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Original Article

Primary Cutaneous CD30+ Lymphoproliferative Disorders in South Korea: A Nationwide, Multi-Center, Retrospective, Clinical, and Prognostic Study

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ABSTRACT

Background: Primary cutaneous CD30+ lymphoproliferative disorders (pcCD30-LPDs) are a diseases with various clinical and prognostic characteristics.
Objective: Increasing our knowledge of the clinical characteristics of pcCD30-LPDs and identifying potential prognostic variables in an Asian population.

Methods: Clinicopathological features and survival data of pcCD30-LPD cases obtained from 22 hospitals in South Korea were examined.

Results: A total of 413 cases of pcCD30-LPDs (lymphomatoid papulosis [LYP], n=237; primary cutaneous anaplastic large cell lymphoma [C-ALCL], n=176) were included. Ninety percent of LYP patients and roughly 50% of C-ALCL patients presented with multiple skin lesions. Both LYP and C-ALCL affected the lower limbs most frequently. Multiplicity and advanced T stage of LYP lesions were associated with a chronic course longer than 6 months. Clinical morphology with patch lesions and elevated serum lactate dehydrogenase were significantly associated with LPDs during follow-up in LYP patients. Extracutaneous involvement of C-ALCL occurred in 13.2% of patients. Lesions larger than 5 cm and increased serum lactate dehydrogenase were associated with a poor prognosis in C-ALCL. The survival of patients with C-ALCL was unaffected by the anatomical locations of skin lesions or other pathological factors.

Conclusion: The multiplicity or size of skin lesions was associated with a chronic course of LYP and survival among patients with C-ALCL.

Keywords: Anaplastic large cell lymphoma; Clinical course; Cutaneous T-cell lymphoma; Lymphomatoid papulosis; Prognostic factors

INTRODUCTION

There is a spectrum of primary cutaneous CD30+ lymphoproliferative disorders (pcCD30-LPDs), with primary cutaneous anaplastic large cell lymphoma (C-ALCL) on one end and lymphomatoid papulosis (LYP) on the other[1,2]. C-ALCL is histologically indistinguishable from LYP. As a result, clinical correlation is crucial for an accurate diagnosis. Both have an excellent prognosis, with 10-year disease-specific survival rates of 90% for C-ALCL and almost 100% for LYP[1,3]. Occasionally, patients experience extracutaneous spread of the disease and require systemic therapy[1,3-5]. Patients with LYP are at increased risk of developing lymphoid malignancies, including mycosis fungoides (MF), ALCL, and Hodgkin lymphoma[3,6,7]. These LYP-associated lymphomas can develop before, contemporaneously with, or after LYP lesions in 4% to 52% of individuals with LYP[3-5,8,9]. The chronic and recurrent skin manifestations of LYP may even persist for decades[10]. Studies examining risk factors for subsequent lymphoid malignancies and the longevity of LYP-related skin lesions have, however, been scarce thus far.

Most of the epidemiological data on C-ALCL have originated from case series and retrospective cohorts. In contrast with patients with solitary C-ALCLs, some patients with C-ALCLs have multiple skin lesions, which are known to recur more often, be more frequently associated with extracutaneous disease, and have a worse 5-year overall survival (OS)[11-13].

Given the paucity of large-scale data regarding pcCD30-LPDs, particularly in Asian populations, clinicopathologic data and prognostic factors of C-ALCL and LYP were examined from a nationwide multicenter cohort in South Korea.

MATERIALS AND METHODS

Patients

This nationwide, multicenter, retrospective cohort study included patients with pcCD30-LPDs who had been diagnosed clinically and histopathologically between January 2001 and December 2021 at 22 tertiary or university hospitals in South Korea. This research protocol was approved by the Institutional Review Boards of Asan Medical Center (2022-0170) and every other study hospital. As a key diagnostic indicator for LYP, the presence of recurrent, self-limiting papular or papulonodular eruptions was required. Some cases with nodule larger than 2 cm were also diagnosed as LYP if they show self-healing and recurrent eruption. C-ALCL was defined as nodules or tumors, histopathologically characterized by a population of cohesive sheets of large CD30 cells (>75%) with anaplastic, pleomorphic, or immunoblastic morphology. Partial spontaneous regression can be seen in a minority of cases of C-ALCL.

The chronicity of LYP cases was defined as follows. Rapidly progressing was defined as cases in which complete remission (CR) was achieved within 6 months of the diagnosis, and recurrence did not happen within 6 months of CR. The term "chronic and recurrent" was used to describe situations wherein the disease persisted for more than 6 months after diagnosis without achieving CR or cases wherein CR was achieved within 6 months after diagnosis, but recurrence occurred within 6 months after CR. Staging evaluation and surveillance for extracutaneous dissemination were assessed by computed tomography or positron emission tomography.

Clinical and molecular variables of interest

The largest diameter of the predominant lesion of cases was classified as <10 mm, 10 to 20 mm, and ≥20 to 40 mm for LYP and <20 mm, 20 to 50 mm, and ≥50 mm for ALCL. The extent of a cutaneous lesion was classified as ''localized'' when 1 or multiple skin lesions were limited to 1 anatomical site and ''disseminated'' when several noncontiguous anatomical sites were involved, based on the guidelines of the International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer[14]. A complete elimination of all lesions was considered CR, while a recurrence was defined as the emergence of any new lesions following CR. OS was calculated from the first sign of disease to the last follow-up appointment or the date of death from any cause. Progression-free survival (PFS) was determined from the date of disease onset to the date of disease progression or last follow-up. We also assessed relapse-free survival (RFS): the interval between the date of CR and the occurrence of relapse.

Histopathologic evaluation

The histopathologic variant of LYP was classified based on descriptions in previous studies[15,16]. The presence of epidermotropism, pseudoepitheliomatous hyperplasia, infiltrates of eosinophils or neutrophils, vasculitis-like infiltrates of tumor cells, red blood cell extravasation, and dermal necrosis was evaluated, as were the distribution and size of atypical lymphoid cells. For the available samples, immunophenotypes, such as CD4, CD8, CD30, and ALK expression variants, were evaluated. T-cell receptor (TCR) gene rearrangement of the pcCD30-LPD lesions was evaluated.

Statistical analysis

While continuous variables were compared using t-tests or Mann-Whitney tests, categorical variables were compared using χ^2 tests or linear association tests. Risk factors for extracutaneous dissemination, secondary hematolymphoid disorders, chronic and recurrent disease course were evaluated using logistic regression modeling. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The multivariate analysis incorporated all significant factors from the univariable analysis. The survival analysis was conducted using the Kaplan-Meier method, and its significance was assessed using the log-rank test. Cox proportional hazards regression modeling was used for PFS and OS, respectively, to assess the factors affecting the survival outcomes. All statistical analyses were conducted using R, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) software. The $p<0.05$ was considered statistically significant.

RESULTS

Our study included 413 patients with pcCD30-LPDs, among whom 237 (57.4%) were classified as having LYP, and the remaining 176 (42.6%) were classified as having C-ALCL.

Clinical features of pcCD30-LPDs

The clinical features of the LYP and C-ALCL are presented in **Tables 1** and **2**, respectively. The mean age at diagnosis was lower in association with LYP (38.6 years) than with C-ALCL (48.1 years). Both were more common among men than women. Ninety percent of patients with LYP had numerous skin lesions, while 50% of patients with C-ALCL had multiple skin lesions. About 35% of patients with C-ALCL had disseminated skin lesions. Both were more prevalent in the extremities than the trunk, particularly in the lower limbs. Papular and nodular morphologic variants were the more commonly associated with LYP and C-ALCL, respectively, and 20% of LYP cases were accompanied by patch lesions. Eighty-seven percent of the LYP lesions had diameters <2 cm, whereas more than half of the C-ALCL lesions had diameters ≥2 cm.

Histopathologic features and immunophenotypes of the pcCD30-LPDs

The histopathologic features of the LYP and C-ALCL cases are summarized in **Tables 1** and **2**, respectively. Tumor cells were medium to large or large in 75% of the ALCLs and 33% of LYP lesions. Type A (56.4%) was the most prevalent pathogenic subtype of LYP, followed by type C (15.6%), type E (11.4%), and type B (9.0%). Remarkable epidermotropism was observed in 6.2% of LYP cases and 8.8% of C-ALCL cases. Pseudoepitheliomatous hyperplasia was more common in association with ALCL (23.3%) than with LYP (15.5%). Moderate to remarkable eosinophil and neutrophil infiltrates were found in 28.5% and 21.5% of LYP cases, respectively. Eosinophilic infiltrates were less common in association with C-ALCL. About one-third of both C-ALCL and LYP tumor cells had infiltrative patterns resembling vasculitis, and dermal necrosis was more prevalent in association with C-ALCL (21.7%) than LYP (6.7%). The expression of cytotoxic markers was observed more frequently in association with LYP (68.4%) than with C-ALCL (46.3%). In terms of TCR gene rearrangement, 72.4% (21/29) of C-ALCL cases and 49.3% (33/67) of LYP cases displayed monoclonality.

Clinical course of LYP and associated LPDs

The median follow-up period was 11.0 months in the LYP group. The 5-year OS rate and median RFS were 98.2% (95% CI, 96.2%–100%) and 18 months (95% CI, 9–32 months), respectively (**Table 3**). The most frequently administered treatment option was topical steroids (62.6%), followed by oral methotrexate (31.9%),

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Table 1. Clinical and pathological features of LYP

Clinical variable	Value	Pathological variable	Value
Age at diagnosis (yr)	38.6±19.5	Tumor cell size	
Sex		Small	36/209 (17.2)
Female	114/237 (48.1)	Small and medium	41/209 (19.6)
Male	123/237 (52.3)	Small to large	1/209 (0.5)
Cutaneous involvement		Medium	62/209 (29.7)
Single	27/226 (11.9)	Medium to large	30/209 (14.4)
Multiple	199/226 (88.1)	Large	39/209 (18.7)
Localized	84/225 (37.3)	Subtype	
Disseminated	141/225 (62.7)	A	119/211 (56.4)
Location of skin lesions		B	19/211 (9.0)
Head and neck	66/237 (27.8)	C	33/211 (15.6)
Trunk	127/237 (53.6)	D	15/211 (7.1)
Upper extremities	146/237 (61.6)	E	24/211 (11.4)
Lower extremities	160/237 (67.5)	F	1/211 (0.5)
Clinical morphology		Epidermotropism	
Papule	192/235 (81.7)	None	96/210 (46.2)
Patch	47/235 (20.0)	Mild	52/210 (25.0)
Plaque	38/235 (16.2)	Moderate	47/210 (22.6)
Nodule	58/235 (24.7)	Remarkable	13/210 (6.2)
Ulcer	31/235 (13.2)	Pseudoepitheliomatous hyperplasia	32/207 (15.5)
Size (mm)		Eosinophil infiltration	
<10	132/218 (60.6)	None	89/210 (42.4)
≥10, <20	57/218 (26.1)	Mild	61/210 (29.0)
≥20, <40	29/218 (13.3)	Moderate	36/210 (17.1)
Accompanying symptoms		Remarkable	24/210 (11.4)
Pruritus	96/195 (49.2)	Neutrophil infiltration	
Pain	35/195 (17.9)	None	114/209 (54.5)
Elevated LDH		Mild	50/209 (23.9)
Yes	5/142 (3.5)	Moderate	32/209 (15.3)
No	137/142 (96.5)	Remarkable	13/209 (6.2)
T stage[14]		RBC extravasation	123/209 (58.9)
T1	28/225 (12.4)	Vasculitic infiltration of tumor cells	77/208 (37.0)
T2	56/225 (24.9)	Angiodestructive infiltration	32/167 (19.2)
T3	141/225 (62.7)	Dermal necrosis	14/208 (6.7)
LPDs after the diagnosis of LYP		Immunophenotype	
Mycosis fungoides	5/225 (2.2)	CD30+	189/204 (92.6)*
Anaplastic large cell	1/225 (0.4)	CD4 predominant	59/107 (55.1)
Lymphoma	4/225 (1.8)	CD8 predominant	28/106 (26.4)
Time to secondary lymphoma development (mo)	15.0 (1.0–98.0)	CD4 and CD8 double positive	12/103 (11.7)
		CD4 and CD8 double negative	8/113 (7.1)
		TCR betaF1+	15/19 (78.9)
		ALK+	0/60 (0)
		Cytotoxic marker+ (granzyme B, TIA-1)	26/38 (68.4)
		Clonal TCR rearrangement	33/67 (49.3)

Values are presented as mean ± standard deviation, number (%), or median (range).
LYP: lymphomatoid papulosis, LDH: lactate dehydrogenase, LPD: lymphoproliferative disorder, TCR: T-cell receptor, RBC: red blood cell.
*The 7.4% of LYP are negative for CD30. In these cases, even though the cases were negative for CD30, LYP was diagnosed based on the characteristic recurrent, self-healing eruption, and typical histopathological findings.

phototherapy (29.4%), oral antibiotics (16.2%), systemic retinoid (7.2%) and topical imiquimod (6.9%). CR was achieved in 48.5% (99/204) of patients, and the median time to CR was 4.0 months (range, 0–374.0 months). Of the individuals who achieved CR, 40.2% experienced recurrence. The median interval between CR and recurrence was 4.5 months (range, 0–135.0 months) (**Table 3**).

In the univariable analysis (**Table 4**), a multiplicity of skin lesions (OR, 4.33; 95% CI, 1.13–16.56; p=0.032) was significantly associated with chronicity and recurrence. Advanced T stage also showed a tendency toward an association with persistence of LYP (p=0.057). Papular-type LYP (OR, 3.2; 95% CI, 1.04–9.82; p=0.025) tended to last longer than other forms of LYP, such as the plaque type or nodular type. Pathological type C showed a tendency toward an association with rapidly improving LYP (p=0.052). Skin lesion multiplicity was significantly associated with higher probabilities of chronic and recurrent disease (OR, 5.33; 95% CI,

Table 2. Clinical and pathological characteristics of cutaneous anaplastic large cell lymphoma

Clinical variable	Value	Pathological variable	Value
Age at diagnosis (yr)	48.1±20.0	Tumor cell size	
Sex		Small	5/152 (3.3)
Female	70/176 (39.8)	Small and medium	1/152 (0.7)
Male	106/176 (60.2)	Small to large	2/152 (1.3)
Cutaneous involvement		Medium	30/152 (19.7)
Single	85/170 (50.0)	Medium to large	29/152 (19.1)
Multiple	85/170 (50.0)	Large	85/152 (55.9)
Localized	102/159 (64.2)	Epidermotropism	
Disseminated	57/159 (35.8)	None	71/147 (48.3)
Location of skin lesions		Mild	50/147 (34.0)
Head and neck	53/176 (30.1)	Moderate	13/147 (8.8)
Trunk	66/176 (37.5)	Remarkable	13/147 (8.8)
Upper extremities	71/176 (40.3)	Pseudoepitheliomatous hyperplasia	35/150 (23.3)
Lower extremities	78/176 (44.3)	Eosinophil infiltration	
Clinical morphology		None	93/152 (61.2)
Papule	58/163 (35.6)	Mild	30/152 (19.7)
Patch	16/163 (9.8)	Moderate	20/152 (13.2)
Plaque	37/163 (22.7)	Remarkable	9/152 (5.9)
Nodule	119/163 (73.0)	Neutrophil infiltration	
Ulcer	43/163 (26.4)	None	75/153 (49.0)
Size (mm)		Moderate	19/153 (12.4)
<20	73/150 (48.7)	Remarkable	14/153 (9.2)
≥20, <50	58/150 (38.7)	RBC extravasation	78/151 (51.7)
≥50	19/150 (12.7)	Vasculitic infiltration of tumor cells	52/153 (34.0)
Accompanying symptoms		Angiodestructive infiltration	27/152 (17.8)
Pruritus	44/137 (32.1)	Dermal necrosis	33/152 (21.7)
Pain	45/137 (32.8)	Immunophenotype	
B symptoms		CD30+	163/166 (98.2)
Yes	152/158 (96.2)	CD4 predominant	64/94 (68.1)
No	6/158 (3.8)	CD8 predominant	12/94 (12.8)
Elevated LDH		CD4 and CD8 double positive	10/94 (10.6)
Yes	26/149 (17.4)	CD4 and CD8 double negative	9/94 (9.6)
No	123/149 (82.6)	TCR betaF1+	16/24 (66.7)
Immunosuppression		Cytotoxic marker+ (granzyme B, TIA-1)	31/67 (46.3)
Yes	2/173 (1.2)	Clonal TCR rearrangement	21/29 (72.4)
No	171/173 (98.8)		
T stage[14]			
T1	79/159 (49.7)		
T2	23/159 (14.5)		
T3	57/159 (35.8)		
Any extracutaneous involvement during follow-up			
Lymph node	4/155 (2.6)		
Visceral involvement	13/154 (8.4)		

Values are presented as mean ± standard deviation or number (%).
LDH: lactate dehydrogenase, TCR: T-cell receptor, RBC: red blood cell.

1.41–20.10; p=0.013) in the multivariable analysis using all the significant variables from the univariable analyses.

Among the entire LYP cohort, 5% (12/236) of the patients experienced other LPDs (**Table 1**). Before LYP diagnoses, MF (2/236, 0.8%), ALCL (2/236, 0.8%), and chronic lymphocytic leukemia (1/236, 0.4%) were identified. ALCL (4/225, 1.8%, primary cutaneous ALCL [n=3], nodal ALCL [n=1]) was the most commonly associated lymphoma after diagnosis of LYP. In these patients, the median time from the LYP diagnosis to the associated lymphoma diagnosis was 15.0 months (range, 1.0–98.0 months). In the univariable analysis (**Table 4**), clinical morphology with patch lesions (OR, 4.30; 95% CI, 1.32–14.03; p=0.015) and elevated serum lactate dehydrogenase (LDH) (OR, 8.74; 95% CI, 1.29–59.22; p=0.026) were significantly associated with the development of secondary LPDs during follow-up. A lesion diameter >10 mm (OR, 3.27; 95% CI, 0.95–11.24; p=0.06) showed a tendency toward an association with the development of secondary LPDs. In the multivariable analysis, elevated serum LDH (OR, 22.14; 95% CI, 2.45–200.30; p=0.005) was significantly associated with a high risk of associated LPDs. The development of secondary lymphoproliferative diseases was not significantly associated with histopathologic characteristics or immunophenotypes.

Table 3. Survival outcomes of primary cutaneous CD30+ lymphoproliferative disorders*

Variables	Value
Lymphomatoid papulosis	
Follow-up duration (mo)	11.0 (0–375.0)
Complete remission	99/204 (48.5)
Time to complete remission (mo)	4.0 (0–374.0)
Recurrence	39/97 (40.2)
Time to recurrence (mo)	4.5 (0–135.0)
5-yr OS rate	98.2 (96.2–100)
5-yr PFS rate	76.9 (67.9–87.1)
Median OS (mo)	375 (334–NE)
Median PFS (mo)	375 (NE–NE)
Median RFS (mo)	18 (9–32)
Cutaneous anaplastic large cell lymphoma	
Follow-up duration (mo)	16.0 (0–297)
5-yr OS rate	81.7 (74.9–89.1)
5-yr PFS rate	49.3 (38.4–63.2)
Median OS (mo)	NE
Median PFS (mo)	58 (38–NE)

Values are presented as median (range), number (%), or % (95% confidence interval).
OS: overall survival, PFS: progression-free survival, RFS: relapse-free survival, NE: not estimated.
*The survival analysis was conducted using the Kaplan-Meier method, and its significance was assessed using the log-rank test.

Clinical course and prognostic factors of C-ALCL

The median follow-up period and the 5-year OS rate of the C-ALCL cohort were 16 months (range, 0–297 months) and 81.7% (95% CI, 74.9%–89.1%), respectively (**Table 3**). The most frequently used treatment option was radiotherapy (24.0%), followed by systemic methotrexate (21.7%), surgery (20.6%), systemic retinoid (7.1%) and brentuximab (6.3%). Extracutaneous invasion of C-ALCL occurred in 13.2% (21/159) of the patients during the course of the disease and was associated with a poorer OS compared to when it was absent (**Table 2**, **Fig. 1A**). Extracutaneous involvement (**Table 5**) was significantly more common in patients with multiple skin lesions (p=0.005) and advanced T stage (p=0.004).

The univariable analysis (**Table 5**) showed that skin lesions >50 mm in diameter (p=0.001, **Fig. 1B**) and elevated serum LDH (p=0.025) were associated with poor OS. In the multivariable analysis, large tumor size (hazard ratio, 3.24; 95% CI, 1.18–8.91; p=0.022) was independently associated with a worse OS. Anatomical sites of skin lesions and pathological variables were not associated with survival outcomes.

DISCUSSION

Some patients with pcCD30-LPDs develop associated LPDs and extracutaneous dissemination during the disease course, so it is necessary to determine how clinicopathologic characteristics affect prognosis. However, extensive research on these risk variables is limited, and contradicting information has been reported[4,9,15,17-20]. To our knowledge, the present study was the largest analysis of pcCD30-LPDs in an Asian population to identify risk factors associated with disease course and mortality.

Although none of the treatments for LYP have been shown to stop the disease from returning or to stop the growth of secondary lymphomas[2-4], they have been used to manage skin lesions, relieve accompanying symptoms, and prevent or mitigate the development of unsightly scars. Patients with LYP must be carefully followed up for life to facilitate the prompt identification of secondary lymphoma development[2]. There are previous studies

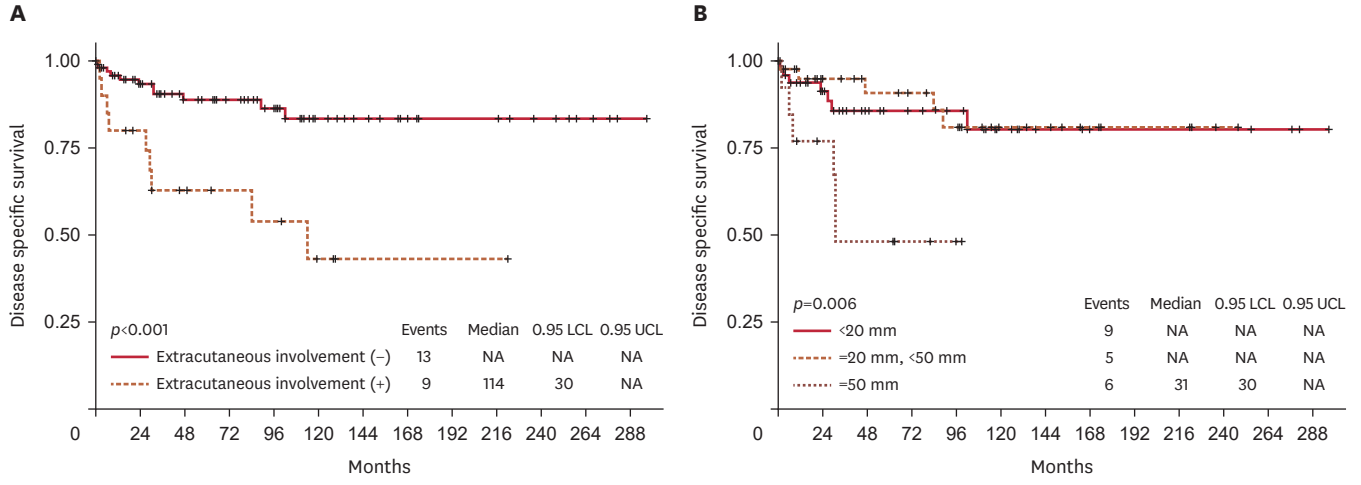

Fig. 1. Survival analysis of primary cutaneous anaplastic large cell lymphoma. Differences in overall survival depended on (A) the development of extracutaneous dissemination during follow-up and (B) lesional size. The survival analysis was conducted using the Kaplan–Meier method, and its significance was assessed using the log-rank test.
0.95 LCL: lower limit of 95% confidence interval, 0.95 UCL: upper limit of 95% confidence, NA: not available.

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Table 4. Univariable analysis* of the causes of secondary lymphoproliferative diseases and the persistence of lymphomatoid papulosis

Variables	Secondary lymphoproliferative disorders		Chronicity of lymphomatoid papulosis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age at diagnosis (yr)	1.02 (0.99–1.05)	0.154	0.99 (0.96–1.02)	0.454
Sex (male vs. female)	1.87 (0.55–6.41)	0.317	0.71 (0.26–1.96)	0.507
Head and neck involvement	2.67 (0.83–8.62)	0.099	0.75 (0.24–2.30)	0.611
Lower extremities involvement	5.74 (0.73–45.3)	0.098	1.59 (0.57–4.47)	0.378
Size (mm)				
≥10 vs. <10	3.27 (0.95–11.24)	0.060	0.83 (0.30–2.33)	0.730
Multiplicity	1.48 (0.18–12.00)	0.712	4.33 (1.13–16.56)	0.032
Lesion number				
≥5, ≤20 vs. <5	0.46 (0.04–5.18)	0.527	1.71 (0.47–6.14)	0.414
>20 vs. <5	2.57 (0.54–12.36)	0.238	5.65 (1.43–22.30)	0.014
T stage[14]				
T2 vs. T1	0.50 (0.03–8.32)	0.629	5.00 (0.92–27.04)	0.062
T3 vs. T1	2.08 (0.26–16.96)	0.494	3.23 (0.83–12.55)	0.091
T2–3 vs. T1	1.62 (0.20–13.03)	0.652	3.61 (0.96–13.56)	0.058
Clinical morphology				
Papule	0.66 (0.17–2.53)	0.540	3.2 (1.04–9.82)	0.042
Patch	4.30 (1.32–14.03)	0.016	1.45 (0.39–5.43)	0.578
Plaque	3.03 (0.86–10.70)	0.085	1.03 (0.27–3.92)	0.962
Nodule	2.58 (0.78–8.50)	0.120	0.49 (0.17–1.46)	0.203
Ulcer	2.28 (0.58–8.97)	0.237	0.63 (0.19–2.16)	0.465
Elevated LDH	8.74 (1.29–59.22)	0.026	NE	
Cell size (large vs. others)	2.00 (0.62–6.46)	0.246	0.66 (0.23–1.92)	0.447
Subtype				
A vs. others	0.52 (0.16–1.69)	0.276	2.21 (0.78–6.26)	0.135
B vs. others	NE		NE	
C vs. others	3.26 (0.91–11.63)	0.067	0.30 (0.09–1.01)	0.052
D vs. others	NE		1.29 (0.15–11.04)	0.814
E vs. others	2.96 (0.74–11.9)	0.125	0.59 (0.15–2.35)	0.454
F vs. others	NE		NE	
PEH	0.52 (0.06–4.21)	0.540	NE	
Eosinophil infiltration	0.50 (0.15–1.63)	0.251	0.57 (0.19–1.76)	0.328
Neutrophil infiltration	0.42 (0.11–1.61)	0.2074	0.72 (0.25–2.08)	0.5451
RBC extravasation	0.71 (0.22–2.27)	0.56	0.9 (0.31–2.61)	0.853
Vasculitic infiltration	1.29 (0.39–4.22)	0.676	0.69 (0.23–2.06)	0.5081
Angiodestructive infiltration	2.18 (0.38–12.49)	0.3822	0.46 (0.10–2.03)	0.3027
CD4 predominant	0.59 (0.12–2.76)	0.4994	0.38 (0.07–2.06)	0.2629
CD8 predominant	NE		2.44 (0.28–21.52)	0.4214
CD4/CD8 double positive	3.36 (0.57–19.65)	0.2996	NE	
CD4/CD8 double negative	2.31 (0.24–21.95)	0.4662	0.63 (0.06–6.15)	0.687
TCR betaF1	0.21 (0.01–4.48)	0.3205	NE	
Cytotoxic marker	NE		5.14 (0.40–66.14)	0.2089
Clonal TCR rearrangement	NE		1.66 (0.25–11.02)	0.6008

OR: odds ratio, CI: confidence interval, LDH: lactate dehydrogenase, PEH: pseudoepitheilomatous hyperplasia, RBC: red blood cell, TCR: T-cell receptor, NE: not estimated.
*Logistic regression modeling.

related to different risk factors associated with the occurrence of secondary LPD in association with LYP, but there are conflicting data in this regard, and studies examining factors associated with the chronicity of skin lesions of LYP itself have been limited.

The way that LYP presents clinically varies greatly. Few to hundreds of papules, nodules—or, in rare cases, pustular lesions—may be present. The disease duration is from several weeks to even decades[5,10]. CR was achieved in approximately half of the patients. This outcome was quite similar to the findings of a previous study, which demonstrated that 48% of patients receiving first-line active therapy had achieved clearance[17]. In our study, 40% of LYP patients experienced relapse after CR. Genetic mutations of transforming growth factor-β type I receptor in CD30+ cells may contribute to the growth of LYP lesions[21]. CD30 and the CD30 ligand system's function of controlling cellular survival and apoptosis has been proposed to explain the waxing and waning nature of LYP[22]. We undertook this study to investigate variables associated with the clinical course of LYP because there have not been many studies that have specifically focused on these characteristics. Although some studies have shown that LYP cases with

Table 5. Univariable study* for cutaneous anaplastic large cell lymphoma factors impacting overall survival and extracutaneous spread

Variables	Overall survival		Extracutaneous dissemination	
	HR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age at diagnosis (yr)	1.03 (1.01–1.05)	0.015	1.01 (0.99–1.04)	0.266
Sex (male vs. female)	1.70 (0.74–3.88)	0.211	0.83 (0.33–2.11)	0.697
Head and neck involvement	0.84 (0.37–1.92)	0.678	2.31 (0.91–5.87)	0.079
Lower extremities involvement	1.11 (0.52–2.36)	0.797	2.11 (0.82–5.42)	0.120
Size (mm)				
≥20, <50 vs. <20	0.66 (0.22–1.98)	0.461	1.13 (0.38–3.34)	0.828
≥50 vs. <20	4.79 (1.82–12.61)	0.002	1.36 (0.32–5.72)	0.676
Multiplicity	1.72 (0.77–3.83)	0.184	5.15 (1.64–16.23)	0.005
T stage[14]				
T2 vs. T1	2.71 (0.96–7.61)	0.059	9.69 (2.48–37.88)	0.001
T3 vs. T1	1.53 (0.59–3.96)	0.386	3.86 (1.12–13.30)	0.033
T2–3 vs. T1	1.88 (0.81–4.35)	0.141	5.24 (1.66–16.55)	0.005
Clinical morphology				
Papule	1.20 (0.53–2.75)	0.661	1.27 (0.48–3.34)	0.625
Plaque	0.96 (0.36–2.57)	0.931	1.60 (0.56–4.56)	0.377
Nodule	1.25 (0.55–2.82)	0.592	1.50 (0.57–3.91)	0.408
Ulcer	1.65 (0.68–4.00)	0.270	0.43 (0.12–1.57)	0.203
Elevated LDH	2.45 (1.12–5.38)	0.025	2.72 (0.96–7.68)	0.058
B symptoms	1.49 (0.2–11.1)	0.697	4.43 (0.74–26.39)	0.102
Cell size (large vs. others)	6.79 (0.91–50.52)	0.061	5.87 (0.75–45.87)	0.092
Pseudoepitheilomatous hyperplasia	0.81 (0.27–2.38)	0.695	0.15 (0.02–1.14)	0.066
Eosinophil infiltration	0.49 (0.18–1.32)	0.158	0.63 (0.22–1.77)	0.377
Neutrophil infiltration	0.57 (0.23–1.41)	0.227	0.84 (0.32–2.22)	0.727
RBC extravasation	0.82 (0.35–1.90)	0.641	0.92 (0.35–2.42)	0.859
Vasculitic infiltration	1.03 (0.40–2.64)	0.950	0.39 (0.11–1.44)	0.159
Angiodestructive infiltration	0.31 (0.04–2.31)	0.253	0.31 (0.04–2.46)	0.267
Dermal necrosis	1.59 (0.62–4.10)	0.335	0.70 (0.19–2.58)	0.590
CD4 predominant	NE		0.98 (0.27–3.57)	0.976
CD8 predominant	NE		1.32 (0.25–6.92)	0.743
CD4/CD8 double positive	NE		0.68 (0.08–5.88)	0.723
CD4/CD8 double negative	NE		0.90 (0.10–8.01)	0.922
TCR betaF1	1.4 (0.12–16.58)	0.79	1.62 (0.14–18.58)	0.7004
ALK	0.81 (0.11–6.08)	0.842	0.61 (0.07–5.15)	0.6476
Cytotoxic marker	2.19 (0.69–6.92)	0.183	0.62 (0.16–2.37)	0.4814
Clonal TCR rearrangement	NE		NE	

HR: hazard ratio, CI: confidence interval, OR: odds ratio, LDH: lactate dehydrogenase, NE: not estimated, TCR: T-cell receptor.
*Logistic regression modeling and Cox proportional hazards regression modeling were used to assess the risk factors.

eczematous morphology have poor responses to treatment[17], LYP consisting of papular lesions was more associated with a chronic disease course than LYP with plaques or nodules in the present study. According to reports, the chronicity of LYP is associated with skin lesion multiplicity, advanced T stage, and widespread distribution[23]. Consistent with this, the multiplicity of skin lesions affected the chronicity of LYP in our study. Previous studies have demonstrated that lower extremity involvement is associated with poor prognosis in several primary cutaneous lymphomas[18,24] and that lower extremity involvement is associated with a chronic course of LYP[23], but the anatomical site of LYP was not associated with the chronic nature of LYP in our study. In our investigation, 49% of the LYP cases had monoclonality in the TCR gene rearrangement, which falls within the previously reported range of 40%–65%[9,25,26]. Consistent with previous studies[17], the monoclonality of TCR gene rearrangement was not associated with chronicity of the disease course. Although type A was the most prevalent histologic subtype and accounted for almost 80% of all LYP cases[9,15], it only accounted for 56.4% of the entire cohort in the present study, and the differences between studies may be attributable to racial variation. However, the proportion of type A in the Asian population is variously reported to be 40%–70%[23,27], so the racial difference is inconclusive. The clinical implications of histopathologic variation of LYP have been reported previously. Type A was associated with early relapse of LYP in a previous study[17]. Our research revealed a weak association between type C LYP and a low probability of a chronic disease course or recurrence.

Secondary LPDs associated with LYP occurred at a lower frequency in our study than in previous reports[3-5,8,9]. Our study's low rate of associated lymphoproliferative diseases may have been attributable to racial variation and the short median follow-up time of 11 months. In our research, the median time from LYP

diagnosis to the development of secondary LPDs was 15 months, and many LYP patients had follow-up durations shorter than 15 months. Several risk factors for the emergence of related lymphoproliferative diseases after LYP diagnosis have been proposed. One study found that the status of LYP at the last follow-up was not associated with secondary lymphoma development[5]. Another study determined that secondary lymphoma incidence was associated with a higher frequency of recurrences and head lesions[19]. Lesion counts and symptom severity have not been associated with secondary lymphoma[4]. Additionally, our current research showed that neither the T stage nor the number of lesions was associated with a higher risk of associated lymphoma development. We found, instead, that LYP with patch lesions and elevated serum LDH was associated with secondary lymphoma development. Cases of agminated LYP with patch lesions have been reported to be associated with MF[28,29]. Male LYP patients have been reported to develop associated lymphoma more frequently[4]. The prognostic significance of histologic findings and immunophenotypes has been uncertain, although type C status has been proposed as a risk factor for developing associated lymphoma[30], and mixed histologic skin lesion subtypes have been associated with a higher incidence of hematologic malignancies[9]. Our research did not determine associations between histopathologic variations and the emergence of related lymphoproliferative diseases.

Previous studies have reported that C-ALCL frequently involves the head and neck area as well as the trunk[12,13]. The most frequent site, however, in our investigation was the lower leg, which is consistent with a previous US population database study[20]. Half of the C-ALCL patients in our study had multiple cutaneous lesions. This was higher than previous reports, and the differences between our study and previous studies may be attributable to racial variation. In a previous study on an Asian population, almost 50% of patients with primary ALCL had multiple lesions[18]. In our study, similar to previous studies[3,13,31], extracutaneous involvement was found in about 13% of patients. However, visceral involvement was seen more frequently than lymph node (LN) dissemination in our investigation, which may be explained by the short follow-up time of just 16 months or inaccurate LN surveillance. It is possible that the detection of LN involvement before visceral dissemination was missed.

Previous research has identified poor prognostic indicators for C-ALCL, such as a presentation with many skin lesions, substantial involvement of a single limb, and head and neck localization[12,13,32-34]. The present study showed that the prognosis of C-ALCL was influenced by the size of the skin lesion and the serum LDH level. In the context of extracutaneous involvement, skin lesion multiplicity was more prognostic than tumor size. Although skin lesion multiplicity was associated with extracutaneous dissemination, it did not affect survival outcomes. Although locoregional spread can easily occur in the presence of multiple skin lesions, skin lesion multiplicity is not considered an independent prognostic factor. Distribution on the leg or head and neck was previously identified as a poor prognostic factor in C-ALCL[13,35,36]. However, a previous study observed that the location on the head and neck had no statistically significant association with survival[12]. In our study, the anatomical site of the tumor lesion was not associated with the prognosis, which may have been because the frequency of C-ALCL cases with multifocal skin lesions was higher compared with other previous studies and because of the tendency of the distribution of these lesions over multiple anatomical sites. Anatomical location was not a prognostic factor for C-ALCL patients in a recent study that included 500 patients from the US National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) database[20].

The limitations of this study were mainly related to its retrospective nature and limited follow-up data for some institutions. Furthermore, our data did not specify the type, dose, or duration of the chemotherapy or radiotherapy used, and it did not specify the factors involved in determining the course of treatment. In addition, accurate categorization was difficult in cases where LYP and C-ALCL characteristics overlap, and some cases did not have TCR gene rearrangement results. Despite these drawbacks, our research indicates that several clinical and pathological characteristics of pcCD30-LPDs are associated with their clinical course.

In conclusion, the clinical characteristics of skin lesions are prognostic in pcCD30-LPDs. The multiplicity and clinical morphology of skin lesions are associated with the development of associated LPDs in LYP, as well as their chronicity. Large lesional size is predictive of poor survival among patients with C-ALCL. Anatomical location is not associated with poor survival.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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