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ORIGINAL ARTICLE

Lymphomatoid papulosis: a clinical and histopathologic review and follow-up study of 34 cases in Taiwan

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ABSTRACT

Background: Lymphomatoid papulosis (LyP) is a rare condition within the spectrum of CD30+ cutaneous lymphoproliferative disorders that is not well documented in Taiwan. This study aimed to analyze its clinical manifestations, diagnostic histopathology, clinical course, and treatment response among Taiwanese.

Methods: A retrospective chart review was performed on patients diagnosed with LyP at a Taiwanese medical center from 1992 to 2008.

Results: There were 34 patients with biopsy-proven LyP. The mean age at diagnosis was 36 years (range: 10–75 years), with male predominance (male:female ratio 3:2). Type-A LyP was identified in 32 patients and Type C in 2 patients. Seven cases showed CD4 predominance and six cases showed CD8 predominance. Of the 34 LyP patients, 2 had coexistent non-Hodgkin's lymphoma, 1 (3%, 1/34) diagnosed before LyP onset and 1 (3%, 1/34) developed lymphoma 3 years after LyP. All of the patients were alive after a mean of 5.2 years (range: 3–12.7 years) of follow-up.

Conclusions: Most of our cases are Type A LyP. No clinical features or pathologic features can predict increased risk for developing malignancy. Although only 6% (2/34) of LyP patients were found to have lymphoma in 3-year follow-up, longer follow up is needed. Regardless of treatment modalities, two-thirds of the patients have a recurrent and relapsing course. Observation is a reasonable approach for patients without cosmetic or symptomatic concerns.

Introduction

Lymphomatoid papulosis (LyP) is a rare skin disease within the spectrum of CD30+ cutaneous lymphoproliferative disorders. This self-healing, paradoxical, rhythmic eruption is histologically malignant but clinically benign.[1–3] The recurrent crops of ulcerating, necrotic papulonodules usually regress spontaneously, leaving residual scars or areas of altered pigmentation. The life cycle of a papule is usually 4–8 weeks, whereas nodules may take several months to resolve.[1–3]

The most common histopathologic subtype of adult-onset LyP is Type A, which is characterized by large, atypical, CD30+ lymphocytes, resembling Reed-Sternberg cells from Hodgkin's lymphoma, and presented in a wedge-shaped distribution throughout the dermis and mixed with various numbers of inflammatory cells. Type B is less common and characterized by small, CD30 lymphocytic cells with cerebriform nuclei in a band-like pattern, with concomitant epidermotropism. Type C is rarer and consists of a monotonous population of large, atypical, CD30+ cells diffusely infiltrating the dermis, with fewer associated inflammatory cells than those seen in the other types.[4,5]

LyP patients have increased risk of developing lymphoid malignancies, including mycosis fungoides, Hodgkin's disease, and cutaneous and systemic CD30+ large-cell lymphoma.[6] Reported case series have estimated the risk of lymphoma varied from 10% to 80% after 15-year follow-up.[5–7] Despite several case series for LyP have been carried out in recent years, there has been no Asian series reported in English-language literature. This study aimed to

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analyze its clinical manifestations, diagnostic histopathology, clinical course, and treatment response among Taiwanese.

Patients and methods

We reviewed 34 cases of LyP diagnosed at a medical center in Taipei from 1992 to 2008. In all patients, general physical examinations and routine hematologic exams were performed. Clinical presentation and pathologic findings, including immunohistochemical stainings for CD2, CD3, CD4, CD8, CD20, CD30, T-cell intracellular antigen-1 (TIA-1), and anaplastic lymphoma kinase (ALK) were reviewed. Follow-up data were obtained through chart review or phone contact with patients.

Results

Clinical features

Of the 34 LyP patients, there were 23 men and 11 women. The mean age at onset of LyP skin lesion was 36 with a range from 10 years to 75 years. The mean disease duration was 4.3 years (1 month–9.6 years), whereas the follow-up was 5.2 years (3 years–12.7 years). Most patients (70.6%, 24/34) developed generalized lesions on limbs and trunk (Figures 1A and 1B), whereas six showed localized LyP. Two patients had papules on the limbs only, whereas one had them only on the upper limbs. One patient had red papules and vesicles on the neck, whereas another had an indurated ulcer on the left thigh. The average number of lesions varied greatly, from several to more than 50. Twenty patients suffered from pruritus associated with the lesions. None of the patients had systemic involvement at diagnosis. The results were summarized in Table 1.

Histology

Cases were divided according to histopathologic findings, namely LyP Type A, B, or C (Table 1). Most cases (94%, 32/34) showed findings of LyP Type A with dermal infiltrates of CD30+ large atypical cells with convoluted nuclei, mixed with neutrophils, small lymphocytes, and occasional eosinophils (Figure 2). Six of the 21 patients had CD8-predominant LyP and 7 patients had CD4-predominant LyP, although immunoperoxidase staining was not performed with antileukocyte monoclonal antibodies against CD4 and CD8 in 11 patients. Six were negative for both CD4 and CD8, and two were positive for both CD4 and CD8. No notable differences distinguished CD8-predominant from CD4-predominant LyP.

None of the biopsy specimens had features compatible with Type B LyP. But two samples ($n = 2$, 6%) revealed patchy dermal infiltrates of large CD30+ anaplastic lymphocytes with epidermotropism, hemorrhage, and few inflammatory cells. These two patients were classified as Type C LyP (diffuse large cell type).

Laboratory investigation

Routine laboratory examinations were within normal limits for all patients. Testing for specific antibodies against human T-cell leukemia virus-1 antigens in five patients showed negative results.

Clinical course and treatment

Most patients (94%, 32/34) did not have other malignancy or lymphoma signs. Four patients had childhood-onset LyP, but none developed non-Hodgkin's lymphoma after follow-up for 3 years. One patient (3%, 1/34, Patient 17) had pre-existing lymphoma diagnosed 2 years before the onset of LyP and another (3%, 1/34, Patient 28) developed lymphoma afterwards. For the latter, the

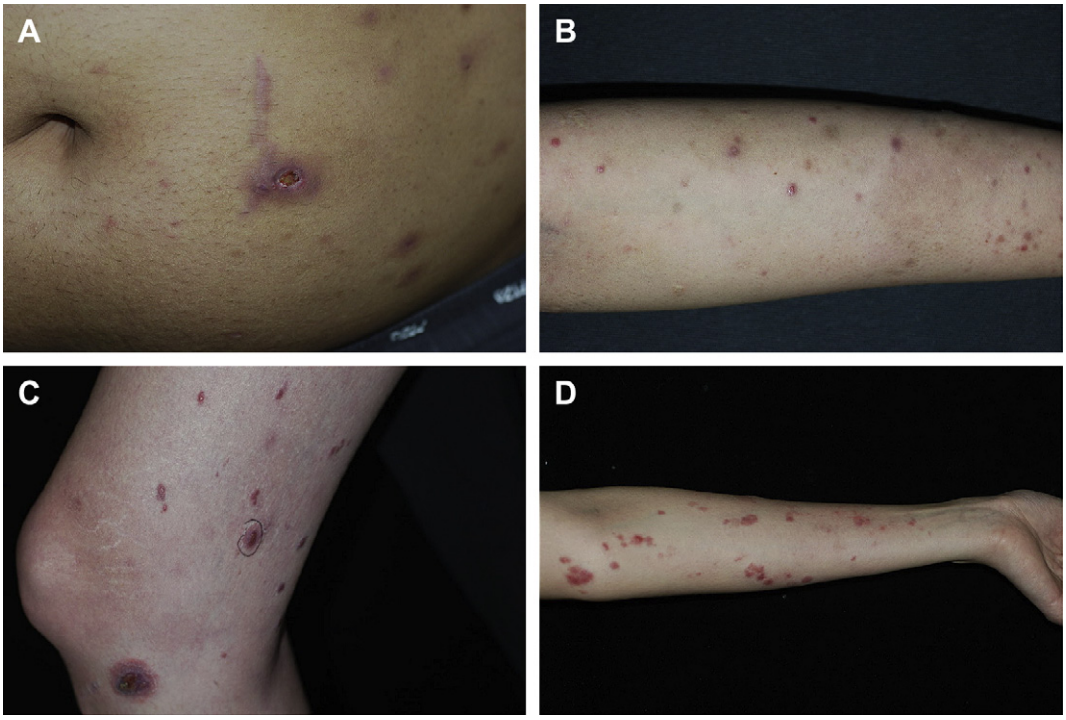

Figure 1 (A) Clinical pictures of Patient 15—discrete erythematous to violaceous papules and hemorrhaging center on the abdomen. (B) Clinical pictures of Patient 20—erythematous and violaceous papules with evidence of central necrosis involving the left forearm similar to pityriasis lichenoides et varioliformis acuta. (C) Purpuric, erythematous nodules 2–8 mm in size, some with hemorrhagic crusts on right lower limb. (D) Clinical pictures of Patient 16—multiple erythematous dermal papulonodules on the left forearm.

Table 1 Clinical and pathologic features of lymphomatoid papulosis in patients who underwent therapy and follow-up.

Patient no./sex/age of diagnosis	Type of LyP lesions	Distribution of LyP lesions	Type/T-cell type	Duration of LyP before diagnosis	Follow-up (mo)	Therapy	Present status
1/F/51	Papules/nodules	Extremities	A/NA	3 yr	72	RA, UVA, TS→OBS	Off and on
2/M/73	Papules/nodules	Extremities	A/NA	6 mo	60	RA, TS	Subsided
3/F/34	Papules/nodules	Extremities	A/NA	6 mo	80	RA	Subsided
4/F/61	Papules/nodules	Extremities	A/NA	2 mo	NA	UVB	Subsided
5/M/72	Papules/nodules	Generalized	C/NA	1 mo	72	RA, UVB	NA
6/M/52	Papules/nodules	Generalized	A/NA	2 mo	42	RA→OBS	Off and on
7/F/42	Papules/nodules	Generalized	C/NA	5+ yr	66	RA→OBS	Off and on
8/M/42	Papules/nodules	Legs	A/NA	1 mo	36	Dapsone	Subsided
9/M/12	Papules/nodules	Generalized	A/CD8	2 wk	38	TS	Subsided
10/F/59	Papules/nodules	Generalized	A/NA	1 mo	72	RA→OBS	Off and on
11/M/28	Plaques	Extremities	A/NA	2 mo	40	Dapsone	Subsided
12/M/46	Plaques/ulcers	Left leg (localized)	A/NA	2 mo	172	RT→OBS	Subsided
13/F/58	Papules/nodules	Extremities	A/CD4	3+ mo	36	CT→RA→OBS	Off and on
14/F/22	Papules/nodules	Generalized	A/NA	1.5 mo	36	OS, RA	Subsided
15/M/38	Papules/nodules	Generalized	A/NA	1 mo	60	RA, UVB, Ab	Subsided
16/F/29	Papules/nodules	Generalized	A/null cell	2 mo	37	AH, TS	Subsided
17/M/20*	Plaques	Generalized	A/CD4	2 mo	36	CT→OBS	Off and on
18/M/36	Papules/nodules	Scalp (localized)	A/CD8	9+ yr	38	AH, TS	Subsided
19/F/19	Papules/nodules	Extremities	A/CD4	1 mo	38	OS→OBS	Off and on
20/F/15	Papules/nodules	Generalized	A/CD8	2 mo	72	Ab→OBS	Off and on
21/M/74	Papules/nodules	Generalized	A/null cell	1 mo	60	MTX→OBS	Off and on
22/M/32	Papules/nodules	Generalized	A/CD8	2 mo	72	Ab→OBS	Off and on
23/M/69	Papules/nodules	Generalized	A/null cell	2 mo	48	Ab→OBS	Off and on
24/M/40	Vesicles/bullae	Right hand (localized)	A/CD8	1 mo	48	Ab→OBS	Off and on
25/M/62	Papules/nodules	Neck (localized)	A/null cell	1 yr	48	SE→OBS	Off and on
26/M/44	Papules/nodules	Right breast (localized)	A/CD8	2 mo	60	AH, TS→OBS	Off and on
27/M/45	Papules/nodules	Generalized	A/CD4 CD8	1 mo	97	AH, TS→OBS	Off and on
28/M/41†	Papules/nodules	Generalized	A/CD4	2 mo	84	PUVA, RA→OBS	Off and on
29/F/56	Papules/nodules	Right breast (localized)	A/CD4	1 mo	96	TS→OBS	Off and on
30/M/41	Papules/nodules	Generalized	A/CD4	1.5 mo	60	OS→OBS	Off and on
31/F/75	Papules/nodules	Left leg	A/CD4	2 mo	72	TS→OBS	Off and on
32/M/50	Papules/nodules	Generalized	A/CD4 CD8	2 mo	84	TS + MTX→OBS	Off and on
33/M/15	Papules/nodules	Generalized	A/null cell	1 yr	96	MTX, OS, TS→OBS	Off and on
34/M/10	Papules/nodules	Generalized	A/null cell	2 mo	96	OS, TS→OBS	Off and on

* Anaplastic large cell lymphoma, Ann Arbor Stage IVA s/p autologous stem cell transplantation and chemotherapy;
† Anaplastic large cell lymphoma developed during follow-up.
Ab = antibiotic; AH = antihistamines; CT = chemotherapy; LyP = lymphomatoid papulosis; MTX = methotrexate; NA = not applicable; OBS = observation; OS = oral corticosteroid; PUVA = psoralen UV-A; RA = retinoid acid; RT = radiation therapy; SE = surgical excision; TS = topical corticosteroid.

time to lymphoma onset was 3 years. Both were non-Hodgkin's lymphoma (anaplastic large T-cell lymphoma [ALCL]). Patient 28 was treated with oral isotretinoin and phototherapy, whereas Patient 17 had received autologous stem cell transplantation before onset of LyP and was undergoing chemotherapy. Both cases had recurrent eruption of LyP despite treatment. One-third of these 34 patients resolved in a mean 2.8 years and two-thirds of these 34 patients had a recurrent and relapsing course.

Eleven patients (Patients 1–3, 5–7, 10, 13–15, and 28) were treated with oral 13-*cis* retinoid acid (RA) (20–30 mg/d). Ten had dramatic improvement in lesions after 3–4 months of treatment, except for Patient 1, who stopped 13-*cis* RA because of intolerable side effects. Four patients achieved complete remission; Patients 2, 3, and 7 in 3 months and Patient 14 in 4 months. After discontinuing therapy, two patients (Patients 3 and 7) experienced relapses but remitted after treatment. Patient 13 was first treated with cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP) chemotherapy at another hospital with quick response to each course of CHOP but relapsed later. After three courses, the regimen was shifted to 13-*cis* RA (1 mg/kg/d) and interferon-α (3 MU/d for 5 days/wk) for 1 year. Her lesions still waxed and waned after treatment.

Patient 12 presented with indurated ulcers on left thigh and was initially diagnosed with immunoblastic lymphoma. He was then treated with radiotherapy with complete remission. However, two satellite lesions were observed 1 year later and a second skin biopsy revealed LyP Type A. The papules spontaneously resolved in 2 years.

Other treatment modalities used in combination included phototherapy (five patients), Dapsone (two patients), oral antihistamine and topical steroids (nine patients), oral doxycycline (two patients), chemotherapy (one patient), oral methotrexate (three patients), and surgical excision (one patient).

Neither clinical appearance nor the maximum number of LyP lesions correlated significantly with remission rate, disease activity, or malignant transformation.

Discussion

The clinical characteristics of our LyP patients are similar to those in prior studies (Table 2).[5,8–12] But patients with LyP in this series have lower associated hematolymphoid malignancy (6%, 2/34) than in previous reports. A smaller cohort and inadequate follow-up period (3–12.7 years) may explain the discrepancy. Since lymphoma can be found up to 41 years after LyP,[13] whether LyP in Asian ethnic groups have a more benign course needs longer follow-up data. There is no difference in the clinical picture and histology of LyP between patients who developed malignant lymphoma and those who did not. Consistent with previous reports, most of our cases are Type A LyP. We noted a higher incidence of CD8-predominant cases, the significance of which remains to be elucidated.[14] There are no clinical or pathologic features distinguishing CD4-predominant from CD8-predominant cases. A CD8+ phenotype in lymphoproliferative disorders is commonly associated with cytotoxic features and may be associated with aggressive lymphoma,[14] but we do not observe a poorer prognosis in this group of patients. In this study, the overall survival of LyP patients is excellent. Prior studies have also shown excellent overall survival of 62%–89% (Table 2).[5,8–12] The development of primary cutaneous ALCL for patients with

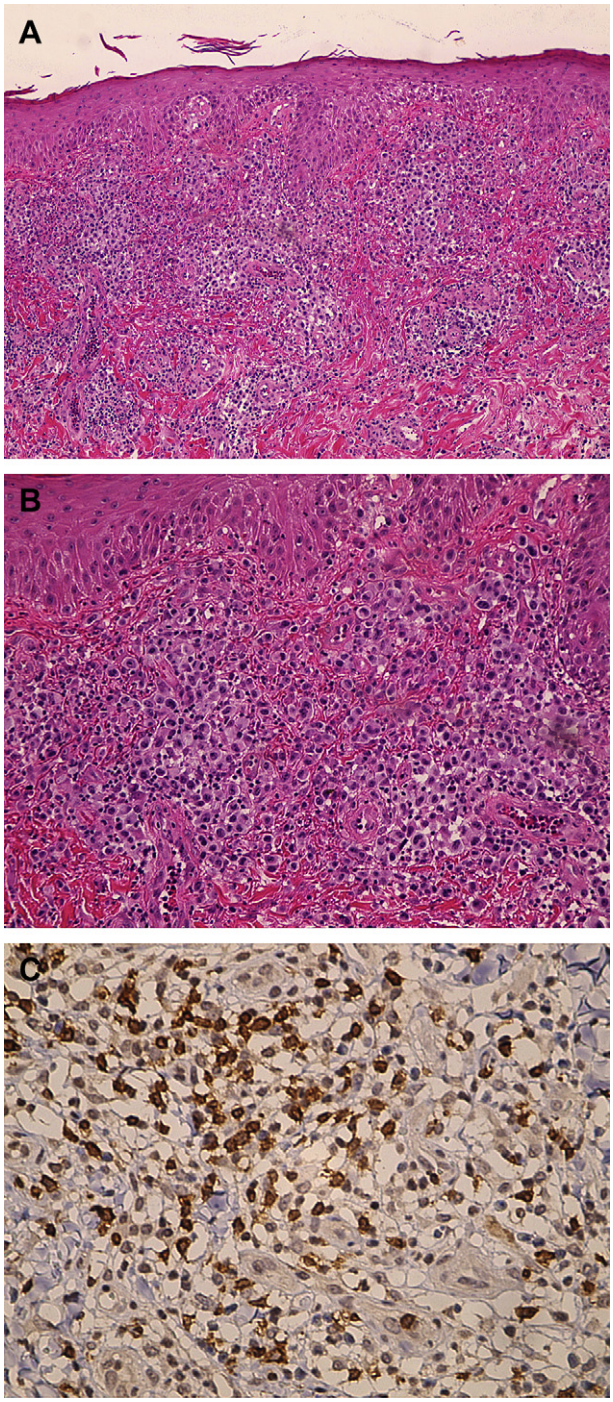

Figure 2 (A) Dermal infiltration by large atypical lymphocytes (H&E; original magnification: 100×). (B) Large atypical lymphocytes have convoluted nuclei mixed with neutrophils, small lymphocytes, and occasional eosinophils and mitotic figures (H&E; original magnification, 400×). (C) Immunohistochemistry shows multiple, large atypical cells that are CD30+ large atypical lymphocytes (original magnification, 400×). H&E = hematoxylin and eosin stain.

pre-existing LyP appears to have a similarly favorable course as primary cutaneous ALCL that develops *de novo*.[15]

LyP is a rare dermatosis in children. Three distinct clinical presentations have been described. The first type involves small outbreaks after initial eruption resolved.[16] The second type has LyP localized in one area for years before becoming generalized, whereas the third type involves hundreds of lesions.[17] In our series, four patients had onset before 18 years of age with clinical course as the first type. No lymphoma was found in 3-year follow-up (Table 1). Tamar et al[17] have also shown that LyP in children does not differ from LyP in adults, including risk of lymphoid malignancies.

The most controversial aspect of LyP is its pathogenesis and classification as a benign or malignant disease.[18] Neoplastic pathogenesis is supported by the higher incidence of lymphomas in LyP and pathological findings of the malignant large atypical cells indistinguishable from transformed mycosis fungoides or ALCL. Reactive etiology is supported by the presence of LyP development a few weeks after bacterial, viral, or yeast infection and resolved after antimicrobial treatment.[19] Most patients with LyP remain in good health, but lymphoid malignancies occur in 8.6%–26.3%.[5,8–12] Cutaneous CD30+ ALCL; mycosis fungoides; systemic malignant lymphomas, such as Hodgkin's disease, lymphocytic lymphoma, or ALCL, have all been documented.[20] Cabanillas et al[7] note that the cumulative risk of transformation from LyP to lymphoma is 80%.

The optimal treatment for LyP has yet to be established and there is no evidence in the literature that the natural course or malignant transformation can be altered by treatment.[21] Thus, many patients may not require active therapy. Indications for treatment include cosmetic concerns or symptom relief. We have no conclusions concerning treatment response because of the limited number of patients receiving therapy. The high percentage of partial response can be related to the natural history of LyP, with spontaneous regression and relapses. Systemic agents or skin-directed treatments may be warranted in generalized disease. Therapies shown to be effective in treating LyP include topical corticosteroids, topical mechlorethamine, oral antibiotics, phototherapy, low-dose methotrexate, interferon-α, and bexarotene,[13] a retinoid not available in Taiwan. Low-dose oral methotrexate (5–20 mg/wk) is the most effective therapy to suppress the development of new skin lesions.[21] In this series, three patients were treated with methotrexate. However, after discontinuation of treatment, the disease relapsed within months. The 13-*cis* derivative of RA, isotretinoin, has been shown to produce good response for refractory Ki-1+ (CD30) ALCL. Cellular differentiation and apoptosis were found in the remitting tumors.[22,23] In this study, 11 patients were treated with isotretinoin (20–30 mg/d) and 10 patients achieved remission after 3–4 months of medication. This supports the effectiveness of isotretinoin.[20] However, the 66% relapse rate in our series suggests that no treatment can modify the disease course. Overly aggressive and potentially harmful chemotherapy may adversely affect the body's tumor surveillance system, allowing progression of ongoing LyP. Observation and a less toxic therapy may be all that is required as long as systemic evaluations are negative.

Although there is consensus that all patients with LyP require long-term observation concerning lymphoma development, there are few established guidelines.[24] A lymphoma-complicating LyP can be recognized by enlarging or persistent skin lesions, peripheral lymphadenopathy, or circulating atypical lymphocytes. Therefore, annual physical examination with biopsy of suspected skin lesions or enlarged lymph nodes for histologic, immunopathologic, and cytogenetic or gene rearrangement studies have been suggested for follow-up.[25,26]

Our study provides data on the association between Lyp and other lymphoproliferative disorders, as well as on the prognosis of LyP patients in Taiwan. This study is limited by the small sample size and retrospective design. Associated studies, including peripheral blood T-cell flow cytometry, T-cell receptor gene rearrangement, and recording any history of acute viral infections (i.e. herpes simplex, herpes varicella zoster, and mononucleosis), as well as serology testing for cytomegalovirus, Epstein-Barr virus, and herpes simplex virus are lacking.[19] As such, further analysis of possible risk factors and prognostic factors cannot be done.

Table 2 Comparison of clinical features and follow-up in different series of lymphomatoid papulosis.

	Our study	Sanchez et al[5]	Christensen et al[8]	El-Azhary et al[9]	Tomaszewski et al[10]	Wang et al[11]	Bekkenk et al[12]
Patient no.	34	31	41	53	50	57	118
Sex (male/female)	23/11	20/11	19/22	37/16	37/13	28/29	69/49
Age of onset, yr (range, mean)	10–75, 36	11–68, 35	20–75, 42.7	11–9, 40	2–74, 44	7–81, 45	4–88, 45.5
Duration of LyP (range, mean)	1 mo–9.6 yr, 4.3 yr	3 mo–38 yr, 9 yr	1–37 yr, 16 yr	6 mo–40 yr, 11.9 yr	2 mo–33 yr, 15 yr	1–35 yr, 9.2 yr	8 mo–29 yr, 12.4 yr
Follow-up duration (range, mean)	3–12.7 yr, 5.2 yr	1–23.6 yr, 7.4 yr	8 mo–25.7 yr, 8.6 yr	1–44 yr, 12.2 yr	1.5–22.4 yr, 6.5 yr	1–26.6 yr, 5.7 yr	1–29.2 yr, 6.4 yr
Clinical lesions							
Papules/nodules	30	31	29	46	50	48	110
Plaques	3	0	5	N/A	0	6	8
Vesicles, bullae	1	0	7	N/A	0	3	0
Associated with lymphoma	2/34 (6%)	6/31 (19%)	6/41 (15%)	8/53 (15%)	3/35 (9%)	15/57 (26%)	23/118 (18%)
Current status (patients)	33*	N/A	N/A	42	35	57	118
No evidence of disease	10 (30%)	N/A	N/A	3 (7%)	2 (6%)	N/A	38 (32%)
Alive with disease	33 (100%)	N/A	N/A	35 (83%)	31 (89%)	N/A	73 (62%)
Died of lymphoma	0	N/A	N/A	4 (10%)	0	1 (2%)	2 (2%)
Died of other causes	0	N/A	N/A	0	2 (6%)	3 (5%)	5 (4%)

* One patient was lost to follow-up.
LyP = ymphomatoid papulosis; N/A = not applicable.

Conclusion

Despite inherent limitations of a retrospective design and significant referral bias stemming from a single institution, this descriptive series provides information on LyP in Taiwan. No clinical features or pathologic features can predict increased risk for developing malignancy. Although only 6% (2/34) of LyP patients were found to have lymphoma in 3-year follow-up, longer follow-up is needed. Regardless of treatment modalities, two-thirds of the patients have a recurrent course. Observation is a reasonable approach for patients without cosmetic or symptomatic concerns.

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