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Original Contribution

Lymphomatoid papulosis in children and adolescents: A clinical and histopathologic retrospective cohort☆

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ABSTRACT

Background, aims and objectives: Lymphomatoid papulosis (LyP) is a CD30+ lymphoproliferative disorder that is rare and not well described within the pediatric subpopulation. We sought to review the literature and characterize clinical and pathologic features among pediatric and adolescent patients diagnosed with LyP at a tertiary care center.

Materials and methods: A retrospective cohort of 27 pediatric and adolescent patients (defined as < 20 years old) diagnosed with LyP at the Weill Cornell Medicine Dermatopathology division from 2006 to 2016 was identified. Subsequently, we reviewed the histopathologic characteristics and collected clinical follow-up data from patients and their providers. The parameters assessed included the pathological LyP subtype including the immunohistochemical staining pattern, the development of secondary lymphoma, disease duration and rate of remission.

Results: While type A was the most prevalent subtype, B and C subtypes were also frequently observed. CD8 predominance was a common finding, especially among type B LyP patients and those with eccrinotropic granulomatous features. None of the patients with clinical follow-up have developed secondary lymphoma, and some patients experienced remission of their disease.

Conclusion: While type A appears to be the dominant variant described in children, types B, C, and even the newly described variants E and F may occur more often than previously reported. Pediatric LyP may be more indolent than the adult variant, but close clinical follow-up is still warranted.

1. Introduction

Lymphomatoid papulosis (LyP) is a CD30+ lymphoproliferative disorder with a broad spectrum of clinical and histopathologic presentations. Clinically, LyP is characterized by self-healing recurrent crops of papules and nodules that occasionally heal with scars.

Historically, lymphomatoid papulosis is divided into four histopathologic subtypes: Type A exhibits a lymphomatoid vascular reaction with many transformed CD30 positive T cells accompanied by eosinophils and neutrophils; in Type B, epidermotropic smaller atypical cerebriform cells simulating mycosis fungoides are observed; Type C LyP also falls under the designation of borderline CD30+ lymphoproliferative disease and shows an effacing sheet like growth of CD30+ atypical transformed lymphocytes to produce a morphology that closely simulates anaplastic large cell lymphoma; the Type D variant is an epidermotropic CD8 positive subset of LyP that resembles primary cutaneous aggressive epidermotropic CD8 T cell lymphoma, including an angiocentric component and the presence of non-cerebriform atypia [1-7]. In recent years, additional subtypes have been described including Type E that exhibits a striking angiodestructive lymphomatoid vasculitis [8] and one that exhibits follliculotropism consistent with type F [9].

The diagnosis of LyP commits a patient to long-term clinical follow-up. Patients who develop new review of systems findings or a change in the morphology of the lesions warrant additional workup to rule out malignancy. Recent reviews [5,10-12] have characterized the rate of secondary lymphomas in LyP patients, which may be higher than previously presumed. These patients can develop a secondary malignancy before, at the time of, or following their diagnosis of LyP. The most common secondary lymphoma described is mycosis fungoides, followed by anaplastic large cell lymphoma, chronic lymphocytic lymphoma, and Hodgkin's disease. Risk factors for secondary lymphoma include male gender and an older age at diagnosis [5,10].

Lymphomatoid papulosis is a rare entity, especially so within the

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Table 1
Clinical characteristics of 16 pediatric and adolescent LyP patients.

	Age at diagnosis/ gender	Clinical description of lesions	Duration of disease	Treatments	Activity of disease	Family history of LyP	Occurrence of secondary lymphoma
1	16 years Female	Papules on chest and back healing with atrophic scar	9 years	Clobetasol, methotrexate, bexarotene	5 flares per year	No	No
2	15 years Female	Intermittent bumps on arms, legs, and abdomen that self-resolve	2 years	Clobetasol, methotrexate	Inactive x 6 months (still on low dose methotrexate)	No	No
3	14 years Male	Recurrent crops of papules on the arms, legs, and buttocks healing with scars	18 months	Triamcinolone, clobetasol, methotrexate	3–4 flares in the past year	No	No
4	9 years Male	Papular rash on the trunk and legs	5 months	Clobetasol, narrow band UVB	New spots every 1–2 months	No	No
5	13 years Female	Erythematous papules on the trunk admixed with hypopigmented macules	15 months	Triamcinolone	New spots monthly	No	No
6	9 months Male	Erythematous papules in the neck, axilla, and penis	4 months	Mometasone	Inactive	Yes - father	No
7	3 years Male	Diffuse rash with scale on back, arms and legs	2 years	Halobetasol	Inactive for 6 months	No	No
8	16 years Female	Red, scaly rash on the left lower extremity	1 year	None	New lesions every 1–2 months	No	No
9	10 years Female	Pink papules on the chest that heal as hypopigmented macules	4 months	Hydrocortisone	New spots weekly	No	No
10	9 years Female	Recurrent pink papules on the trunk	3 years	Natural sunlight	Inactive for 1 year	No	No
11	19 years Female	Ulcerating nodules on the leg	10 years	Clobetasol	Flares 3–4 times yearly	No	No
12	5 years Male	Ulcerating nodule on the trunk	9 years	Triamcinolone, clobetasol	Inactive for 3 years	No	No
13	17 years Male	Nodule on the right cheek	7 years	Unknown	Inactive for > 5 years	No	No
14	16 years Male	Papules and patches on the right anterior thigh	3 years	Clobetasol UV light	Inactive for 2 years	No	No
15	16 years Male	Scattered papules on the arms and legs that spontaneously regressed with attendant scars	7 years	Clobetasol, methotrexate (previously)	1–2 flares per year	No	No
16	10 years Male	Diffuse papules on the trunk that occur in crops and spontaneously regress	2 years	Methotrexate	Flares every 3 months	No	No

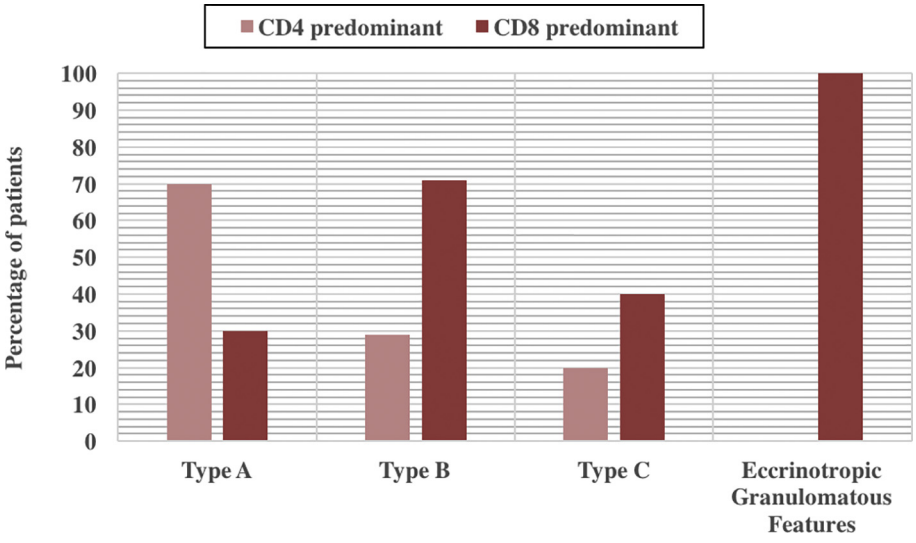

Fig. 1. Percentage of patients with predominantly CD4 versus CD8 expression among different histologic subtypes.

pediatric and adolescent subpopulation. The available data suggest that LyP may be more indolent, show a higher rate of spontaneous regression, and a lower rate of secondary malignancy in this patient population [13-18].

We present a retrospective review to characterize the clinical and histopathologic characteristics of pediatric and adolescent patients with LyP at a tertiary care institution. We seek to build on previous studies and investigate the unique features of pediatric LyP that distinguish this entity from the adult variant. Elucidation of salient clinicopathologic features will aid clinicians in providing a timely diagnosis and its prognostic implications for this rare subset of patients.

Table 2
Cases of lymphoma and myeloproliferative disease in pediatric lymphomatoid papulosis patients.

Age at onset/gender	Study	Associated lymphoma	Time between LyP and lymphoma diagnosis
15 years/M	Nijsten et al. [14]	Cutaneous ALCL	17 years
12 years/M	Nijsten et al. [14]	Cutaneous ALCL	Concurrent
12 years/F	Nijsten et al. [14]	Non-Hodgkin's Lymphoma	3 months
12 years/F	Rifkin et al. [20]	Systemic ALCL	3 months
16 years/F	Rifkin et al. [20]	Cutaneous ALCL	5 weeks
13 years/F	Miquel et al. [15]	Systemic ALCL	6 months
8 years/F	Queller et al. [21]	Mycosis Fungoides	3 years prior to LyP
Childhood/M	Zirbel et al. [16]	Hodgkin's Lymphoma	~50 years
10 years/M	Zirbel et al. [16]	Undifferentiated Lymphoma	40 years
11 years/M	Bekkenk et al. [12]	Cutaneous ALCL	1 year
14 years/M	Tomaszewski et al. [23]	Mutinous ALCL	3 years
5 years/M	Beljaards et al. [22]	Systemic ALCL	13 years
9 years/M	Lange et al. [24]	Mastocystosis	8 years prior to LyP

ALCL = anaplastic large cell lymphoma; M = male; F = female.

Table 3
Lymphomatoid papulosis variants observed among pediatric cohorts.

	Type A	Type B	Type C	Type D
Wieser et al	79%	3.7%	11.9%	0.7%
De Souza et al	86%	7%	7%	0%
Martorell-Calatayud et al	100%	0%	0%	0%
Miquel et al	82%	0%	18%	0%
Our cohort	37%	26%	19%	0%

2. Materials and methods

2.1. Patient population

A search of the dermatopathology database of Weill Cornell Medicine was performed using the keyword “lymphomatoid papulosis”. This yielded 619 specimens between January 2006 and August 2016. These cases were screened and 316 biopsies in 288 patients had received a final diagnosis of LyP both clinically (via International Classification of Diseases coding) and pathologically.

Among all cases of LyP, using age parameters, 25 patients were identified that were 19 years of age or younger at the time of diagnosis. These encompass patients that were part of one of the author's (CMM) routine diagnostic practice (40% of patients in the final cohort) and her consultative practice (60% of patients in the final cohort). Therefore, 8.7% (25 out of 288) of the LyP cases diagnosed at our institution since 2006 were pediatric or adolescent patients, defined as being 19 years of age or younger. Two additional cases of pediatric LyP were diagnosed by CMM while this study was being conducted, and these cases were added to the cohort, bringing the total to 27 patients.

2.2. Data collection

In each patient, a detailed account of the pathology was reviewed including light microscopic findings along with the phenotypic and molecular profile. The top three clinical differential diagnoses submitted on each pathology requisition form were recorded. Subsequently, we reviewed the electronic medical records and/or contacted outside consulting physicians to obtain the most updated clinical follow-up documentation. Sixteen patients (64%) were deemed to have accurate and updated clinical information for further review. The remaining were excluded from this subset due to inadequate clinical follow-up information for 8 patients (defined as having < 3 follow-up visits), transfer of care to another provider for 1 patient, or incomplete medical documentation for 2 patients (treatments, disease activity, and/or occurrence of secondary lymphoma were not sufficiently delineated). In our targeted review of the medical records, we sought to determine the following pre-determined primary outcomes: if patients had a family history of LyP, if they developed lymphoma, what treatments were attempted, reported symptoms, clinical description, duration of disease, and present activity of disease. Finally, clinical and histopathologic data were summarized and represented graphically.

3. Results

3.1. Clinical follow-up

The subset of patients with detailed clinical follow-up includes 7 females and 9 males with a mean age of 12.7 years old. Follow-up ranges between 4 months and 10 years, with a mean follow-up of 43.5 months. Clinical features are summarized in Table 1.

Among the cohort of patients with clinical follow-up, the most common differential diagnoses submitted on the pathology requisition form included pityriasis lichenoides chronica, pityriasis lichenoides et varioliformis acuta (PLEVA), pityriasis rosea, guttate psoriasis, and eczema. All patients in this cohort exhibited clinical histories consistent with LyP and have responded to appropriate therapy. The most common clinical characteristics included a tendency for recurrence, a localized anatomic distribution with an extremity or trunk predilection, a tendency for healing with scars or atrophy, and occasional ulceration of lesions.

As highlighted in Table 1, the most common treatment was high potency topical steroids. Four patients in this cohort are on low dose methotrexate, one is on narrow band ultraviolet light therapy, and one is on oral bexarotene. Of those patients with currently active disease, 6 patients are on topical steroids only. The majority of patients in this cohort are being managed by their dermatologist, though one patient has established care with an oncologist. The primary symptom, reported by 7 of 16 patients (43.8%), was pruritus. Notably, none of the patients in this subcohort have any personal or family history of lymphoma. One of the patients does have a family history of LyP.

3.2. Histologic findings and phenotypic profile

Herein we summarize the histopathology findings from the entire cohort of 27 pediatric and adolescent LyP patients represented by 14 females and 13 males.

Among the 27 patients studied, 10 patients (37%) were designated as having type A, 7 patients (26%) as having type B, and 5 patients (19%) as having type C. Two patients had overlapping features of both type A and type B. Three patients had a distinctive morphologic variant with eccrinotropic granulomatous features. Of note, one case in this study could be retrospectively designated type E [8], one as type F [9], and three additional cases demonstrate overlapping features of the type E and/or F variants. Prior to the additional type E and F designations, the type E case was included under the type A category while the

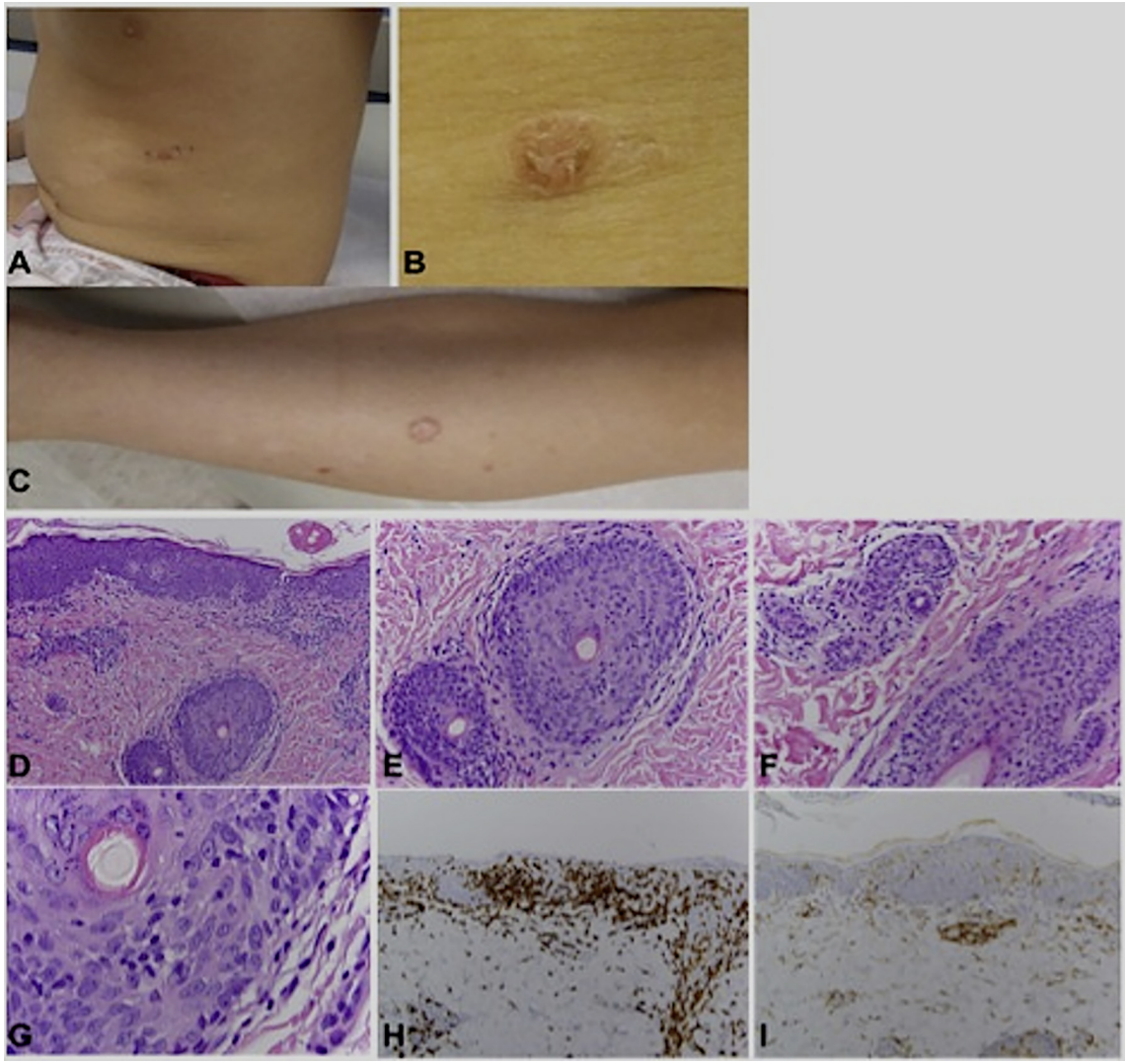

Fig. 2. 9-Year-old male with clinical and histopathologic presentation of CD8+ type B lymphomatoid papulosis.
A) Pink papule on abdomen.
B) Close-up of pink papule.
C) Papule on the left anterior shin.
D) Hematoxylin&eosin, 20×: atypical epidermotropic and folliculotropic lymphocytic infiltrate.
E) Hematoxylin&eosin, 40×: atypical small cerebriform lymphocytes infiltrate the outer root sheath epithelium.
F) Hematoxylin&eosin, 40×: proclivity of the abnormal cell populace for the eccrine structures.
G) Hematoxylin&eosin, 100×: highlights the striking morphologic semblance to mycosis fungoides.
H) CD8, 20×: There is a striking predominance of CD8 lymphocytes infiltrating the epidermis and adnexal structures.
I) CD4, 20×: In contradistinction there is minimal staining of lymphocytes for CD4. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

follicular LyP case was categorized as a type B variant.

Among 13 patients (48%), the atypical lymphoid infiltrate was CD8 positive while 10 patients (37%) demonstrated CD4 positive phenotype and 4 patients (15%) exhibited a null/double negative phenotype as identified by immunohistochemical double-labeling.

The phenotypic profile differed within the various subtypes of LyP. Among those patients designated as having type A LyP, 70% of cases showed a predominance of CD4+ T cells while in 30% of cases the abnormal cell population was CD8 positive. Of interest, among those cases designated as type B LyP, 71% demonstrated a CD8 predominance within the aberrant cell populace while 29% were of the CD4 subtype. It should be emphasized that the CD8+ type B LyP cases were not examples of so called type D LyP in light of the cerebriform quality of the lymphocytes and lack of epithelial necrosis; the histomorphology truly resembled mycosis fungoides (MF). In the type B MF-like category of LyP, two cases with interstitial granulomatous features exactly recapitulating the morphology of interstitial granulomatous MF were observed. Both cases were CD8 positive and were in males aged 3 and 5 years old. Among those designated with type C, 40% exhibited CD8 positivity of the abnormal cell population, while 20% were CD4 predominant and 40% were of the null phenotype. Among the three patients with eccrinotropic granulomatous features, the atypical cells were CD8 positive in all cases (Fig. 1).

While the type A and type C cases had many CD30+ staining cells, the extent of CD30 staining in the type B cases was much less and was largely confined to the few large cells that coursed through the infiltrate.

There were significant reductions of CD7 in all cases ranging from 30 to 90% (with a mean reduction of 59%), while CD5 was reduced in most cases, ranging from 0 to 60% (with a mean reduction of 27.5%).

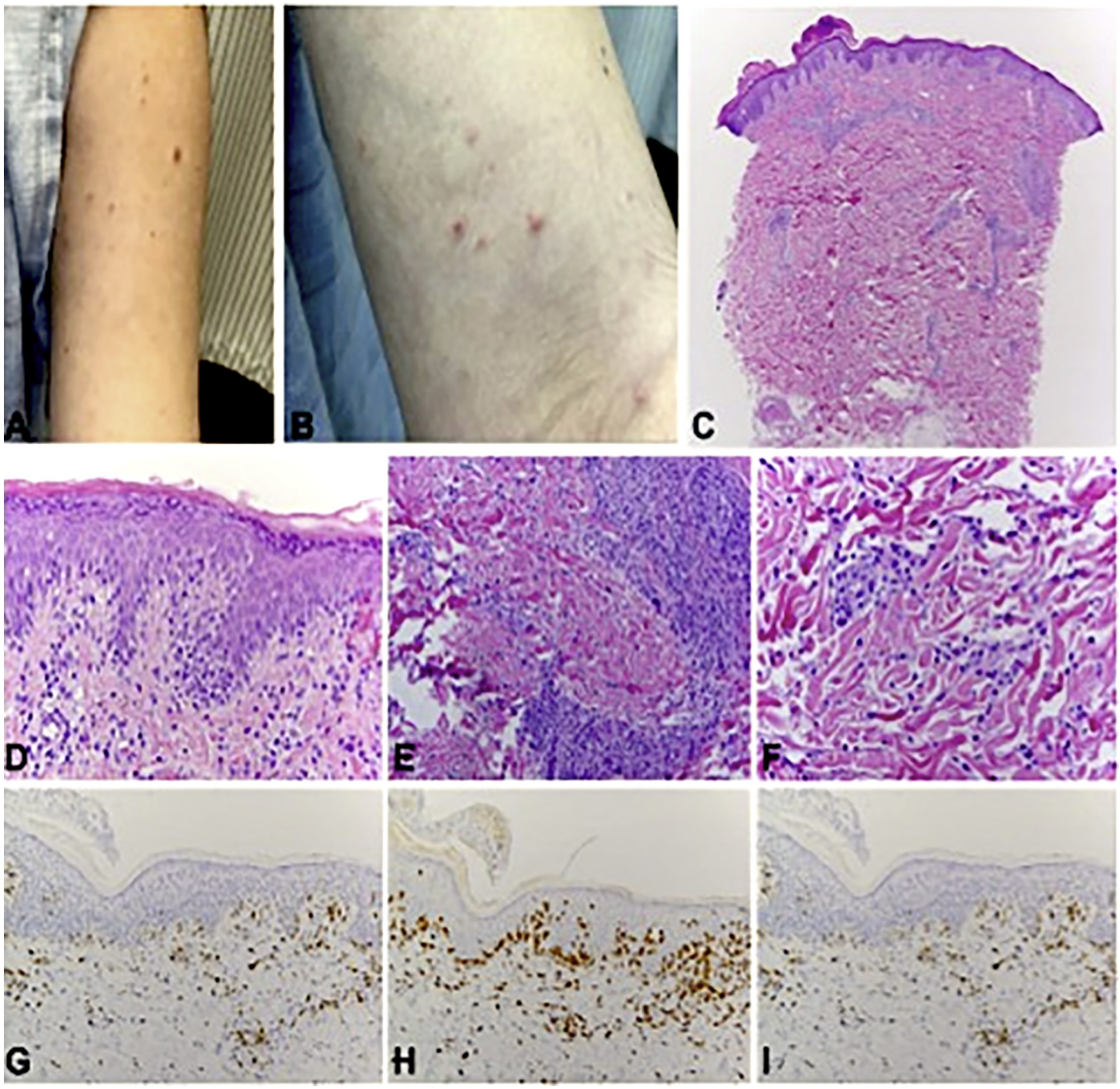

Fig. 3. 10-Year-old female with clinical and histopathologic presentation of CD8+ type B lymphomatoid papulosis.
A) Pink papules on the upper arm.
B) Pink papules on the left antecubital fossa.
C) Hematoxylin&eosin, 4×: The biopsy shows a psoriasiform epidermal hyperplasia. The overlying stratum corneum is imbued with serum and leukocytes. A superficial and deep perivascular and periadnexal lymphocytic infiltrate with significant epidermotropism is noted.
D) Hematoxylin&eosin, 20×: The epidermotropic lymphoid populace shows localization within the basilar and parabasilar portions of the epidermis. The lymphocytes are predominantly small with discernible nuclear contour irregularity.
E) Hematoxylin&eosin, 40×: The deeper-seated extension of the infiltrate including its accentuation around the eccrine apparatus, hair follicle and nerves along with the interadnexal interstitial pattern of infiltration of the dermis serves as differentiating features from pityriasis lichenoides.
F) Hematoxylin&eosin, 40×: The interstitial pattern recapitulates interstitial granulomatous mycosis fungoides, expanding the morphologic spectrum of so-called type B lymphomatoid papulosis.
G) CD8, 20×: A very distinctive feature of pediatric lymphomatoid papulosis is the predominance of CD8 lymphocytes. In essence the morphology closely recapitulates CD8 positive mycosis fungoides.
H) CD3, 20×: The full extent of epidermotropism is appreciated on the CD3 preparation.
I) CD5, 20×: There is a reduction in the expression of CD5, defining a phenotypic aberration that can be encountered in lymphomatoid papulosis and is similar to the potential abnormal phenotypic profile encountered in mycosis fungoides. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Overall, the extent of CD5 reduction was less than that noted for CD7. Cytotoxic protein expression, including granzyme and T-cell intracytoplasmic antigen (TIA), was noted in varying degrees in over half of the biopsy specimens. Cytotoxic protein expression was most common in type B, type C, and those cases with CD8 predominance.

4. Discussion

LyP is a rare entity in pediatrics and adolescents. Our study found that 7.9% of the patients diagnosed with LyP between 2006 and 2016 were 19 years or younger. This is comparable to data from de Souza et al. [18] (11% of cohort was classified as pediatric patients) and Wieser et al. [13] (4% of cohort was classified as pediatric patients), among others [14-17,19].

Identification of LyP heralds important clinical considerations. While patients were previously thought to have a low rate of progression to lymphoma, recent studies in adults [5,10,11] have shown that this risk may be higher. Some authors [5,11] have even suggested that

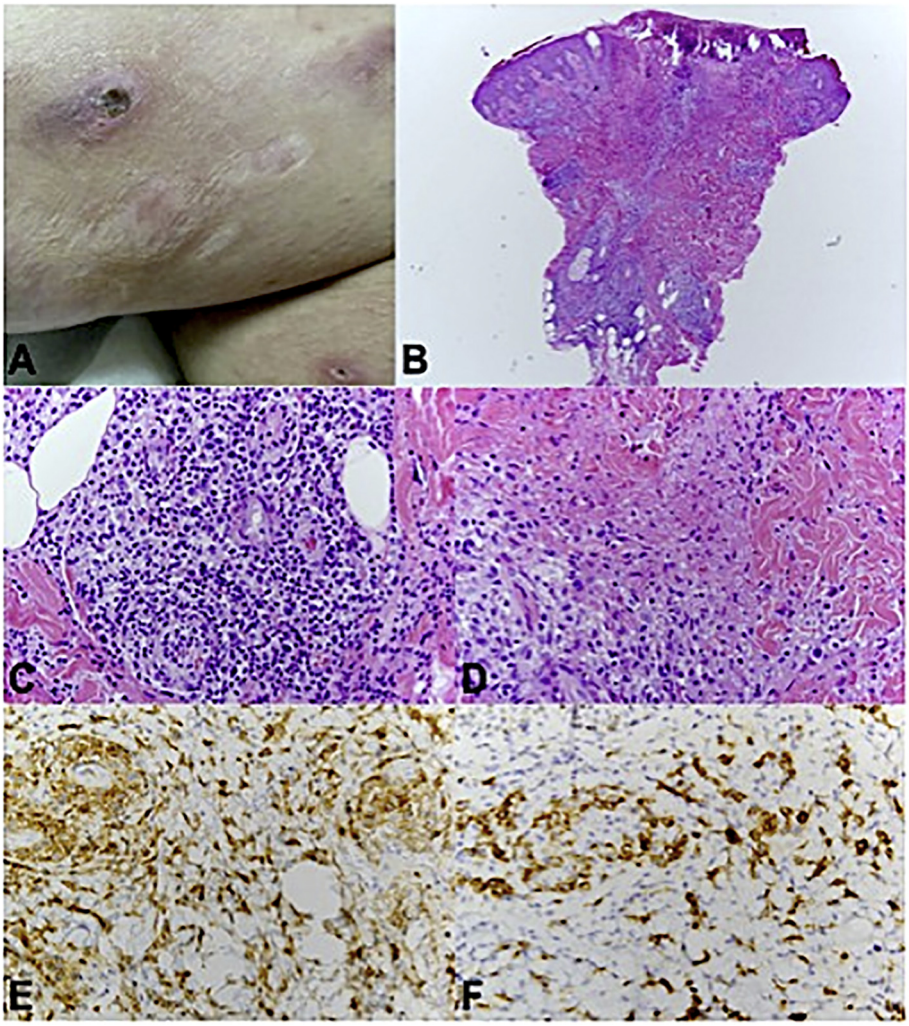

Fig. 4. 19-Year-old female with ulcerating nodules on the leg. Pathologic features are characteristic for angioinvasive type E lymphomatoid papulosis.
A) Ulcerating nodules on left thigh and calf.
B) Hematoxylin&eosin, 4×: Wedge-shaped ischemic epidermal and dermal necrosis is associated with a dense atypical vasocentric and adnexal tropic lymphocytic infiltrate.
C) Hematoxylin&eosin, 40×: Higher magnification discloses a significant lymphomatoid vasculitic component characterized by large atypical immunoblastic appearing cells surrounding and permeating vessels with evidence of vascular injury as characterized by mural and luminal fibrin deposition.
D) Hematoxylin&eosin, 40×: In this particular field the large atypical immunoblastic infiltrate is concentrated around vessels and in close apposition to nerves.
E) CD4, 40×: The abnormal lymphoid populace expresses CD4.
F) CD30, 40×: The immunoblastic elements are CD30 positive.

lymphomas may occur in 40–50% of adult LyP patients.

Pediatric LyP patients do not appear to develop associated lymphomas as frequently as adults. The recent meta-analysis by Wieser et al. [13] reviewed 251 cases of pediatric LyP and found that only 14 of these patients progressed to secondary lymphoma, suggesting that the pediatric variant of this disease may be more indolent. No cases of associated lymphoma were identified in another cohort of 25 pediatric LyP patients by Miquel et al. [15] at a mean follow-up of 10 years. Additionally, 44% of the patients in this study had a spontaneous remission of their disease. Among the pediatric and adolescent LyP patients in our clinical cohort, with a mean follow-up of 43.5 months, none have developed an associated lymphoma, and 36.5% of patients report that their disease has been inactive for six months or more. Clinicians should be aware of these favorable prognostic tendencies and articulate it to their patients accordingly.

Adult LyP patients who progress to lymphoma are diagnosed most often with mycosis fungoides. Among the Weiser et al. [5] cohort of 93 LyP patients with associated lymphoma, 61% of these malignancies were mycosis fungoides and 26% were anaplastic large cell lymphoma. However, this contrasts with pediatric patients described in the literature [12,14-16,20-24] (Table 2), wherein the most frequently reported associated malignancy is anaplastic large cell lymphoma. In fact, among 251 cases of pediatric LyP in the most recent meta-analysis [13], only one patient developed mycosis fungoides.

Most cases of associated pediatric lymphomas and myeloproliferative disease have occurred after the original LyP diagnosis (Table 2). Only 2 cases [21,24] were identified that occurred prior to the diagnosis of LyP, and one case [14] was diagnosed at the same time as LyP. This is in stark contrast to adult cohorts [5,11] whereby around 60% of patients were diagnosed with an associated lymphoma concomitantly with or prior to their original LyP diagnosis. Finally, while it appears that pediatric patients tend to develop lymphomas less often than adults, it does deserve mention that these lymphomas can occur many years [14,16,22] after the primary LyP diagnosis, rendering long-term clinical follow-up of paramount importance.

In our cohort, 37% of pediatric and adolescent LyP patients diagnosed at our institution have been designated with type A. This is concordant with previous studies [13,15,17,18] that found type A to be the predominant subtype within the pediatric population. However, it occurred less often than previously reported rates of 80–100% within the pediatric population (Table 3). Notably, within the meta-analysis [13] of 251 pediatric LyP patients, which extended back to 1973, the authors state that the prevalence of type A may be overestimated due to the fact that 1) the understanding of the histopathological features of LyP was not as elaborated as today, and 2) in many children the subtype was not explicitly described.

Furthermore, we found that 26% of the pediatric and adolescent patients at our institution were diagnosed with the type B variant (Figs. 2, 3) and 19% exhibited features of the type C variant. The proportion of these subtypes is higher than previously reported [13,15,17-18] (Table 3). When considering the type B variant, the greatest diagnostic dilemma is its separation from pityriasis lichenoides, which is often a distinction that can be made clinically. Pityriasis lichenoides, in contrast to LyP, is characterized by red-brown

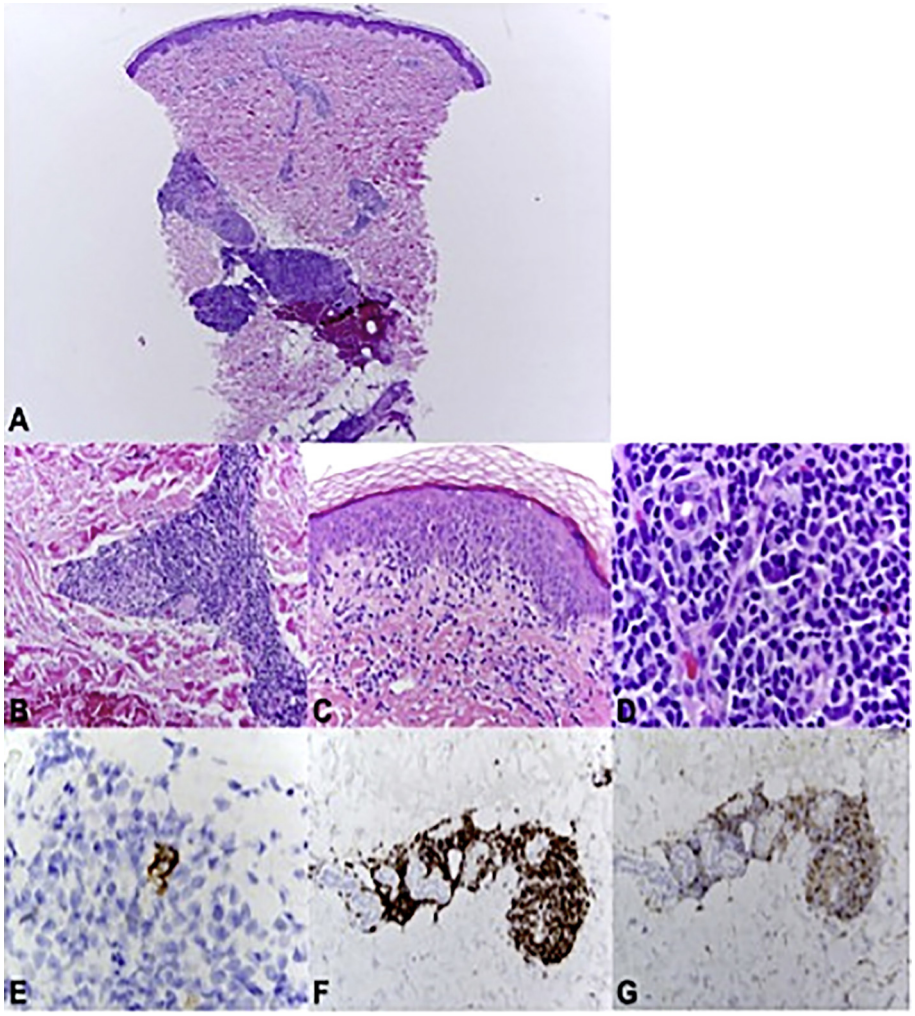

Fig. 5. 16-Year-old female with recurrent coalescing crusted papules on the left leg. Pathologic features are characteristic for eccrinotropic granulomatous lymphomatoid papulosis.
A) Hematoxylin&eosin, 4×: This low power view shows a nodular lymphohistiocytic infiltrate around the eccrine coil and nerves with focal extension into fat.
B) Hematoxylin&eosin, 40×: This section illustrates the small well-differentiated appearance of the lymphocytes along with a focus of granulomatous inflammation. Perineural accentuation as noted here defines another characteristic morphologic hallmark of granulomatous eccrinotropic lymphomatoid papulosis.
C) Hematoxylin&eosin, 20×: While the infiltrate is primarily located in the dermis and subcutaneous fat, small foci of basilar colonization of the epidermis by mildly atypical lymphocytes accompanied by laminated fibroplasia and attendant hemorrhage are noted in deeper sections.
D) Hematoxylin&eosin, 100×: The diagnosis of granulomatous eccrinotropic lymphomatoid papulosis is challenging because of the small well-differentiated appearance of the cells. However, the obscuring pattern of infiltration of the eccrine coil by mildly atypical irregularly contoured lymphocytes along with a few larger monocytoid appearing cells, the latter cells typically showing CD30 positivity (E: CD30, 40×), defines the pathological hallmarks. Critical however is the corroborative clinical history supportive of lymphomatoid papulosis.
F) CD8, 40×: The small lymphocytic populace in this case is primarily of the CD8 subset with only a minor CD4 population represented by a mixture of CD4+ lymphocytes and histiocytes (G: CD4, 40×).

scaling papules that heal with non-scarring, transient hypopigmentation. In type B LyP, overall the extent of lymphoid atypia is greater, the infiltrate extends deeper, and the classic thick parakeratotic scale of pityriasis lichenoides is not seen. Additionally, there are often identifiable CD30+ larger atypical cells found within the infiltrate in type B LyP even though the dominant cell populace is a smaller CD30 negative cerebriform lymphocyte.

When considering the type C variant, the differential diagnosis would primarily be with anaplastic large-cell lymphoma (ALCL). Phenotypically over 75% of the infiltrate in ALCL is composed of large cells that expresses certain pan T cell markers and CD30; the neoplastic cells oftentimes express CD4 but they can also be CD8 positive or double negative for CD4 and CD8. Clinically, the lesions typically attain sizes of 3 cm or more and in the majority of cases are solitary and do not undergo regression. In contrast, all cases of pediatric LyP undergo regression, are relatively small (typically < 1 cm and almost never > 3 cm), and characteristically multiple [25,26].

We also encountered a very distinctive variant of type B LyP, namely one which exactly recapitulates interstitial granulomatous MF with both cases occurring in very young boys with a mean age of 4 years of age and exhibiting a CD8 positive phenotype. In fact, the senior author of this study (CMM) has only observed this “interstitial granulomatous type B” variant of LyP in the pediatric setting to date. There is a significant degree of overlap morphologically with mycosis fungoides, though the clinical presentation of LyP is not congruous with mycosis fungoides based on the papulonodular morphology of the lesions and their tendency toward spontaneous regression.

One of the cases in our cohort may now alternatively be designated as the type E variant [8] (Fig. 4) and one the type F variant [9]. As we continue to modify the different presentations of LyP, further studies within the pediatric population will elucidate the prevalence of newly described variants.

A CD8 predominance is often observed within pediatric LyP patients [13,18,27]. In the review by Wieser et al. [13], 25 of 30 patients (83%) with information regarding CD8 status had positive CD8 expression. CD8 dominant LyP comprises various subtypes including the conventional type A, B and borderline C cases. There is a degree of overlap between the type D variant and type B LyP. However, the type D form of CD8 LyP denotes cases with features closely mimicking primary cutaneous aggressive cytotoxic CD8 T cell lymphoma. Many of the CD8 cases in our cohort showed features that would be more in keeping with type B LyP in that the lymphocytic infiltrate simulates CD8 positive mycosis fungoides whereby the cells are cerebriform, predominantly small, and significant epithelial necrosis and angioinvasion are not seen. In type D LyP, there is often a striking predominance of CD8 T cells with an atypical noncerebriform appearance and the presence of architectural disposition of atypical lymphocytes infiltrating the epidermis, destroying vessels and extending into the fat. Additionally, a number of cases in out cohort exhibited folliculotropism and syringotropism with supervening granulomatous inflammation, features included within the morphologic heterogeneity of mycosis fungoides and another helpful differentiating feature more often encountered in the type B variant [28-31] (Figs. 2, 3).

Additionally, three patients in this cohort (11%) demonstrated

granulomatous eccrinotropism as a predominant feature (Fig. 5). All three of these patients had CD8 predominance. The "eccrinotropic granulomatous" variant of LyP is described as one defined by nodular lymphohistiocytic infiltrates showing perieccrine and perineural accentuation [32,33]. In our original series describing eccrinotropic granulomatous LyP, a few of our patients were teenagers [32]. In this variant, reactive infiltrates of small bland lymphocytes oftentimes predominate and the larger atypical CD30 positive populace may be obscured, sometimes resulting in a delay in diagnosis due to its morphologic semblance to reactive conditions such as secondary syphilis and post herpetic eruptions.

To extract further from this data, we highlight the discordance of CD8 and CD4 staining within different variants of our cohort (Fig. 1). While only 30% of pediatric and adolescent patients designated with type A LyP demonstrate CD8 predominance, a striking 71% of pediatric and adolescent patients designated with type B show CD8 predominance. We propose that the CD8+ type B subtype may be more common in pediatric LyP patients than it is in adults.

5. Conclusion

Pediatric LyP has garnered attention as a diagnosis with unique clinical and histopathologic features. Among the pediatric and adolescent LyP patients at our institution with clinical follow-up, none have developed a secondary lymphoma and several are in remission. This clinical course aligns with previous data suggesting that LyP may be more indolent in pediatrics than it is in adults. In any case, pediatric LyP patients do necessitate long-term follow-up, as cases of anaplastic large cell lymphoma (in addition to other malignancies) have been reported to occur months to years following the original LyP diagnosis.

While type A appears to be the dominant variant described in children, types B, C, and even the newly described variants E and F may occur more often than previously reported. CD8 predominant LyP is known to occur more frequently in pediatrics than the adult populations, and this may be especially true among type B LyP patients and those cases with granulomatous eccrinotropic features. Further studies into the distinguishing features of this disease will aid clinicians in recognizing LyP in the pediatric population.

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