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ORIGINAL ARTICLE

Paediatric cutaneous lymphomas including rare subtypes: A 40-year experience at a tertiary referral centre

Silvia Alberti-Violetti[1,2] | **Gianluca Avallone**[1,2,3] | **Cristiana Colonna**[4] | **Gianluca Tavoletti**[1,2] | **Luigia Venegoni**[2] | **Valentina Merlo**[2] | **Stefano Cambiaghi**[4] | **Angelo V. Marzano**[1,2] | **Emilio Berti**[1,5] | **Riccardo Cavalli**[4]

[1]Dermatology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

[2]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

[3]Dermatology Clinic, Department of Medical Sciences, University of Turin, Turin, Italy

[4]Pediatric Dermatology Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[5]Inter-Hospital Pathology Division, IRCCS MultiMedica, Milan, Italy

Correspondence
Gianluca Tavoletti, Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Pace 9, 20122 Milan, Italy.
Email: gianlucatavoletti@gmail.com

Abstract

Background: Primary cutaneous lymphomas are neoplasms of the immune system with a distinct tropism for the skin and an absence of extracutaneous manifestations at the time of diagnosis. Studies focusing on cutaneous lymphomas in children and adolescents remain scarce and often do not encompass the rare subtypes.

Objectives: To address this knowledge gap by describing the clinical, histological and molecular characteristics of a large group of paediatric patients affected by primary cutaneous lymphoma. We also provided the *Paediatric Primary Cutaneous Lymphoma Atlas* that illustrates the clinicopathological spectrum of observed presentations, in the hope of supporting other physicians in the diagnostic process.

Methods: Retrospective chart review of paediatric patients diagnosed with primary cutaneous lymphomas between 1980 and 2022 at the Paediatric Dermatology Unit of Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico, Milan.

Results: A total of 101 patients (58 males, 43 females) met the inclusion criteria. The most common subtypes were lymphomatoid papulosis ($n = 48$) and mycosis fungoides ($n = 31$). These were followed by primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorders ($n = 7$), primary cutaneous anaplastic large-cell lymphomas ($n = 5$), primary cutaneous marginal zone B-cell lymphomas ($n = 3$), primary cutaneous follicle centre lymphomas ($n = 2$), subcutaneous panniculitis-like T-cell lymphomas ($n = 2$), primary cutaneous peripheral T-cell lymphoma not otherwise specified ($n = 1$), primary cutaneous precursor B-lymphoblastic lymphoma ($n = 1$) and Sézary syndrome ($n = 1$). Clinical follow-up data covering a median of 70.8 months (range 1–324) were available for 74 patients, of whom three died due to cutaneous lymphoma.

Conclusions: Our findings shed light on the peculiar aspects and long-term outcomes of paediatric cutaneous lymphomas, particularly emphasizing their distinctive features in comparison to their adult counterparts and exploring the less common subtypes. Further larger-scale studies are warranted to better characterize these entities and to achieve a more rapid and accurate diagnosis.

Silvia Alberti-Violetti and Gianluca Avallone contributed equally to this article and shared first authorship.

Emilio Berti and Riccardo Cavalli contributed equally to this article and shared senior authorship.

INTRODUCTION

Primary cutaneous lymphomas are neoplasms of the immune system, characterized by a proliferation of T, natural killer (NK) or B lymphocytes, with a distinct tropism for the skin and an absence of extracutaneous manifestations at the time of diagnosis.[1] These lymphomas usually arise in adults and are extremely rare in paediatric patients.[2] As observed in adults, the most prevalent cutaneous lymphomas in the paediatric population are T-cell neoplasms. Specifically, mycosis fungoides (MF) and lymphomatoid papulosis (LyP) are the most common subtypes, exhibiting an incidence rate of 0.96 per 100,000 person-years.[3] Primary cutaneous B-cell lymphomas are less frequent, whereas other forms are even rarer.[2,4] Although primary cutaneous lymphomas are comprehensively documented in the adult population, studies focusing on cutaneous lymphomas in children and adolescents remain scarce and often do not encompass long-term outcomes or their rare subtypes[2,5–10] (Table 1). Consequently, the natural history, therapeutic strategies and overall understanding of these entities remain poorly understood.[2,6] This study sought to address this knowledge gap by describing the clinical, histological and molecular characteristics of a large group of paediatric Italian patients affected by primary cutaneous lymphoma. We also provide the *Paediatric Primary Cutaneous Lymphoma Atlas* that illustrates the spectrum of observed presentations, hoping to support other physicians in the diagnostic process (Appendix S1).

MATERIALS AND METHODS

Patients

We performed a retrospective chart review to assess the clinicopathological data of paediatric patients diagnosed with primary cutaneous lymphomas between 1980 and 2022 at the Paediatric Dermatology Unit of Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico, Milan. The Institutional Review Board approved the study protocol, and the study was conducted according to the principles of the Declaration of Helsinki. Patients were eligible if they were aged ≤18 years old at the time of diagnosis and if they had a biopsy-confirmed cutaneous lymphoma. All diagnoses underwent a re-evaluation and reclassification by a dermatopathologist experienced in cutaneous lymphomas (EB) in accordance with the 2018 updated version of the World Health Organization (WHO) and the latest fifth edition of the WHO Classification of Haematolymphoid Tumours.[1,11]

For initial staging, patients were assessed using the standard diagnostic methods available at their time of diagnosis, including a physical examination, blood cell count, computed tomography scan and lymph node sonography. Lymph node and bone marrow biopsies were conducted as needed.[12] Data were collected on demographics, clinical and histological outcomes, stage of the disease, management, disease status at the last follow-up and cause of death when appropriate. Patients without a histologically confirmed diagnosis of cutaneous lymphoma were excluded from this study.

Histology and immunohistochemistry

The histological examinations were based on haematoxylin and eosin-stained sections of paraffin-embedded skin biopsies. Immunohistochemical analyses were carried out based on the diagnostic hypothesis and included a large panel of monoclonal antibodies: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD19, CD20, CD22, CD23, CD25, CD30, CD33, CD34, CD45RA, CD45RO, CD56, CD68, CD79a, CD123, ALK-1, BDCA2, Tcl-1, TIA1, Granzyme B, LFA-1, PD-1, TdT, Mib-1, Bcl2, Bcl6, Pax5, MPO, Kappa light chain, Lambda light chain, and T-cell receptors (TCR) βF1 and TCRδ1.

Molecular analyses

DNA was isolated from frozen biopsies or peripheral blood samples, when available. TCR-gamma and beta and immunoglobulin heavy and light chain gene rearrangements were evaluated using multiplex polymerase chain reaction in accordance with the BIOMED-2 standardized protocol.[13]

Data analyses

All of the numeric variables were presented with median and range (minimum–maximum), whereas categorical ones were summarized using absolute frequency and percentage values.

RESULTS

We retrospectively screened records of 145 patients who had received a diagnosis of paediatric cutaneous lymphoma. A total of 101 patients (58 males and 43 females) met the inclusion criteria, with a median age at diagnosis of 10.4 years (ranging from 6 months to 17 years) as detailed in Table 2. Notably, 97% of the patients were of Caucasian ethnicity. The most common subtypes were Lyp ($n = 48$) and MF ($n = 31$) (Figure 1). These were followed by, primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder (PCSM-LPD) ($n = 7$), primary cutaneous anaplastic large-cell lymphoma (cALCL) ($n = 5$), primary cutaneous marginal zone B-cell lymphoma (PCMZL) ($n = 3$), primary cutaneous follicle centre lymphomas (PCFCL) ($n = 2$), subcutaneous panniculitis-like T-cell lymphoma (SPTCL) ($n = 2$),

TABLE 1 Frequency and gender of patients with paediatric cutaneous lymphomas in large case series.

Entity	Fick-Puches et al.[6]	Boccara et al.[5]	Moon et al.[8]	Kempf et al.[2]	Colmant et al.[9]	Present series
Mycosis fungoides	24 (M = 12, F = 12)	5 (M = 4, F = 1)	9 (M = 5, F = 4)	12 (M = 8, F = 4)	6 (M = 5, F = 1)	31 (M = 16, F = 15)
Sezary syndrome	0	0	0	0	0	1 (M = 1)
Lymphomatoid papulosis	11 (M = 5, F = 6)	24 (M = 15, F = 9)	10 (M = 7, F = 3)	10 (M = 6, F = 4)	10 (M = 7, F = 3)	48 (M = 29, F = 19)
Cutaneous anaplastic large-cell lymphoma	13 (M = 7, F = 6)	0	8 (M = 5, F = 3)	3 (M = 1, F = 2)	4 (M = 1, F = 3)	5 (M = 4, F = 1)
Subcutaneous panniculitis-like T-cell lymphoma	1 (F = 1)	1 (M = 1)	1 (M = 1)	0	0	2 (M = 1, F = 1)
Cutaneous extra-nodal NK/T-cell lymphoma, nasal	1 (F = 1)	1 (M = 1)	2 (M = 1, F = 1)	0	1 (F = 1)	0
Chronic active EBV infection	0	5 (M = 2, F = 3)	0	0	1 (M = 1)	0
Primary cutaneous γ/δ T-cell lymphoma	0	1 (F = 1)	0	0	0	0
Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma	0	0	0	0	0	0
Primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder	2 (M = 1, F = 1)	0	1 (M = 1)	1 (F = 1)	1 (M = 1)	7 (M = 3, F = 4)
Primary cutaneous acral $CD8^+$ T-cell lymphoma	0	0	0	0	0	0
Primary cutaneous peripheral T-cell lymphoma, not otherwise specified	0	0	0	0	0	1 (M = 1)
Cutaneous marginal zone lymphoma	7 (M = 2, F = 5)	0	1 (M = 1)	3 (M = 1, F = 2)	4 (M = 3, F = 1)	3 (M = 1, F = 2)
Cutaneous follicle centre lymphoma	1 (F = 1)	0	0	0	0	2 (M = 2)
Cutaneous diffuse large-cell lymphoma, leg	0	0	0	0	0	0
Cutaneous lymphoblastic lymphoma	6 (M = 3, F = 3)	7 (M = 4, F = 3)	6 (M = 6)	2 (M = 1, F = 1)	1 (M = 1)	1 (F = 1)
Other/unclassified	3 (F = 3)	7 (M = 3, F = 4)	3 (M = 2, F = 1)	0	8 (M = 5, F = 3)	0
Total	69 (M = 33, F = 36)	51 (M = 30, F = 21)	41 (M = 29, F = 12)	31 (M = 17, F = 14)	36 (M = 22, F = 14)	101 (M = 58, F = 43)

Abbreviations: EBV, Epstein–Barr virus; F, female; M, male; NK, natural killer.

primary cutaneous peripheral T-cell lymphoma not otherwise specified (PTL-NOS) ($n = 1$), primary cutaneous precursor B-lymphoblastic lymphoma (PCLBL) ($n = 1$) and Sézary syndrome (SS) ($n = 1$) (Figure 2). Clinical follow-up data covering a median of 70.8 months (range 1–324 months) were available for 74 patients, of whom three died due to cutaneous lymphoma.

Mycosis fungoides and variants

Out of the 31 patients affected by MF (30.7%), with a median age at diagnosis of 11.4 years (range 2–17), six had an unknown immunophenotype because the samples were no longer available for re-staining. Of the other 25 patients, 18 exhibited a $CD4^+$ phenotype with the following clinical

TABLE 2 Classification and clinical data of 101 paediatric patients with cutaneous lymphoma.

Subtype	No. of cases (%)	Sex (M/F)	Median age at diagnosis (range), years	Median follow-up (range), months	Rearrangement[a]
Mycosis fungoides	31 (30.7%)	16/15	11.4 (2–17)	100.4 (10–340)	18/23
Sezary syndrome	1 (1.0%)	1/0	17	100	1/1
Lymphomatoid papulosis	48 (47.5%)	29/19	6.8 (0–17)	58.6 (1–281)	23/33
Primary cutaneous anaplastic large-cell lymphoma	5 (5.0%)	4/1	8.8 (3–13)	20.3 (6–36)	2/3
Subcutaneous panniculitis-like T-cell lymphoma	2 (2.0%)	1/1	12 (10–14)	90 (12–168)	2/2
Primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder	7 (6.9%)	3/4	10.6 (5–16)	25.5 (6–48)	3/6
Cutaneous peripheral T-cell lymphoma, not otherwise specified	1 (1.0%)	1/0	12	132	1/1
Cutaneous marginal zone lymphoma	3 (3.0%)	1/2	12.3 (10–17)	84	1/2
Cutaneous follicle centre lymphoma	2 (2.0%)	2/0	16.5 (16–17)	182.5 (41–324)	2/2
Cutaneous B-cell lymphoblastic lymphoma	1 (1.0%)	0/1	2	156	0/0
Total	101 (100%)	58/43	10.1 (1–17)	70.8 (1–324)	53/73

Abbreviations: F, female; M, male.

[a]Monoclonal gene rearrangement of TCR-gamma and/or beta for T-cell lymphomas, and immunoglobulin heavy and light chain for B-cell lymphomas.

presentations: eight classical MF, three folliculotropic, three hypopigmented, two granulomatous, one erythrodermic and one with pagetoid reticulosis. The subsequent seven displayed a $CD8^+$ phenotype with four cases clinically classified as classical MF, two as folliculotropic and one as hypopigmented. Twenty-eight patients had early stage MF at the time of diagnosis (19 stage IA, 9 stage IB), two tumoral MF (stage IIB) and one erythrodermic MF (stage IIIA). Three patients (9.7%) died with progressive disease (Table 3). Further details regarding the clinical history, prognosis can be found in Appendix S2.

Sézary syndrome

The only case of SS involved a 17-year-old Hispanic male who presented with a 6-month history of confluent plaques that progressed to erythroderma. An identical T-cell clone was found in the skin, blood and bone marrow. Comprehensive staging revealed the presence of Sézary cells in peripheral blood, with elevated flow cytometry counts of $CD4^+$, $CD7^-$ and $CD26^-$ cells (constituting 82% of lymphocytes). There was also evidence of bone marrow infiltration by atypical lymphoid cells. The patient underwent four courses of gemcitabine followed by extracorporeal photopheresis. However, as this regimen led only to partial remission, he underwent an allogeneic SCT. At his last follow-up visit, which was 8 years post-diagnosis, he had experienced no recurrence.

Lymphomatoid papulosis

Out of the 48 patients diagnosed with LyP (47.5%), the median age at diagnosis was 6.8 years, with a range of 6 months to 17 years. Follow-up data were available for 34 of these patients (with a median duration of 58.6 months, ranging from 1 to 281 months). No evidence was found to suggest any association with another type of lymphoma or deaths attributed to LyP. The majority of the patients exhibited erythematous papules or papulo-necrotic lesions on the trunk and/or extremities. Importantly, mucosal lesions were absent, and there was no evidence of extracutaneous involvement (Table 4).

Primary cutaneous anaplastic large-cell lymphomas

Patients with primary cutaneous ALCLs clinically presented with solitary or localized papules and nodules in four cases,

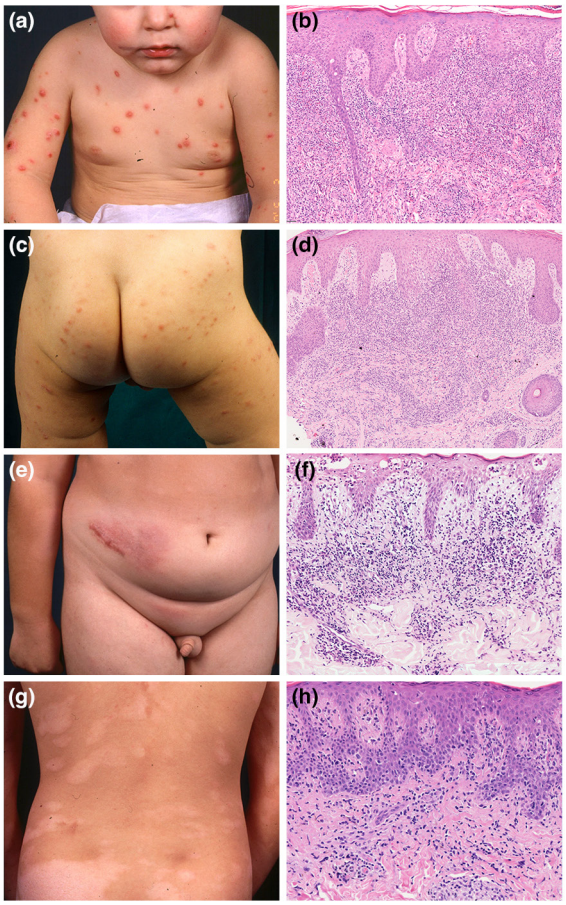

FIGURE 1 Clinical and histological presentations of lymphomatoid papulosis and mycosis fungoides. (a) Lymphomatoid papulosis. Generalized papular eruption. Some of these lesions show bullous and necrotic evolution. (b) Lymphomatoid papulosis, type A. Scattered and clustered large atypical cells, along with small lymphocytes, histiocytes and a few eosinophils. Haematoxylin and eosin (H&E), original magnification × 100. (c) Lymphomatoid papulosis. Generalized papular eruption in different stages of evolution. (d) Lymphomatoid papulosis, type A. Wedge-shaped infiltrate with perivascular and periadnexal involvement, characterized by several large, atypical cells admixed with some granulocytes. H&E stain, original magnification × 20. (e) Mycosis fungoides. Erythematous finely scaling plaque on the right side of the abdomen. (f) Mycosis fungoides. Band-like lymphoid infiltrate with prominent epidermotropism and intraepidermal collections of lymphocytes (Darier's nests). H&E stain, original magnification × 200. (g) Mycosis fungoides. Multiple hypopigmented patches. (h) Mycosis fungoides. Epidermal hyperplasia and acanthosis with some necrotic keratinocytes associated with an infiltrate of atypical lymphocytes in the superficial dermis, showing epidermotropism. H&E stain, original magnification × 100.

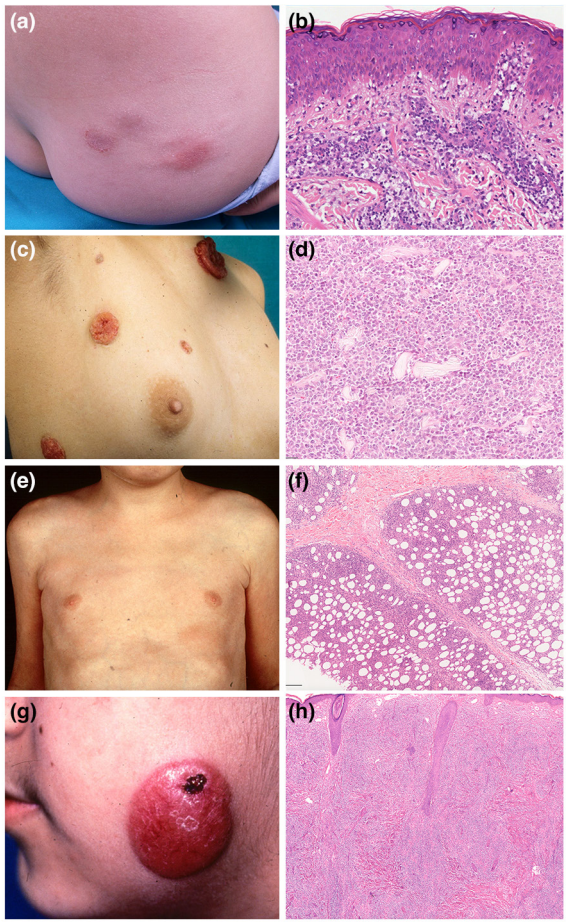

FIGURE 2 Clinical and histological presentations of rarer subtypes. (a) Cutaneous peripheral T-cell lymphoma, not otherwise specified. Erythematous plaques on the buttock. (b) Cutaneous peripheral T-cell lymphoma, NOS. Perivascular and periadnexal atypical medium- and large-sized lymphoid infiltrate, with focal epidermotropism. Haematoxylin and eosin (H&E), original magnification × 200. (c) Cutaneous anaplastic large-cell lymphoma. Multiple ulcerated tumours and plaques on the trunk. (d) Cutaneous anaplastic large-cell lymphoma. Diffuse infiltrate characterized by cohesive sheets of large cells. H&E stain, original magnification × 200. (e) Subcutaneous panniculitis-like T-cell lymphoma. Subcutaneous nodules, covered by slightly erythematous/brown skin, on the trunk. (f) Subcutaneous panniculitis-like T-cell lymphoma. A dense infiltration of small-medium-sized pleomorphic lymphocytes involving the subcutaneous fat. H&E stain, original magnification × 200. (g) Cutaneous marginal zone lymphoma. Solitary nodule on the cheek. (h) Cutaneous marginal zone lymphoma. Marginal zone cells ('centrocyte-like') with abundant cytoplasm mixed with plasma cells, small lymphocytes and eosinophils. H&E stain, original magnification × 100.

and with multifocal lesions in one case. One patient with localized lesions experienced extracutaneous dissemination to local lymph nodes. Histologically, all of the cases were ALK-1 negative. T-cell clonality assessments were possible in only three cases, two of which (including the patient with multifocal lesions) showed clonal rearrangements of TCR-gamma genes, and one was polyclonal. The skin lesions spontaneously regressed in one case. As for the management, one patient was successfully treated with local radiotherapy and three received multi-agent chemotherapy. All the patients were still alive at the time of the last follow-up visit, with the exception of the patient with multifocal lesions who subsequently relapsed and died of lymphoma 9 months of follow-up.

Primary cutaneous CD4$^+$ small/medium pleomorphic lymphoproliferative disorder

Only three out of the seven patients with PCSM-LPD were clinically characterized by classic single nodules, located on

TABLE 3 Clinical data of 31 patients with paediatric mycosis fungoides.

MF variant	No. of patients (%)	Morphology	No. of patients (%)[a]	Suspected diagnosis	No. of patients (%)	Clinical stage at diagnosis	No. of patients (%)
Classical	16 (51.6%)	Patches	25 (80.6%)	Cutaneous lymphoma	17 (54.8%)	IA	19 (61.3%)
Follicular	5 (16.1%)	Plaques	6 (19.4%)	Pityriasis lichenoides	3 (9.7%)	IB	9 (29.0%)
Hypopigmented	4 (12.9%)	Papules	3 (9.7%)	Follicular mucinosis	3 (9.7%)	IIA	0 (0.0%)
Pagetoid reticulosis	2 (6.5%)	Nodules	2 (6.5%)	Purpuric dermatoses	2 (6.5%)	IIB	2 (6.5%)
Granulomatous	2 (6.5%)	Erythroderma	1 (3.2%)	Pityriasis rosea	1 (3.2%)	IIIA	1 (3.2%)
Erythrodermic	1 (3.2%)	Unknown	1 (3.2%)	Morphoea	1 (3.2%)	IIIB	0 (0.0%)
Ichthyosiform	1 (3.2%)			Unknown	4 (12.9%)	IV	0 (0.0%)

Location	No. of patients (%)[a]	Treatment[b]	No. of patients (%)[c]	Treatment[b]	No. of patients (%)[c]	Treatment[b]	No. of patients (%)[c]
Limbs	21 (67.7%)	Topical corticosteroids	13 (41.9%)	Radiotherapy	3 (9.7%)	Acitretin	1 (3.2%)
Trunk/back	18 (58.1%)	nb-UVB	8 (25.8%)	Chemotherapy	2 (6.5%)	Bexarotene	1 (3.2%)
Face/neck	4 (12.9%)	pUVA	3 (9.7%)	Systemic corticosteroids	2 (6.5%)	Methotrexate	1 (3.2%)
Unknown	1 (3.2%)	TSEB	2 (6.5%)	Interferon	3 (9.7%)	SC transplant	3 (9.7%)

Abbreviations: nb-UVB, narrow-band ultraviolet B; pUVA, psoralen and ultraviolet A; SC transplant, stem cell transplant; TSEB, total skin electron beam.
[a]Numbers do not add up to 31 because some patients exhibited multiple variables.
[b]Data relate to 16 patients.
[c]Numbers do not add up to 16 because some patients exhibited multiple variables.

TABLE 4 Clinical data of 48 patients with paediatric lymphomatoid papulosis.

Histology subtype	No. of patients (%)	Morphology	No. of patients (%)[a]	Suspected diagnosis	No. of patients (%)	Number of lesions at diagnosis	No. of patients (%)
A	25 (52.1%)	Papules	38 (79.2%)	LyP	16 (33.3%)	<10	11 (22.9%)
A + B	5 (10.4%)	Nodules	13 (27.1%)	PL	16 (33.3%)	10–30	11 (22.9%)
A + C	3 (6.3%)	Vesicles	2 (4.2%)	Insect bites	3 (6.3%)	30–50	10 (20.8%)
B	2 (4.2%)	Pustules	1 (2.1%)	Infectious exanthem	2 (4.2%)	>50	7 (14.6%)
C	1 (2.1%)	Macules	1 (2.1%)	Other	7 (14.6%)	Unknown	9 (18.8%)
D	12 (25.0%)	Unknown	7 (14.6%)	Unknown	4 (8.3%)		

Location	No. of patients (%)[a]	CD30 expression	No. of patients (%)	Therapeutic approach	No. of patients (%)	Treatment	No. of patients (%)[b]
Limbs	36 (75.0%)	$CD30^{+}$	21 (43.8%)	Treatment	24 (50.0%)	Topical corticosteroids	20 (41.7%)
Trunk/back	21 (43.8%)	$CD30^{+/-}$	12 (25.0%)	Wait and see	9 (18.8%)	Methotrexate	10 (20.8%)
Face/neck	8 (16.7%)	$CD30^{-}$	8 (16.7%)	Unknown	15 (31.3%)	Phototherapy	9 (18.8%)
Unknown	5 (10.4%)	Unknown	7 (14.6%)			Systemic corticosteroids	3 (6.3%)

Abbreviations: Lyp, lymphomatoid papulosis; PL, pityriasis lichenoides.
[a]The numbers do not add up to 48 because some patients exhibited multiple variables.
[b]The numbers do not add up to 24 because some patients exhibited multiple variables.

the face and trunk, respectively. Nodules were surgically removed without any subsequent signs of relapse. In addition, two patients presented with multiple red-brown to yellow purpuric MF-like plaques that lacked desquamation. These patients underwent phototherapy because of the waxing and waning disease course. Two other patients exhibited multiple papules, one of them received systemic chemotherapy at a different medical centre, achieving a lasting complete remission.

Subcutaneous panniculitis-like T-cell lymphomas

Two patients, a 10-year-old boy and a 14-year-old girl, were diagnosed with SPTCLs, presenting with subcutaneous nodules on their body. The boy also had involvement of lymph nodes, liver and spleen. Molecular tests confirmed clonal TCR-gamma and TCR-beta chain rearrangements in both.

He was treated with multiple drugs, including the cyclophosphamide, hydroxy-daunorubicin, oncovin and prednisone (CHOP) chemotherapy protocol, but died from hemophagocytic syndrome. The girl achieved remission with CHOP but relapsed after 5 years. A subsequent autologous stem cell transplant (SCT) resulted in a prolonged clinical remission, with a follow-up duration of 14 years.

Primary cutaneous peripheral T-cell lymphoma not otherwise specified

The only patient with a primary cutaneous PTL-NOS was a 12-year-old male who presented with diffuse erythematous patches and nodules but no systemic involvement. Histology showed an angiocentric infiltrate of small/medium-sized pleomorphic lymphocytes with numerous mitotic figures. The tumour cells were characterized by an aberrant $CD4^+$ and $CD8^+$ T-cell phenotype, and TCR-gamma genes were clonally rearranged. The patient was successfully treated with multi-agent chemotherapy and was alive and disease-free after 11 years of follow-up.

Primary cutaneous B-cell lymphomas

In our study sample, five patients were diagnosed with primary cutaneous B-cell lymphoma. Among these, two patients presented with PCFCLs, and three patients had PCMZLs. Notably, all these patients had a good prognosis. Further information on the clinical history and the management is available in Appendix S2.

Primary cutaneous precursor B-lymphoblastic lymphoma

An isolated case of PCLBL was documented in a 2-year-old female. Upon physical examination, a single erythematous alopecic nodule in the right parietal region was seen. Histopathological analysis of the biopsy specimen displayed a nodular and diffuse infiltration of small to medium-sized lymphoid cells within the dermis and subcutaneous tissue. The cytomorphological characteristics were consistent with PCLBL. Complete haematological staging was negative for systemic involvement. The patient was treated with a multi-agent chemotherapy regimen and achieved complete remission but died of Ewing sarcoma 13 years later.

DISCUSSION

We present demographic and clinical data from 101 confirmed cases of paediatric primary cutaneous lymphomas, representing the largest published series to date with the most extended follow-up duration. The size of our sample substantially exceeds that considered in previous studies.[2,5,6,8,9] This likely reflects the prolonged follow-up period and the referrals to our centre from throughout the country over the past decades for second opinions. In conjunction with the results presented in this study, the *Paediatric Primary Cutaneous Lymphomas Atlas* provides further clinical and histological details with the goal of enhancing the diagnosis of these rare entities.

Consistent with past research,[2] our findings confirm that MF and LyP are the most prevalent forms of cutaneous lymphoma among the paediatric population.

Classic MF was the most frequently observed clinical variant in our records, and its clinical manifestation was indistinguishable from adult-onset cases. Notably, both the folliculotropic MF and the hypopigmented MF were observed less frequently in our study compared to other case series.[14,15] The under-representation of the hypopigmented form might be partially due to the lower prevalence of the $CD8^+$ phenotype[16,17] in our MF cases. Additionally, the reduced number of non-Caucasian patients in our series could be a contributing factor, as the hypopigmented MF is more commonly diagnosed among patients from the Middle East and those with darker skin types.[15] Based on our observations, the course of paediatric MF is generally indolent, with only a few cases progressing to an advanced stage. However, its earlier onset theoretically allows a longer time for progression and makes it essential for patients to be carefully monitored.

We have previously detailed a paediatric SS case, and only one other similar case exists in literature.[18,19] Other erythrodermic atypical form, such as erythrodermic follicular mucinosis, have been previously reported in childhood but did not follow the criteria for SS diagnosis according to WHO classifications.[20] The reasons for the extreme rarity of this condition remain unknown.

Unlike in adults,[21] we found that LyP was the most frequent form of primary cutaneous lymphoma in our series and accounted for almost half of all our cases. Notably, the median age at the time of the onset of LyP was lower than that reported in all previous studies.[2,5,6,8,9,22] Furthermore, our series documents the earliest reported diagnosis in a 6-month-old child who developed recurrent papulo-necrotic lesions.

Our data suggest that the most prevalent histological subtypes of Lyp are A, B and C and these findings are in line with previous studies.[22] Notably, the subtype D has also emerged as a frequently observed subtype in our research. Its increased prevalence might be due to its more recent characterization compared to other subtypes, and likely because it is challenging to differentiate it from pityriasis lichenoides, especially its acute manifestation often observed in paediatric cases.[23] Though a younger

onset age for LyP is linked with a heightened risk of neoplastic lymphoproliferative disorders,[24] none in our cohort developed malignancy.

Consistent with prior studies[2,5,9] we observed that primary cutaneous ALCL is rare among paediatric patient who predominantly present with nodal form.[25]

While PCSM-LPD in paediatric patients has been suggested to primarily affect males aged 3–16 months, often presenting as a solitary nodule,[2,26–29] our findings indicate a later onset and a female predilection, as we previously reported.[27] Regarding those characterized by MF-like plaques, these display an infiltrate of small/medium-sized pleomorphic cells with T follicular helper (TFH) phenotype. These cells are mixed with reactive ones and arranged in PD1^{+} aggregates of rosettes, as seen in nodular lesions. However, they are organized in a band-like or multinodular pattern in the upper dermis, especially in the papillary dermis, showing only focal epidermotropism. In recent years, the TFH phenotype has also been related to MF, and the latest WHO classification[11] differentiate the presentation of single nodules on acral sites in PCSM-LPD from MF-like plaques, including in the MF group, although multiple plaques have also been reported.[30,31] Nonetheless, the histological picture of our cases differs from that of classical MF, such as the presence of spongiosis and only focal epidermotropism, reflecting the ongoing debate about defining TFH cutaneous lymphomas as potentially separate entities.[32] As for the treatment of PCSM-LPD, only one patient underwent aggressive chemotherapy, reflecting the management approach at the time of diagnosis when the nature and prognosis of PCSM-LPDs were poorly understood.

SPTCLs are infrequently encountered, with approximately 40 paediatric cases reported in the literature.[2] Predominantly, these cases affect adolescents and typically follow a benign clinical course; therefore, conservative management should be considered as the initial therapeutic approach, except in instances where there is evidence of hemophagocytic syndrome.[2] Among our two SPTCL patients, one died due to complications associated with hemophagocytic syndrome despite aggressive treatment, while the other exhibited favourable outcomes post-allogeneic SCT. The aggressive course observed in our two patients poses a diagnostic challenge, particularly in the case of hemophagocytic syndrome. This syndrome, especially in paediatric cases, could be linked to non-neoplastic rheumatic or viral panniculitis, which may exhibit a clonal T infiltrate like in forms associated with congenital immunodeficiency syndrome and linked to mast cell activation syndrome.[33]

PCLBLs are uncommon, yet distinctly recognized lymphomas, predominantly documented in paediatric or adolescent population. Our earlier reported case[34] manifested as a solitary nodule on the upper trunk when the patient was 2 years old, reflecting prior descriptions.[35,36] While there has been no evidence of secondary involvement for the PCLBL in our patient thus far, vigilance is crucial as the potential for subsequent localizations in the future cannot be definitively excluded.

Current literature on paediatric primary cutaneous PTL-NOS is limited, leading to ongoing debate about its existence in this population.[37] To the best of our knowledge, we believe our report presents the first paediatric ascertained case that meets the fifth edition of WHO classification criteria.[1] Nonetheless, given the singular nature of this case, drawing comparisons to the typically aggressive forms observed in adults remains challenging.

The incidence of primary CBCLs in paediatric patients is unknown, with most data on childhood and adolescent forms coming from isolated cases or single-centre reports.[2,38–40] In our series, PCMZL was the most common primary CBCL and typically showed an indolent course. However, our conclusions are limited because the diagnosis of our patient goes back several decades, when CBCLs were considered to have a poor prognosis and therefore required chemotherapy.

Limitations of the present study are its retrospective design and confinement to a single-centre setting, potentially introducing a selection bias. The sample size did not allow for discerning statistically significant differences within the patient subset, a challenge anticipated given the infrequent occurrence of these conditions. Furthermore, complete data reconstruction was not feasible for all patients. This limitation was either due to the historical nature of some records or because several patients, after seeking a second opinion, continued their follow-up at their original institutions.

CONCLUSIONS

This retrospective analysis, along with the clinical-pathological Atlas provided, sheds light on the peculiar aspects and long-term outcomes of paediatric cutaneous lymphomas, particularly emphasizing some distinctive features in comparison to adult counterparts and exploring the less common subtypes. In clinical practice, these data support other physicians involved in the management and diagnostic process of these rare conditions, which remain a significant challenge. Further larger-scale studies are warranted to better characterize these entities and to achieve a more rapid and accurate diagnosis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available upon request from the corresponding author.

ETHICS STATEMENT

This study was conducted in accordance with applicable laws, regulations and guidelines for the protection of human subjects. The patient's parents/guardians in this manuscript have given written informed consent to the publication of their case details.

ORCID

Silvia Alberti-Violetti https://orcid.org/0000-0001-7163-1035
Gianluca Avallone https://orcid.org/0000-0001-7253-2370
Gianluca Tavoletti https://orcid.org/0000-0001-8901-318X
Luigia Venegoni https://orcid.org/0000-0002-1846-1206
Valentina Merlo https://orcid.org/0000-0003-1438-4052
Angelo V. Marzano https://orcid.org/0000-0002-8160-4169

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SUPPORTING INFORMATION

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