologist.

We attempted to locate the patients via their medical records, referring physicians, and/or recent e-mail addresses. When a telephone number was obtained and permission granted, the patient or the legal guardian (if the patient was <18 years at the time of the interview) was interviewed. The questionnaire was standardized and conducted by 2 of us (T.N. and C.C.-L.). Participants were asked more than 50 questions concerning demographic variables, personal and familial medical history, disease characteristics, use of treatment, and clinical response to each treatment used on a scale from 1 (ineffective) to 10 (highly effective). We defined a therapy being effective as the 4 most extreme ratings on the 10-point scale. Participants were considered to be atopic when they reported ever being diagnosed by a physician as having atopic dermatitis, allergic rhinitis, seasonal allergy, and/or asthma. A written informed consent, and corresponding assent, if applicable, for patients younger than 16 years was obtained.

The relative risk (RR) and 95% confidence intervals (CIs) of NHL in childhood LyP cases were calculated using the expected number of NHL cases in persons younger than 45 years from the Surveillance, Epidemiology, and End Results data.23

The RR and 95% CI of atopy were calculated using the expected numbers for persons 45 years or younger with asthma, rhinitis, and/or conjunctivitis from the Surveillance, Epidemiology, and End Results registry; and for the risk estimate of white children developing LyP compared with nonwhite children, we used the population census data for children 18 years and younger.

We used the Mann-Whitney test to determine the statistical significance in the distribution of continuous variables, and the χ² test or the Fisher exact test to determine the statistical significance in the distribution of categorical variables. P<.05 was considered significant, and all statistical tests were 2 sided. All statistical analyses were performed with Stata 7.0 (Stata Corp, College Station, Tex) and Crunch, version 4 (Crunch Software Corp, Oakland, Calif).

RESULTS

Of the 48 patients with childhood-onset LyP, we were able to contact 35 (73%) in the spring of 2002. Of those contacted, all agreed to participate in the registry. We interviewed the parents of the affected individuals, except for 3 participants whom we interviewed personally. The results are summarized in Table 1.

Of the 35 patients, 19 were male and 16 were female; the median age at onset of LyP was 8.0 years (75th percentile, 14.0 years; and 25th percentile, 4.0 years). The age at the interview ranged from 2 to 52 years (median, 16.0 years; 75th percentile, 27.0 years; and 25th percentile, 9.5 years). The distribution of the age at onset of LyP was significantly different (P = .03), with boys having an earlier onset of LyP (median, 5.50 years; 75th percentile, 13.3 years; and 25th percentile, 3.0 years) compared with girls (median, 12.0 years; 75th percentile, 16.0 years; and 25th percentile, 6.0 years) (Figure 2). Except for one patient with Asian ancestry, all other patients were white, which is more than expected compared with the general population among individuals younger than 19 years (RR, 1.60; 95% CI, 1.26-2.04). The median duration of follow-up was 9.0 years (75th percentile, 17.5 years; and 25th percentile, 2.5 years). Female patients were significantly more likely to report a longer follow-up (P = .04).

Of the 35 LyP patients, 3 (9%) developed an NHL (Table 2). Patients with childhood-onset LyP have a significantly increased risk (RR, 226.2; 95% CI, 73.4-697.0) of developing NHL compared with the general population 44 years or younger in the United States. We did not detect significant associations between the development of NHL and sex, age at onset of LyP, duration of follow-up, maximum number of lesions at one point in time, positive family history of lymphoid malignancies, or active disease at the interview (data not shown). The time relation between the onset of
Table 1. Clinical Characteristics of Patients With Childhood Onset of LyP

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y*</th>
<th>Allergy</th>
<th>Type of LyP Lesions†</th>
<th>Minimum/Maximum No. of Skin Lesions Ever</th>
<th>Distribution of LyP Lesions</th>
<th>Scarring</th>
<th>主动</th>
<th>Response to Sunlight</th>
<th>Therapies‡</th>
<th>Follow-up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/14</td>
<td>Atopic dermatitis/penicillin</td>
<td>Papules</td>
<td>0/≤100</td>
<td>Extremities</td>
<td>Some</td>
<td>Active</td>
<td>Improved</td>
<td>TS(5), Ab(1), UV-B(1), RA(1), and methotrexate(9)</td>
<td>2½</td>
</tr>
<tr>
<td>2/M/15</td>
<td>None</td>
<td>Papules/nodules</td>
<td>0/≤10</td>
<td>Extremities</td>
<td>Some</td>
<td>Active</td>
<td>None</td>
<td>TS(1) and UV-B(7)</td>
<td>8½</td>
</tr>
<tr>
<td>3/F/7</td>
<td>None</td>
<td>Papules/nodules</td>
<td>0/≤10</td>
<td>Extremities</td>
<td>Always</td>
<td>Active</td>
<td>None</td>
<td>TS(1) and UV-B(7)</td>
<td>2½</td>
</tr>
<tr>
<td>4/M/3</td>
<td>Seasonal</td>
<td>Papules/nodules</td>
<td>1/≤10</td>
<td>Extremities</td>
<td>Some</td>
<td>Active</td>
<td>Improved</td>
<td>TS(1) and Ab(1)</td>
<td>1½</td>
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<tr>
<td>5/F/16</td>
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<td>Papules/nodules</td>
<td>1/≤10</td>
<td>Generalized</td>
<td>Never</td>
<td>Active</td>
<td>Improved</td>
<td>TS(2), Ab(1), UV-B(8), and Protopic(1)</td>
<td>1½</td>
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<tr>
<td>6/F/15</td>
<td>Asthma</td>
<td>Papules/nodules</td>
<td>0/≤10</td>
<td>Arms</td>
<td>Always</td>
<td>Active</td>
<td>Improved</td>
<td>TS(5) and UV-B(8, and Pimaclid(1)</td>
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</tr>
<tr>
<td>7/F/12</td>
<td>None</td>
<td>Papules/nodules</td>
<td>1/≤10-49</td>
<td>Extremities/face</td>
<td>Some</td>
<td>Active</td>
<td>Improved</td>
<td>TS(4), methotrexate(7), and CT(1)</td>
<td>40</td>
</tr>
<tr>
<td>8/F/17</td>
<td>Urticaria</td>
<td>Papules</td>
<td>0/100</td>
<td>Generalized</td>
<td>Some</td>
<td>Active</td>
<td>Improved</td>
<td>TS(5) and Pimaclid(1)</td>
<td>23</td>
</tr>
<tr>
<td>9/M/5</td>
<td>None</td>
<td>Papules</td>
<td>0/10</td>
<td>Legs</td>
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<td>Active</td>
<td>Improved</td>
<td>TS(5)</td>
<td>2½</td>
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<td>None</td>
<td>Papules</td>
<td>10/≤10-100</td>
<td>Extremities/face</td>
<td>Never</td>
<td>Active</td>
<td>Improved</td>
<td>TS(1)</td>
<td>1½</td>
</tr>
<tr>
<td>11/F/9</td>
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<td>Papules/nodules</td>
<td>1/≤10-50</td>
<td>Generalized</td>
<td>Some</td>
<td>Active</td>
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<td>TS(5), Ab(1), and UV-B(7)</td>
<td>2½</td>
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<tr>
<td>12/F/4</td>
<td>Atopic dermatitis/penicillin</td>
<td>Papules</td>
<td>0/≤10-50</td>
<td>Generalized</td>
<td>Never</td>
<td>Active</td>
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<td>TS(2) and Ab(2)</td>
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<tr>
<td>13/F/0.8</td>
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<td>Papules/nodules</td>
<td>0/≤10</td>
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<td>Some</td>
<td>Active</td>
<td>None</td>
<td>Ab(1)</td>
<td>4½</td>
</tr>
<tr>
<td>14/F/5</td>
<td>None</td>
<td>Papules/nodules</td>
<td>1/≤10-49</td>
<td>Legs</td>
<td>Never</td>
<td>Active</td>
<td>Improved</td>
<td>TS(8) and Ab(2)</td>
<td>21½</td>
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<tr>
<td>15/M/8</td>
<td>None</td>
<td>Papules/nodules</td>
<td>0/≤10</td>
<td>Trunk/legs</td>
<td>Always</td>
<td>Active</td>
<td>None</td>
<td>TS(1), prednisone(5), and IL corticosteroids(1)</td>
<td>3</td>
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<tr>
<td>16/M/8</td>
<td>Cefaclor</td>
<td>Nodules</td>
<td>0/≤10</td>
<td>Extremities</td>
<td>Always</td>
<td>Active</td>
<td>Improved</td>
<td>TS(10)</td>
<td>3½</td>
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<tr>
<td>17/F/18</td>
<td>None</td>
<td>Papules</td>
<td>1/≤10-49</td>
<td>Extremities</td>
<td>Always</td>
<td>Active</td>
<td>Improved</td>
<td>TS(1), Ab(1), UV-B(8), Tazorac(7), and Elidel(5)</td>
<td>18</td>
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<tr>
<td>18/F/12</td>
<td>Seasonal</td>
<td>Papules/nodules</td>
<td>1/≤10-50-99</td>
<td>Trunk/face</td>
<td>Never</td>
<td>Active</td>
<td>Improved</td>
<td>TS(1), RT(7), and CT(1)</td>
<td>9½</td>
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<tr>
<td>19/F/8</td>
<td>Seasonal</td>
<td>Papules/nodules</td>
<td>0/≤10</td>
<td>Extremities/face</td>
<td>Never</td>
<td>Active</td>
<td>Improved</td>
<td>TS(5)</td>
<td>2½</td>
</tr>
<tr>
<td>20/M/13</td>
<td>Asthma</td>
<td>Papules/nodules</td>
<td>1/≤10-50</td>
<td>Arms/trunk/face</td>
<td>Most</td>
<td>Active</td>
<td>Improved</td>
<td>TS(9) and Ab(9)</td>
<td>3½</td>
</tr>
<tr>
<td>21/F/15</td>
<td>Seasonal</td>
<td>Nodules</td>
<td>0/≤10-49</td>
<td>Extremities</td>
<td>Some</td>
<td>Active</td>
<td>Worse</td>
<td>TS(1), Elidel(1), and IL corticosteroids(1)</td>
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<tr>
<td>22/M/3</td>
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<td>Papules/nodules</td>
<td>1/≤10-10</td>
<td>Generalized</td>
<td>Some</td>
<td>Active</td>
<td>None</td>
<td>TS(8) and Ab(8)</td>
<td>2½</td>
</tr>
<tr>
<td>23/M/14</td>
<td>Seasonal/atopic dermatitis</td>
<td>Papules</td>
<td>0/≤10</td>
<td>Extremities</td>
<td>Some</td>
<td>Active</td>
<td>None</td>
<td>Ab(9)</td>
<td>4½</td>
</tr>
<tr>
<td>24/F/1</td>
<td>None</td>
<td>Papules/nodules</td>
<td>0/≤10-50</td>
<td>Extremities/face</td>
<td>Some</td>
<td>Active</td>
<td>None</td>
<td>TS(5) and Ab(6)</td>
<td>9½</td>
</tr>
<tr>
<td>25/M/6</td>
<td>Cefaclor</td>
<td>Papules/nodules</td>
<td>10/≤10-100</td>
<td>Extremities</td>
<td>Some</td>
<td>Active</td>
<td>Improved</td>
<td>TS(1)</td>
<td>1½</td>
</tr>
<tr>
<td>26/M/14</td>
<td>Seasonal</td>
<td>Papules/nodules</td>
<td>1/≤10-50-99</td>
<td>Generalized</td>
<td>Most</td>
<td>Active</td>
<td>Improved</td>
<td>TS(1), and Ab(1)</td>
<td>4½</td>
</tr>
<tr>
<td>27/M/16</td>
<td>Seasonal</td>
<td>Papules/nodules</td>
<td>0/≤10</td>
<td>Extremities</td>
<td>Some</td>
<td>Active</td>
<td>Improved</td>
<td>TS(2) and UV-B(5)</td>
<td>17½</td>
</tr>
<tr>
<td>28/M/1.5</td>
<td>Seasonal</td>
<td>Papules/nodules</td>
<td>1/≤10-90</td>
<td>Legs</td>
<td>Some</td>
<td>Active</td>
<td>None</td>
<td>TS(1) and Ab(1)</td>
<td>12½</td>
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<td>29/M/5.5</td>
<td>Dust mite</td>
<td>Papules</td>
<td>0/≤10-49</td>
<td>Generalized</td>
<td>Some</td>
<td>Active</td>
<td>None</td>
<td>TS(1) and Ab(1)</td>
<td>8½</td>
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<tr>
<td>30/F/15</td>
<td>Seasonal</td>
<td>Papules/nodules</td>
<td>0/≤10-49</td>
<td>Generalized</td>
<td>Some</td>
<td>Active</td>
<td>None</td>
<td>TS(3)</td>
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<td>Papules</td>
<td>0/≤10-49</td>
<td>Extremities</td>
<td>Never</td>
<td>Active</td>
<td>None</td>
<td>TS(2) and Ab(5)</td>
<td>9½</td>
</tr>
<tr>
<td>32/M/2</td>
<td>Seasonal</td>
<td>Papules</td>
<td>1-10/≤50-100</td>
<td>Generalized</td>
<td>Some</td>
<td>Active</td>
<td>Improved</td>
<td>TS(1) and Ab(1)</td>
<td>1½</td>
</tr>
<tr>
<td>33/M/4</td>
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<td>Papules/nodules</td>
<td>1-10/≤100</td>
<td>Generalized</td>
<td>Some</td>
<td>Active</td>
<td>None</td>
<td>TS(1) and Ab(8)</td>
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<td>34/M/6.5</td>
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<td>Papules/nodules</td>
<td>0/≤10</td>
<td>Generalized</td>
<td>Never</td>
<td>Active</td>
<td>None</td>
<td>Ab(1) and SE(5)</td>
<td>8½</td>
</tr>
<tr>
<td>35/M/12</td>
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<td>Nodules</td>
<td>0/≤10-10</td>
<td>Generalized</td>
<td>Some</td>
<td>Active</td>
<td>None</td>
<td>Ab(7) and SE(10)</td>
<td>2½</td>
</tr>
</tbody>
</table>

Abbreviations: Ab, antibiotic; CT, chemotherapy; IL, interleukin; LyP, lymphomatoid papulosis; NA, data not applicable; PUVA, psoralen–UV-A; RA, oral retinoid; RT, radiation therapy; SE, surgical excision; TS, topical corticosteroid.

*At LyP onset.
†Papules were 5 mm or smaller; nodules, larger than 5 mm.
‡Active indicates LyP lesions were present at the interview.
§Numbers in parentheses indicate the effectiveness of the therapy, rated by the patient, on a scale from 1 to 10 (10 indicates very effective). The generic name for Protopic is tacrolimus ointment; for Tazorac, tazarotene gel; and for Elidel, pimecrolimus.
¶This patient had an associated lymphoma.
†Familial history of hematologic malignancies.
1/M/14 had an associated lymphoma.

LyP and the development of NHL varied from simultaneous up to more than 15 years after the onset of LyP (Table 2). No other cancers were reported in the 35 patients. Three patients reported a family history of hematologic malignancies in a first- or second-degree relative (Table 1).
At some point, almost all patients developed papular lesions; about half of those also reported having had nodules as well (Table 1). Four patients developed plaquelike lesions of LyP. Only 6 subjects (17%) indicated that none of the LyP lesions left residual scars. About half of the patients reported at least 1 episode with 50 or more LyP lesions. Of the 35 patients, 15 reported never experiencing complete remission, with a minimum number of active lesions of 1 or more since the onset of the disease. Neither clinical appearance nor the maximum number of LyP lesions correlated significantly with ever having complete clearance, activity of disease, or malignant transformation (data not shown).

Most patients (31 of 35) had skin lesions that resolved spontaneously within 1 to 3 months. Four patients observed the same lesion for 6 months or more. Six individuals categorized the average duration of episodes of LyP as less than a month; 14, between 1 and 3 months; and 11, more than 3 months. About a third of the patients (13 of 35) reported that the average duration between episodes of LyP lasted 3 months or less, and 12 reported intervals of longer than 3 months. Of the 35 patients, 3 (patients 7, 23, and 35) reported a single episode of LyP. When asked whether the disease had changed in time, 10 patients (29%) indicated that the disease was stable; 23 (66%), the frequency of episodes decreased; 1 (3%), the frequency of episodes increased; and 1 (3%), the disease went into complete remission (percentages do not total 100 because of rounding). Of the 35 patients, 14 (40%) reported pruritus in association with the LyP lesions. About two thirds of the patients (21 of 35) reported having active disease at the interview. Patients with a short follow-up were significantly more likely to have active disease (P = .04). Except for persons reporting 50 or more LyP lesions (P = .05), none of the clinical characteristics was significantly associated with a likelihood of having active disease at the interview (data not shown). However, the risk of having active disease in patients with 50 or more lesions decreased significantly in time compared with patients who had fewer than 50 lesions (P = .009) (Figure 3). Ten years after the onset of LyP, 14 (40%) patients had active disease.

The pathology slides corresponding to 11 patients were reviewed by 1 of us (M.E.K.). The following subtypes of LyP were identified: 5 type A, 2 type B, and 1 type C; 3 simultaneous features of LyP type A/B (n = 2) and A/C (n = 1) were observed in the same patient.

Sun exposure seemed to be beneficial in most individuals (19 of 35 patients), except for patient 21, who reported worsening of her LyP after intense sun exposure. Except for 2 patients, all participants received therapy for LyP (Table 1). The most commonly reported treatments included topical corticosteroids (n = 29), antibiotics (n = 19), and phototherapy (n = 8). Topical corticosteroids and antibiotics were significantly less likely to be effective compared with phototherapy, primarily UV-B, which was rated as effective by all but one patient (P = .01). Low-dose methotrexate showed good results in 2 patients. Two patients received chemotherapy (patient 18 for her NHL and patient 7, who was initially misdiagnosed as having a lymphoma >25 years ago). In both patients, LyP lesions recurred a few months after completion of the chemotherapy regimen. The use of phototherapy and/or methotrexate was not significantly associated with extensive (maximum number of lesions, >50), active, or scarring disease (P = .26, .43, and >.99, respectively). Reporting the use of 3 or more different treatments was significantly associated with an increased age of onset (P = .001), but not with duration of follow-up or maximum number of lesions (P = .24 and .52, respectively).

At the interview, more than two thirds of the participants reported having atopic dermatitis, seasonal allergies (rhinitis and/or conjunctivitis), and/or asthma diagnosed by a physician. Atopy was associated with increasing age at the interview (P = .01). Compared with the general US population 45 years or younger, patients with childhood LyP are significantly more likely to be diagnosed as having atopy (RR, 3.1; 95% CI, 2.2-4.3). Four persons reported cutaneous drug reactions induced by antibiotics (Table 1).

The subjects participating in the study are being clinically managed by dermatologists (n = 17), oncologists (n = 8), or a dermatologist and an oncologist (n = 5). Five participants are no longer being observed by a physician for LyP.

**COMMENT**

Compared with adult LyP, childhood LyP has not been well described because of its rarity. The risk of associated lymphoid malignancies in pediatric patients is not known. In this case series, 3 patients developed NHL. The observed incidence of NHL in patients with childhood-onset LyP is more than 200 times the expected incidence of NHL in a comparable population without childhood-onset LyP. None of the participants have been seriously ill or have died of extracutaneous disease. Compared with adults with LyP, the risk of developing hematologic malignancies is similar (about 10%). We observed only NHL and no other lymphomas associated with LyP. However, another 6-year-old patient referred to 1 of us (M.E.K.), not included in the study for lack of follow-up, developed HD, nodular sclerosing type, and LyP (M.E.K., unpublished data, 1995). In this patient, the HD went into remission after chemotherapy, but LyP persisted for 2½ years after treatment. The period in which...
IH, immunohistochemistry; LCA, leukocyte common antigen; LyP, lymphomatoid papulosis; NHL, non-Hodgkin lymphoma.

Moreover, to our knowledge, 10 children with LyP by the Dutch Cutaneous Lymphoma Working Group.3,4

The strength of this study includes the many patients assessed and the substantial follow-up, with a median of almost 10 years. This case series exceeds by far the episodes or in the appearance of the lesions during the follow-up period (data not shown).

The clinical characteristics of LyP in children do not seem to differ substantially compared with those in adults.18 Although LyP is a chronic disease, the risk of having active disease decreases significantly in time, especially for patients affected by more lesions, for which we do not have an explanation. More than three quarters of the patients did not perceive changes in the frequency or duration of the episodes or in the appearance of the lesions during the follow-up period (data not shown).

Because cases were ascertained at a tertiary dermatologic clinic and white persons are more likely to have access to specialized medical care, the increased risk of white children developing LyP is probably overestimated.

Although the sample size is limited, the increased risk of atopy in patients with childhood LyP is notable.

Table 2. Characteristics of Patients With Childhood Onset of LyP Who Developed a Lymphoma*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Onset of LyP/Lymphoma</th>
<th>Interval Between LyP and Lymphoma</th>
<th>Type of Lymphoma (Stage/Type)</th>
<th>Treatment of Lymphoma</th>
</tr>
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<tr>
<td>18</td>
<td>12/13 y</td>
<td>3 mo</td>
<td>NHL CD30⁺ (systemic/nodal)/IgG-positive for Ki-1, LCA, UCHL-1, L26, B1, B4, κ, and λ and negative for T1, T2, T3, T4, and T8</td>
<td>CT/BMTX Yes</td>
</tr>
<tr>
<td>21</td>
<td>15/32 y</td>
<td>17 y</td>
<td>Primary cutaneous CD30⁺ stage ALCL/positive for CD30, CD30⁺, LCA, and CD3</td>
<td>Spontaneous regression No</td>
</tr>
<tr>
<td>35</td>
<td>12/12 y</td>
<td>0 mo</td>
<td>Primary cutaneous CD30⁺ stage ALCL/positive for CD30, CD43, LCA, and CD3 and negative for Leu M1, EMA, c-kit, and Alk-1</td>
<td>Spontaneous regression No</td>
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Abbreviations: ALCL, anaplastic large cell lymphoma; BMTX, bone marrow transplantation; CT, chemotherapy; EMA, endomysial antibody; IH, immunohistochemistry; LCA, leukocyte common antigen; LyP, lymphomatoid papulosis; NHL, non-Hodgkin lymphoma.

*All 3 patients were white; the lymphoma was in remission in all 3 patients.
†Active disease at the interview.

minimized patients’ recall bias. The validity of self-reported atopy is reasonable.23 However, the significance of the association between atopy and LyP may be overestimated, because the estimate of expected prevalence of atopy in the general population (Surveillance, Epidemiology, and End Results data) did not include atopic dermatitis. Excluding the 2 patients who reported atopic dermatitis alone did not substantially change the risk estimate (RR, 2.9; 95% CI, 2.0-4.2). We compared the prevalence of atopy in our population with that in the general population 44 years or younger because all but one subject belonged in that category at the interview. The risk would further increase if we compared our cohort with those younger than 18 years in the general population (RR, 3.9; 95% CI, 2.7-5.6).

Although all ascertained cases were confirmed by pathology reports, we were unable to classify the LyP cases into the 3 histologic subtypes because we could not obtain every diagnostic skin biopsy result. The appearance and distribution of histologic subtypes do not seem to differ between adults and children.3 Lymphomatoid papulosis type A was observed on pathological examination in 2 patients who developed an associated NHL in this cohort. In adults, LyP type A has also been observed in association with lymphoid malignancies.19,25,26

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The strength of this study includes the many patients assessed and the substantial follow-up, with a median of almost 10 years. This case series exceeds by far the largest existing registry of children with LyP by the Dutch Cutaneous Lymphoma Working Group.3,4 Moreover, to our knowledge, we are the first to report childhood cases of LyP associated with lymphoid malignancies. All included patients in this registry have histologically proved diagnoses of LyP and NHL. We obtained detailed information about the patient variables, the clinical characteristics and course of LyP, and the use of treatment.

It is not likely that a selection bias substantially confounded our observations because all contacted patients participated in the study. An observational bias may have affected the high risk of NHL in those with childhood LyP because these patients are more likely to be closely monitored than children in the population without LyP. The resultant potential bias might have led to a modest overestimate of the associated risk of lymphoid malignancies. By using clear standardized questions, we

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Figure 3. The absolute risk of having active lymphomatoid papulosis (LyP) in time for all persons, for those with fewer than 50 lesions, and for those with 50 or more lesions.
Other lymphoproliferative diseases, such as HD and mycosis fungoides, are possibly associated with atopy.27,28 An atopic history seemed to have a protective effect in patients with HD.27 This may be because of an increased proportion of activated T helper (Th) 2–type T cells in patients with atopic disease, which is linked to an increased expression of CD30, a member of the tumor necrosis factor/nerve growth factor receptor superfamily.29 CD30 is preferentially expressed by Th2 cells and is consistently expressed by the large atypical cells in patients with LyP.30,31 The natural ligand for CD30 (CD133) is expressed at higher levels in regressing than non-regressing skin lesions, and this may explain the unique clinically benign behavior of LyP and CD30+ cutaneous anaplastic large cell lymphomas.32,33 It is also possible that a high expression of CD30 contributes to the abnormal proliferation of atypical cells in patients with LyP, as it does in Hodgkin or Reed-Sternberg cells in patients with HD.34 In vitro studies35-37 have given conflicting results on the effect of CD30 activation in patients with lymphoproliferative disorders. It is possible that the different effects (proliferation vs cell death) are determined by the strength of the signal activating CD30, just as the differentiation of healthy T lymphocytes toward Th1 vs Th2 is determined by the strength of the signal activating the T-lymphocyte receptor.38 The exact role of CD30 in patients with LyP, while most interesting, remains to be defined.

Except for race, atopy, and an earlier onset of LyP in boys, we could not identify other possible precipitating factors of LyP, such as infection, trauma, stress, exposure to chemicals, use of drugs or blood products, and menarche or puberty (data not shown).

Childhood LyP should be differentiated from arthropod bites, which have a shorter course and have a mixed inflammatory infiltrate on histologic examination; pityriasis lichenoides et varioliformis acuta (PLEVA), which has few or no CD30+ cells in the histologic infiltrate; and CD30+ anaplastic large-cell lymphoma, which may be difficult to differentiate from LyP on clinical and histologic features. Some investigators2 believe that the latter and LyP are closely related, and are part of a continuous spectrum of CD30+ lymphoproliferative disorders. In this cohort, the most common initial diagnosis by a physician was indeed insect bites (n = 13), followed by PLEVA (n = 7), cutaneous lymphoma (n = 4), impetigo (n = 3), and others. However, most participants (n = 25) were diagnosed as having LyP within a year of onset of the disease (data not shown).

The rarity of childhood LyP, the multifocal skin lesions, and the malignant histologic features of LyP can produce the erroneous diagnosis of malignancy, leading to unnecessarily aggressive treatment (eg, in patient 7). Treatment of LyP is usually not necessary, except for cosmetic or symptomatic reasons. The patients in this cohort, especially those with an increased age of onset, were more likely to have received therapy for their LyP compared with the children in the Dutch registry.7 The results of different treatments varied among the children, but UV-B seemed to have acceptable results, which was confirmed by the positive effect of natural UV light on LyP. Low-dose methotrexate is an alternative, but the long-term use of this drug should be carefully balanced against the risk of using it in a pediatric population.

In summary, our study shows that LyP in children does not differ from LyP in adults, including the increased risk of lymphoid malignancies. No clinical features could be identified to predict an increased risk for developing malignancies. Therefore, all patients should be carefully monitored throughout their lives. Further studies to investigate potential causative factors are warranted.

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REFERENCES


