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How to cite

BLANCHARD, Maël et al. Paediatric-onset lymphomatoid papulosis : results of a multicentre retrospective cohort study on behalf of the EORTC Cutaneous Lymphoma Tumours Group (CLTG). In: British journal of dermatology, 2024, vol. 191, n° 2, p. 233–242. doi: 10.1093/bjd/ljae150

This publication URL: https://archive-ouverte.unige.ch/unige:183445

Publication DOI: 10.1093/bjd/ljae150

Br J Dermatol 2024; **191**:233–242
https://doi.org/10.1093/bjd/ljae150
Advance access publication date: 10 April 2024

BJD
British Journal of Dermatology
Epidemiology

Paediatric-onset lymphomatoid papulosis: results of a multicentre retrospective cohort study on behalf of the EORTC Cutaneous Lymphoma Tumours Group (CLTG)

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Linked Article: Battistella *Br J Dermatol* 2024; **191**:158–159.

Abstract

Background Lymphomatoid papulosis (LyP) is a rare cutaneous T-cell lymphoproliferative disorder. Comprehensive data on LyP in the paediatric population are scarce.

Objectives To characterize the epidemiological, clinical, histopathological and prognostic features of paediatric LyP.

Methods This was a retrospective multicentre international cohort study that included 87 children and adolescents with LyP diagnosed between 1998 and 2022. Patients aged ≤ 18 years at disease onset were included. LyP diagnosis was made in each centre, based on clinicopathological correlation.

Results Eighty-seven patients from 12 centres were included. Mean age at disease onset was 7.0 years (range 3 months–18 years) with a male to female ratio of 2 : 1. Mean time between the onset of the first cutaneous lesions and diagnosis was 1.3 years (range 0–14). Initial misdiagnosis concerned 26% of patients. LyP was most often misdiagnosed as pityriasis lichenoides et varioliformis acuta, insect bites or molluscа contagiosa. Erythematous papules or papulonodules were the most frequent clinical presentation. Pruritus was specifically mentioned in 21% of patients. The main histological subtype was type A in 55% of cases. When analysed, monoclonal T-cell receptor rearrangement was found in 77% of skin biopsies. The overall survival rate was 100%, with follow-up at 5 years available for 33 patients and at 15 years for 8 patients. Associated haematological malignancy (HM) occurred in 10% of cases (n = 7/73), including four patients with mycosis fungoides, one with primary cutaneous anaplastic large cell lymphoma (ALCL), one with systemic ALCL and one with acute myeloid leukaemia. If we compared incidence rates of cancer with the world population aged 0–19 years from 2001 to 2010, we estimated a significantly higher risk of associated malignancy in general, occurring before the age of 19 years (incidence rate ratio 87.49, 95% confidence interval 86.01–88.99).

Conclusions We report epidemiological data from a large international cohort of children and adolescents with LyP. Overall, the disease prognosis is good, with excellent survival rates for all patients. Owing to an increased risk of associated HM, long-term follow-up should be recommended for patients with LyP.

Lay summary

Lymphomatoid papulosis is a very rare skin condition caused by an abnormal increase in white blood cells (called 'lymphocytes') in the skin. The condition rarely affects children, so most of the scientific data published about this disease focuses on adults.

Accepted: 9 April 2024

This study involved 12 academic dermatology centres in Europe, the Middle East and North America, and gathered data from about 87 children who presented with symptoms of lymphomatoid papulosis before the age of 19 years. The aim of this study was to better describe this disease in the paediatric population and discuss its treatment options and evolution.

We found that the presentation of the disease in children is roughly the same as in adults. Safe and effective treatment options exist. The disease is not life threatening, but it requires investigation by a dermatologist, both to make a careful diagnosis and to monitor it as sometimes associated cancers that originate from blood cells can occur, mostly on the skin.

What is already known about this topic?

- Lymphomatoid papulosis (LyP) is a cutaneous T-cell lymphoproliferative disorder that is more common in adults than in children.
- In adults, LyP is associated with an increased risk of associated malignancies.
- Data on comorbidities in paediatric populations are scarce – some of the few available case reports and small case series date back to a time when the understanding of this condition was different from the one we have now.

What does this study add?

- LyP in children has similar clinical and histological characteristics as in adults.
- We confirm the association between paediatric LyP and haematological malignancies occurring before the age of 19 years, with a significantly higher incidence rate compared with the general population.
- The overall prognosis is good, with excellent survival rates for all patients.

Lymphomatoid papulosis (LyP) is a rare primary cutaneous CD30$^+$ T-cell lymphoproliferative disorder that can develop at any age. There is an incidence peak in individuals between 40 and 50 years of age and a slight male predominance (male to female ratio 1.3 : 1).[1–4]

In the early 1960s, the Belgian dermatologist Adolphe Dupont was the first to observe a clinically benign skin condition with strikingly 'malignant' histological manifestation (Figures 1, 2). Dupont named this new entity 'reticulopathy'.[5] A few years later, in the USA, Warren L. Macaulay made a comparable observation and coined the term 'lymphomatoid papulosis'.[6] Indeed, the alarming histological appearance of LyP contrasts with its excellent prognosis, with a disease-specific 10-year survival rate approaching 100%.[2] Nevertheless, adults with LyP have an increased risk of associated malignancies, which can occur before, concomitantly or many years after the onset of LyP.[7–9] The most frequently associated malignancies are mycosis fungoides (MF) and both primary cutaneous and systemic anaplastic large cell lymphoma (ALCL).[3]

LyP is characterized by a chronic waxing and waning evolution, with self-healing recurrent erythematous skin papulonodules occurring on any body site but most commonly on the extremities, with the trunk being the second most common location.[10] The aetiology of this lymphoproliferative disease is unknown. The hypothetic role of viral diseases, including human T-cell lymphotropic virus 1, herpesviruses and endogenous retroviruses, has been discussed but is still not commonly accepted.[11] Histology is extremely variable. CD30 expression is an essential characteristic of the lymphoid infiltrate cells, although some CD30$^-$ cases have been described for histopathological subtypes B and D.[12,13] Classically, LyP is divided into five main histological subtypes (A–E) recognized by the World Health Organization–European Organisation for Research and Treatment of Cancer (WHO-EORTC), plus a rare category of cases with *DUSP22–IRF4* rearrangement and a biphasic infiltrate.[2] Despite the distinct histological subtypes, this histological subdivision has not been clearly linked to disease prognosis and has no practical implications in patient management.[14] Additionally, several histological subtypes can occur concomitantly or successively in the same patient.[15] Some authors have recommended avoiding the use of a rapidly growing list of histological subtypes, reasonably arguing that they complicate the diagnostic approach.[16,17] T-cell receptor (TCR) monoclonal rearrangement is frequent.[18] Clinicopathological correlation is essential to avoid misdiagnosis as LyP may clinically and histologically mimic several conditions, including arthropod bites, bacterial skin infections, benign inflammatory dermatosis, ALCL and other cutaneous lymphoproliferative disorders.

The incidence rate of paediatric cutaneous T-cell lymphoma (CTCL), including primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders, is estimated between 0.1 and 0.3 per 1 million person-years (PY).[19] Therefore, it is a very rare disease. This figure should be contrasted with the incidence rate in the adult population, which reaches 24.6 per 1 million PY between 70 and 79 years of age. However, LyP accounts for 15.9–47% of all paediatric cutaneous lymphoproliferative disorders and thus represents one of the two most frequent paediatric skin lymphoproliferative conditions with MF.[20–23]

Data on paediatric LyP are scarce and although a systematic review has been performed, it was based mainly on case reports and small retrospective cohorts.[24–26] These date as far back as 1973,[9,27] when the understanding of this condition was much different. Indeed, molecular biology allowed scientists to find the clonal T-cell population in LyP in 1986 and some histological subtypes have been described only quite recently.[18,28] In this retrospective multicentre international study, we aimed to characterize the epidemiological, clinical, histopathological and prognostic features of LyP in a large multicentric cohort of paediatric patients.

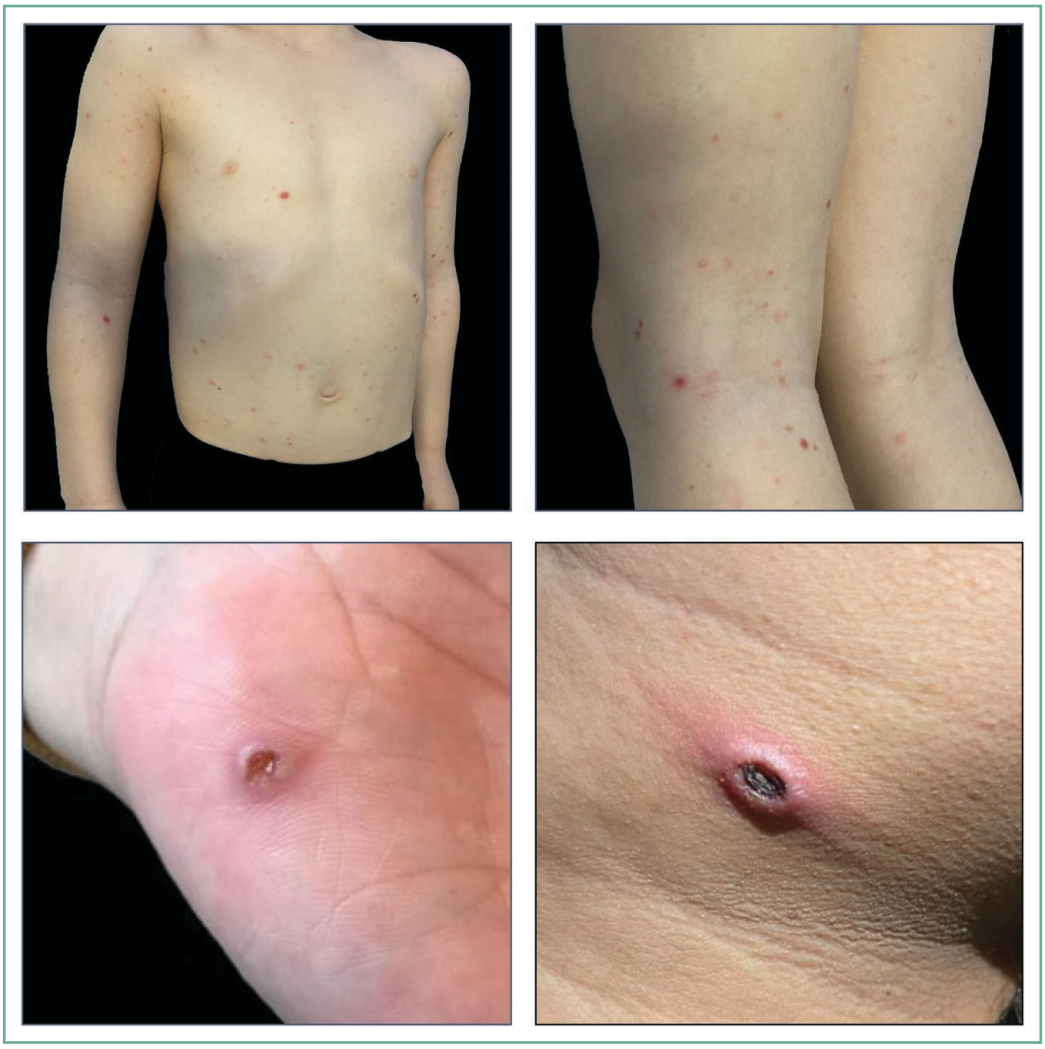

Figure 1 Paediatric lymphomatoid papulosis: clinical presentation.

Materials and methods

This study was conducted as a retrospective multicentre international cohort involving 12 academic medical centres with expertise in lymphoproliferative skin disorders from 11 different countries in Europe, the Middle East and North America.

Data collection

Patients aged 0–18 years at disease onset with a diagnosis of LyP were included. Diagnosis was made in each centre between 1 January 1998 and 1 July 2022 based on clinicopathological correlation, in line with the WHO-EORTC classification of cutaneous lymphomas at the time of diagnosis.[1,2,29] A dataset, including baseline and longitudinal follow-up data on the epidemiological, clinical, pathological and prognostic features of paediatric LyP, was sent to each centre. Information was collected by local study investigators at each centre individually, deidentified and sent to the data controller and study coordinator for completeness verification and formal data analysis. A reassessment of histology was originally planned, but its implementation turned out to be impossible as > 40% of diagnoses dated back over 10 years with the result that not all histological material could be retrieved. Thus, the assessment of histological features was based on histological reports.

Analysis

Descriptive statistics were used for standard epidemiological data. Continuous variables were summarized using mean (SD) and using number (percentage) for categorical variables. Summaries are given for all data and by group (patients with and without associated cancer). When data were missing, for example owing to a loss of follow-up, the case was excluded from subgroup analysis.

Patients with (coded 1) and without (coded 0) malignancies were compared using a logistic regression model. The strength of association between each risk factor and the malignancies was measured using the odds ratio (OR) and its associated *P*-value. To consider the clustered data structure [i.e. observations were independent across countries (cluster) but not necessarily within each country], we used a robust estimator for standard error estimation. Factors with *P*-value < 5% were considered to be statistically significant.

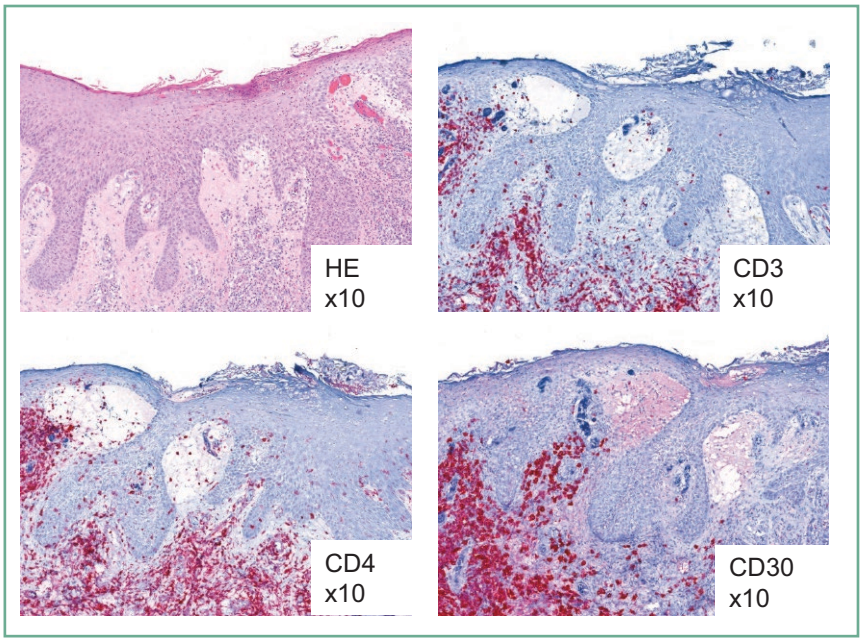

Figure 2 Paediatric lymphomatoid papulosis: histological presentation. HE, haematoxylin and eosin.

Given the small number of patients with malignancy (n=7/73), no multivariable model was fitted. Statistical analyses were performed using STATA 17 (StataCorp, College Station, TX, USA).

Results

Patient population

Our study included 87 confirmed cases of LyP in paediatric and adolescent patients, diagnosed between 1998 and 2022 in 1 of the 12 participating academic medical centres (Table 1). The mean (SD) age at disease onset was 7.0 (4.9) years (range 3 months–18 years). The mean (SD) age at diagnosis of LyP was 8.3 (5.8) years. We found a male predominance (n=58; 67%). Most patients were White (n=81; 93%), but African, Arabic, Asian, Hispanic and Indian patients were also represented. No patient in the cohort had a first-degree familial history of cancer or LyP.

Diagnostics

The mean (SD) diagnostic delay was 1.3 (2.8) years (range 0–14). Initial misdiagnosis (clinical and/or histopathological) involved 26% of cases (n=23). Clonality assessment was performed for 57% of the initially misdiagnosed cases (n=13/23) and 10 of these 13 cases showed TCR monoclonality. LyP was most often misdiagnosed as pityriasis lichenoides et varioliformis acuta (PLEVA; 9%), insect bites (5%), molluscum contagiosum (5%) and papular urticaria (3%).

Clinical characteristics

Patients with LyP presented most often with 10–50 lesions (49%; n=37/75), mostly papular (n=77/80; 96%), sometimes ulcerated (n=7/80; 9%), lasting a few weeks (n=25/44; 57%). Colour was mainly erythematous (n=49/54; 91%) with an occasionally associated brown hue (n=6/54; 11%) or purpuric features (n=4/54; 7%). The extremities and trunk were involved in, respectively, 86% (n=70/81) and 62% (n=50/81), but all body regions could be involved, including dissemination across most of the body surface in 16% of cases (n=13/81). Pruritus was specifically mentioned for 18 patients. When atopic dermatitis (AD) status was reported, the prevalence rate was 18% (n=12/67).

Histological characteristics

Histological subtype A was the most frequently reported (n=43/78; 55%), followed by subtype D (n=13/78; 17%). Seven patients had overlapping features of both subtypes A and B, and four had overlapping features of both subtypes A and C. No cases of subtype E or with *DUSP22–IRF4* rearrangement were reported. Immunohistochemistry of the lymphoid infiltrate was positive for CD30 in the majority of cases (n=68/78; 87%). Of all cases reported to be CD30$^-$, four were of subtype A (n=4/10; 40%), five (n=5/10; 50%) were of subtype D and one (n=1/10; 10%) was described as having features of both subtypes A and B. Six (n=6/10; 60%) of these cases were identified as TCR monoclonal, two (n=2/10; 20%) were classified as TCR polyclonal and clonality information was unavailable for three cases (n=3/10; 30%). CD4 was expressed in 80% (n=55/69) and CD8 in 75% of cases (n=51/68), with a range in the level of expression. The CD4 or CD8 expression pattern was documented for the entire infiltrate, and the expression of CD4 and/or CD8 specifically on the tumour cells was referred to as 'predominant'. CD4$^+$CD8$^+$ double positivity was found in 59% (n=40/68) and only 2 cases of double-negatives were reported (n=2/68; 3%). Overall, CD4 expression was predominant over CD8 in 44% of patients (n=28/64) and CD8 expression was predominant over CD4 in 34% of cases (n=22/64). CD4 predominance over CD8 was found in most subtypes (A, B and

Table 1 Patient demographics ($n=87$) and lymphomatoid papulosis disease characteristics

Age	
Age at onset (years), mean (SD)	7.0 (4.9)
Age at diagnosis (years), mean (SD)	8.3 (5.8)
Sex	
Male	58 (67)
Female	29 (33)
Ethnicity	
White	81 (93)
African, Arabic, Asian, Hispanic, Indian	6 (7)
Diagnosis	
Diagnostic delay (years), mean (SD)	1.3 (2.8)
Initial misdiagnosis	23 (26)
Number of lesions ($n=75$)	
< 10	28 (37)
10–50	37 (49)
> 50	10 (13)
Lesion type ($n=80$)	
Papules	77 (96)
Nodules	26 (33)
Ulcerations	7 (9)
Lesion colour ($n=54$)	
Erythematous	49 (91)
Brown	6 (11)
Evolution pattern ($n=72$)	
One episode	19 (26)
Multiple recurrent episodes	49 (68)
Continuous lesions with variable intensity	4 (6)
When multiple episodes, duration of 1 episode ($n=44$)	
Days	5 (11)
Weeks	25 (57)
Months	14 (32)
When multiple episodes, duration of symptom-free interval ($n=35$)	
Weeks	9 (26)
Months	26 (74)

Data are presented as *n* (%) or mean (SD).

C). Subtype D accounted for most cases with CD8 predominance over CD4, but this profile was not rare in subtype A and B. TCR gene monoclonal rearrangement was found in most of the investigated cases ($n=39/51$; 76%).

Management

Topical corticosteroids were the most common treatment used ($n=21/49$; 43%), followed by phototherapy ($n=16/49$; 33%) with a clear predominance of narrowband ultraviolet (UV)B modality over psoralen + UVA. Methotrexate was used in the treatment regimen of two patients, and never as a first-line therapy. A 'watch-and-wait' approach was chosen for 41% of patients ($n=20/49$).

Prognosis

The mean duration of follow-up was 5.3 years (range 0–22.9) (Table 2). The overall survival rate in our cohort was 100%, including patients with follow-up reaching 5 ($n=33/87$) and 15 years ($n=8/87$) after disease onset.

LyP presented most often with multiple recurrent episodes ($n=49/72$; 68%) lasting weeks ($n=25/44$; 57%), with symptom-free intervals of several months ($n=26/35$; 74%). If we defined complete remission at the last follow-up as 'lack of disease recurrence for more than 12 months', 16 patients in the subgroup with multiple recurrent episodes ($n=16/49$; 33%) could be classified as being in complete remission. The rash could also occur once and regress with no further recurrence reported, despite the possibility of several years of follow-up ($n=19/72$; 26%). A continuous disease course, with variable intensity and absence of a symptom-free interval, was reported in 6% of patients ($n=4/72$). In one patient with a continuous disease course (n = 1/4; 25%), complete

Table 2 Univariate analysis

Variable	Patients without associated HM ($n=66$)	Patients with associated HM ($n=7$)	OR, with SE adjusted for 11 clusters	*P*-value
Age at onset of LyP (years), mean SD	6.89 (4.5)	11.60 (5.9)	1.23	0.001
Age at diagnosis of LyP (years), mean (SD)	7.87 (5.3)	16.19 (6.5)	1.25	0.004
Male	46 (70)	5 (71)	1.09	0.93
White	61 (92)	6 (86)	0.49	0.53
Histological subtype A	32/59 (54)	2/6 (33)	0.42	0.19
Histological subtype A + B	2/59 (3)	2/6 (33)	14.25	0.001
Histological subtype A + C	3/59 (5)	0/6 (0)	[a]	
Histological subtype B	5/59 (8)	1/6 (17)	2.16	0.30
Histological subtype C	4/59 (7)	1/6 (17)	2.75	0.50
Histological subtype D	13/59 (22)	0/6 (0)	[a]	
All with histological subtype A	37/59 (63)	4/6 (67)	1.19	0.79
All with histological subtype B	7/59 (12)	3/6 (50)	7.43	0.01
All with histological subtype C	7/59 (12)	1/6 (17)	1.49	0.77
CD30 strong positivity[b]	41/61 (67)	5 (71)	1.22	0.88
CD4 strong positivity[b]	36/56 (64)	5/6 (83)	2.78	0.32
CD8 strong positivity[b]	25/55 (45)	3/6 (50)	1.20	0.85
TCR monoclonality	30/38 (79)	4/5 (80)	1.07	0.95
TCR oligoclonality	1/38 (3)	0/5 (0)	[a]	
TCR polyclonality	7/38 (18)	1/5 (20)	1.11	0.93

Data are presented as *n* (%) unless otherwise stated. HM, haematological malignancy; TCR, T-cell receptor. [a]Predicts failure perfectly for the outcome 'associated malignancy'; [b]immunohistochemistry was assessed at each centre by a local expert, using a scale (negative, slight positivity, strong positivity).

Table 3 Associated malignancies in our paediatric cohort of patients with lymphomatoid papulosis (LyP)

Patient no.	Sex	Histological subtype	Clonality	Age at onset of LyP/cancer (years)	Type of cancer	Last FU information	Patient alive at last FU?	Past treatment regimen	Treatment at last FU	TNMB staging
1	M	C	TCR monoclonality; identical clone in both LyP and associated HM	16/28	Systemic ALCL	30 October 2023, age 43 years; chronic recurrent LyP; systemic ALCL: CR	Y	Brentuximab vedotin	None	NA
2	F	A	NA	12/20	MF	24 October 2023, age 30 years; LyP: CR; MF: CR	Y	TCS, UVB, PUVA, focal RT, MTX, IFN, bexarotene, ECP, brentuximab vedotin, gemcitabine, mogamulizumab	None (CR after mogamulizumab)	Stage IIB (T3N0M0B0)
3	M	A+B	TCR monoclonality	16/17	MF	3 November 2023, age 29 years; chronic recurrent mild LyP; MF: SD	Y	LyP: TCS and IL corticosteroids; MF: TCS, topical carmustine, PUVA	None	Stage IA (T1bN0M0B0)
4	F	NA	TCR monoclonality	5/5	Juvenile myelomonocytic leukaemia evolving to AML	27 February 2023, age 20 years; LyP: not mentioned; AML: CR	Y	Cyclophosphamide, busulfan, rATG before unrelated ASCT	None	NA
5	M	B	NA	17/17	Primary cutaneous ALCL	24 November 2020, age 34 years; primary cutaneous ALCL: CR	Y	LyP: watch-and-wait; primary cutaneous ALCL: excised	None	Single cutaneous lesion only
6	M	A	TCR polyclonality	5/10	MF	23 November 2003, age 11 years; MF: CR	Y	MF: NB-UVB	None	Stage IA (T1N0M0B0)
7	M	A+B	TCR monoclonality	13/10	MF	17 April 2023, age 23 years; MF: CR	Y	MF: TCS, NB-UVB, UVA; acne: doxycycline	None	Stage IA (T1N0M0B0)

ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukaemia; ASCT, allogenic stem cell transplant; CR, complete remission; ECP, extracorporeal photopheresis; F, female; FU, follow-up; HM, haematological malignancy; IFN, interferon; IL, interleukin; M, male; MF, mycosis fungoides; MTX, methotrexate; NA, not available; NB-UVB, narrowband ultraviolet B; PUVA, psoralen plus ultraviolet A; rATG, rabbit anti-thymocyte globulin; RT, radiotherapy; SD, stable disease; TCR, T-cell receptor; TCS, topical corticosteroids; UVA, ultraviolet A; UVB, ultraviolet B; Y, yes.

remission of LyP was seen after multiple systemic treatments targeting associated haematological malignancy (HM; Table 3). In our analysis, we considered these three variables (multiple recurrent episodes, single episode and continuous disease) as ordinal categorical.

Associated malignancies were all haematological and concerned 10% of the cohort (n=7/73) (Table 3), including four patients with MF, one with primary cutaneous ALCL, one with systemic ALCL and one with of acute myeloid leukaemia (AML). Associated HMs occurred before (n=1), concomitantly (n=2) or after (n=4) the onset of LyP. A case of associated cutaneous B-cell *Borrelia*-negative pseudolymphoma appearing 9 years after the onset of LyP and treated with complete surgical excision was also described. Patients with associated HMs had no known familial history of cancer. When we considered only follow-up to the age of 19 years vs. the world's population aged 0–19 years from 2001 to 2010 (age-standardized overall incidence rate),[30] the incidence rate ratio for associated cancer in general was 87.49 [95% confidence interval (CI) 86.01–88.99].

Patients with associated HM were older at LyP onset than the rest of the cohort [mean (SD) age at LyP onset 11.6 (5.9) years]. Univariate logistic regression analysis showed that older age at LyP onset was significantly associated with a higher risk of associated HM [odds ratio (OR) 1.23, 95% CI 1.09–1.38; P=0.001].

The LyP was CD30$^-$ in two patients with associated HMs (n=2/7; 29%). LyP presenting with histological subtype B was significantly associated with a higher risk of associated HM (adjusted OR 7.43, 95% CI 1.59–34.74; P=0.01). Of the three patients with histological subtype B associated with HM, two presented with MF and one with primary cutaneous ALCL. No case of associated cancer was observed in the samples of patients with LyP labelled as having histological subtype D.

None of the 18 patients with LyP with evolution of disease as a single episode presented with an associated HM. However, LyP with multiple recurrent episodes (n=4/44; 9%) and – notably – LyP with continuous disease (n=2/4; 50%) showed significantly higher rates of associated HM.

In our cohort, the risk of associated HM was not found to be significantly associated with sex, being of a White background, TCR gene monoclonal rearrangement, number of lesions, histological subtype A or C, AD status or strong expression of CD4 or CD8.

Discussion

We report epidemiological data from a large retrospective multicentric international cohort of 87 children and adolescents with LyP.

LyP can affect all ages. Melchers *et al.* previously found a median age at LyP diagnosis of 47 years (range 2–92) in a large cohort of 504 cases, including 54 patients younger than 20 years old (n=54; 10.7%).[3] The mean age at diagnosis and male predominance found in our study are consistent with the literature. Wieser *et al.* included 251 paediatric and adolescent patients with a diagnosis of LyP in a systematic review.[24] The mean age at diagnosis of paediatric (< 18 years at age of diagnosis) LyP was 9.3 years and the male to female ratio was 1.4 : 1. The 2-month-old patient included in our cohort is, to our knowledge, the youngest case of LyP onset thus far reported.[31,32] As previously described, White patients with LyP are most frequently encountered,[33] which is unsurprising considering that the majority of the included centres are European. However, our findings showed that different ethnicities can be affected. The clinical picture in our cohort did not differ significantly from the presentation in the adult population.[11] Our data suggest that two courses of paediatric LyP can occur: 'acute LyP' (< 12 months of evolution) and 'chronic relapsing LyP' (several episodes over > 12 months). The high variability in follow-up makes it difficult to categorize them accurately, but some paediatric patients with LyP still counted only one occurrence of skin lesions after several years of follow-up. Spontaneous remission (lack of disease recurrence for > 12 months) could also be observed for patients with chronic relapsing LyP.

Patients with LyP labelled as having continuous disease in the 'Results' section were most probably cases with highly active chronic recurrent disease and a short interval between episodes. The range in diagnostic delay and proportion of initial misdiagnosis in our cohort illustrate the diagnostic challenge of paediatric LyP. Clinicopathological correlation and clinical follow-up are key to differentiating LyP from PLEVA,[34] insect bites, inflamed molluscum contagiosum and – most importantly – CTCL. The delineation of single-episode LyP and PLEVA remains challenging. The major diagnostic criteria used in this study encompassed the combination of clinical features (grouped or generalized papules and nodules in different stages of evolution, some with central ulceration, crusting or eschar in LyP vs. acute eruption of multiple erythematous macules that rapidly evolve to form 3–15-mm inflammatory papules and papulovesicles, some of which develop haemorrhagic or necrotic crusts, and collarette desquamation in PLEVA), histology (for PLEVA: vacuolization in the junctional zone; apoptotic keratinocytes; mostly CD8$^+$/CD30$^-$ small-sized lymphocytes; extravasated erythrocytes) and immunohistochemistry (loss of T-cell antigens in LyP such as CD2, CD5 and/or CD7). In the case of ambiguity, the clinical appearance and dynamic nature of the lesions was considered leading for the diagnosis.

Unlike some previous cohort studies,[33,35] we found a prevalence of AD consistent with the prevalence in the general paediatric population.[36]

Type A was the most common histological subtype, although it was less frequently reported than in previous cohorts.[37,38] However, the prevalence rate of subtype D was larger than previously described. Our cohort did not include any cases of histological subtype E, although it was originally described in paediatric patients.[28] The relatively late description of subtypes D in 2010 and subtype E in 2013 may account for the variations in histological epidemiology found in the literature.[39] Recruiting from January 2006 until August 2016, Georgesen and Magro found that only 36.7% of patients had subtype A LyP.[40]

Consistent with previous reports,[37,40] CD8 positivity was frequently encountered in our study and CD8 predominance over CD4 expression was not rare. The CD8-predominant profile accounted for the cases of histological subtype D LyP, as expected from its original description, but was not rare in subtype A or B. Interestingly, juvenile-onset MF is also characterized by over-representation of a CD8$^+$ cytotoxic phenotype.[41] Univariate analysis did not find any prognostic

value of CD4/CD8 histological profiles. Our study included a surprisingly high number of CD30⁻ cases ($n=10/78$; 13%). One limitation of our study design was that reassessment of histology for patients with a diagnosis prior to 2010 ($n=21$) was not possible, as the routine samples were not stored for more than 10 years. A major flaw is therefore the interexaminer variability, limiting conclusions regarding histology. As a potential reason for CD30 negativity, especially in the oldest cases, we consider technical problems (e.g. lack of sufficient antigen retrieval in old immunohistochemical stains). A central pathology review of all cases would be ideal but, practically, difficult to perform in retrospective studies targeting long-term disease outcomes.

An association between LyP and HM has long been known,[7] with a few cases of HM occurring before the age of 19 years.[42,43] Some series have found a prevalence rate of HM as high as 52%.[44,45] In the largest cohort to date of 504 Dutch patients with LyP, associated malignancy was reported in 15.5% ($n=78$). T-cell lymphomas [MF ($n=31$) and ALCL ($n=29$)] were the most frequent. Adults with LyP were also shown to have a higher risk of developing other malignancies, including squamous cell carcinoma, melanoma, and pulmonary and bladder cancer.[3] Patients with childhood-onset LyP were also found to have a significantly increased risk (relative risk 226.2, 95% CI 73.4–697.0) of developing non-Hodgkin lymphoma compared with the general population aged ≤44 years in the USA.[33] An extensive systematic review of paediatric LyP identified 14 cases (5.6%) of associated lymphomas, including 10 patients with primary cutaneous ALCL, two with systemic ALCL and, interestingly, only one with MF.[24,46] With a mean follow-up duration of 5.3 years (range 0–22.9), our large paediatric cohort confirmed the association of paediatric LyP with the development of HM before, concomitantly or after the onset of LyP. If we consider the younger age of the population included in our cohort, and the effect of age we discuss further, the prevalence rate of associated HM is comparable with that reported in the Dutch cohort. We showed that associated HMs, consistent with the adult population, were predominantly MF and ALCL. The same clone has been reported in LyP and MF lesions in the same patients,[11] and also in one patient in our cohort (patient 1, Table 3). We might thus suggest that LyP and MF might be part of the same disease spectrum, where only the clinical appearances differ. In general, MF associated with LyP does not develop into an advanced stage.[3] Similarly, primary cutaneous ALCL and LyP are difficult to distinguish. Some cases reported as primary cutaneous ALCL arising from LyP may, in fact, be primary cutaneous ALCL from the start.[3]

To our knowledge, we also report the first case of association of a myeloid proliferation (AML) and LyP in a paediatric patient. Melchers *et al*. reported two patients with associated AML and LyP in their cohort,[3] concluding that the association of LyP with HMs other than MF or ALCL is probably coincidental, given the impossibility of shared clonality of the lesions. This association in a child could happen by chance, but it raises the suspicion of the possibility of a genetic predisposition to malignancies.

If we compare with the world population aged 0–19 years from 2001 to 2010,[30] the incidence rate ratio for associated cancer in general was 87.49 (95% CI 86.01–88.99). Thus, the incidence of paediatric-onset malignancy was 87 times higher in our cohort than in the general paediatric population. Nevertheless, this striking figure needs to be put into perspective in view of the relatively low incidence of HMs in the general paediatric population and the good (ALCL)[47] or even excellent (MF)[48,49] prognosis of the most commonly associated ones. However, it emphasizes the need for specialized long-term monitoring of paediatric patients with LyP. In our study, associated HM could occur up to 12 years after the onset of LyP. Notably, Melchers *et al*. reported cases of patients with MF and extracutaneous ALCL occurring >22 years after the onset of LyP.[3] Therefore, we propose a long-term follow-up schedule: yearly for the first 5 years, followed by biennial appointments for a total of at least 15 years. This recommendation could be considered for inclusion in paediatric guidelines.

Several factors influencing the risk of associated malignancies for patients with LyP have been suggested, with various and sometimes conflicting results. Older age at the onset of LyP, TCR gene monoclonality, male sex and histological subtype B or C are the most frequent variables associated with an increased risk of associated malignancies.[44,45,50–54] However, cases with subtype A and subtype D histology are suspected to have a decreased risk of associated malignancies.[45,50] Our results confirm these tendencies with regard to older age at the onset of LyP and histological subtype B, which show a higher risk of associated HMs. However, this result must be put into perspective, as histological subtype B is described as being 'MF-like' and the retrospective format of the study makes it difficult to distinguish between LyP evolving into MF and MF that was initially misdiagnosed. On the contrary, histological subtype D was not associated with a risk of associated HM. Indeed, no case of HM was associated with this histological subtype, although it was the second most identified subtype in our cohort. No case of associated HM was found in the subgroup of children who presented with only one episode ('acute LyP'), suggesting the possibility of a contingent of patients with a more indolent disease evolution.

As no treatment regimen has proven efficient in altering the LyP disease course or preventing associated neoplasms, a 'wait-and-see' strategy is often chosen and should be considered as an appropriate first-line strategy when there is a limited number of lesions and/or little impact on the patient's quality of life.[14] Moderate-to-high potency topical or intralesional corticosteroids are recommended for cases with few lesions. In patients with widespread disease, treatment usually consists of phototherapy (mainly narrowband UVB). In addition, or as an alternative, low-dose methotrexate can also be a suitable therapeutic option for those with extensive or scarring lesions.[55] The therapeutic approaches applied in our cohort were mainly in line with these treatment recommendations. Numerous additional therapy options have been suggested in the literature, including topical or systemic bexarotene, topical nitrogen mustard or systemic treatments, including mycophenolate mofetil, brentuximab vedotin, imatinib or interferon-α.[11] Most of these options do not have a favourable risk/benefit ratio in a paediatric setting. Aggressive chemotherapies are not recommended.

Although our study had limitations, including the retrospective design, absence of histology reassessment and variable duration of follow-up, it further describes the characteristics of paediatric LyP.

Paediatric LyP is a rare, usually chronic skin disorder that follows a benign course. However, patients have a noticeable chance of developing a HM, and, as such, require careful clinicopathological correlation for diagnosis and long-term follow-up by specialists. Although caregivers should be aware that the incidence rate of HMs is significantly higher than in the general population, the disease-specific survival rate for all paediatric patients with LyP is excellent.

Funding sources

This work was financially supported by the Promedica Stiftung (1406/M and 1412/M), Swiss Cancer Research (KFS-4243-08-2017), the Swiss National Science Foundation (IZLIZ3_200253/1) and the University of Lausanne (SKINTEGRITY.CH collaborative research programme). E. Guenova and W. Kempf are members of the SKINTEGRITY.CH collaborative research programme.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethics statement

The centres obtained approval for the study from their respective institutional review boards, including CER-VD, the institutional review board of the study coordinator in Lausanne, Switzerland [Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD). Project-ID: 2022-02151 (autorisation accordée)]. They had approval to share deidentified data with the data controller and study coordinator.

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