BRIEF REPORT
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Retrospective Evaluation of Clinical And Follow-Up Outcomes in Primary Cutaneous CD30+ Lymphoproliferative Disorders

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INTRODUCTION

Primary cutaneous CD30+ lymphoproliferative disorders (LPD), including lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (pcALCL), are rare conditions characterized by cutaneous involvement and an overall excellent prognosis. The 5-year survival rates are 99% for LyP and 95% for pcALCL [1].

Although both diseases express CD30, they differ significantly in clinical presentation and management. LyP typically manifests as multiple recurrent papulonodular lesions, while pcALCL usually presents as solitary or localized nodules/tumors [2]. Asymptomatic LyP often requires no treatment, but symptomatic cases are typically managed with phototherapy or methotrexate. For pcALCL, localized lesions are treated with surgery or radiotherapy, and chemotherapy is utilized for cases with extracutaneous involvement [3].

LyP patients are at an increased risk of developing secondary malignancies, especially mycosis fungoides (MF), highlighting the need for long-term monitoring [2].

This study aims to evaluate the clinical features, treatment strategies, and outcomes of primary cutaneous CD30+ LPDs at a tertiary care center.

MATERIALS AND METHODS

We conducted a retrospective review of 43 patients diagnosed with primary cutaneous CD30+ LPD at Ankara University Faculty of Medicine from January 2006 to July 2023. Ethical approval (No:19-1190-17) was obtained, and informed consent was provided by all patients.

Diagnosis was confirmed through clinical assessment, histopathological examination, and immunohistochemistry. Systemic anaplastic large cell lymphoma was excluded through clinical, laboratory, and imaging investigations. Clinical data including patient demographics, lesion types, lesion distribution, and extent were documented according to the ISCL/EORTC criteria [4].

Histopathology involved hematoxylin and eosin (H&E) staining, with immunohistochemistry performed using antibodies against CD2, CD3, CD4, CD5, CD7, CD8, CD20, and CD30 with additional tests for CD56, TIA-1, cytotoxic markers (ALK, perforin, and granzyme B) as needed. Fluorescence in situ hybridization analyses were performed using an *IRF4-DUSP22* break-apart probe (Kreatech, Leica) for the study of the 6p25.3 rearrangement.

Treatment responses were categorized as complete response (CR), partial response (PR), or no response (NR). Patients achieving CR but later relapsing were considered as relapsed [3]. Spontaneous regression of individual lesions within weeks or months, regardless of whether new lesions appear, was defined as self healing. Survival data [(overall survival (OS) and disease-specific survival (DSS)] were recorded until July 1, 2023.

Statistical Analysis

Data were analyzed using SPSS (Version 25.0), and statistical comparisons were made using chi-square tests, independent t-tests, and Mann-Whitney U test with a significance threshold set at $p<0.05$.

RESULTS

1. Demographic and Clinical Findings

Out of 43 patients, 34 were diagnosed with LyP and 9 with pcALCL. The mean follow-up duration was 54 months (range 4–180 months). LyP patients predominantly presented with papular lesions (94.1%), while pcALCL was more commonly associated with tumoral lesions (77.8%) ($p<0.001$). LyP lesions were often generalized (70.6%), whereas pcALCL lesions were typically solitary (77.8%) ($p<0.001$) (Figure 1). Self-healing occurred in all LyP patients but only 11.1% of pcALCL patients ($p<0.001$). Extracutaneous involvement, specifically inguinal lymph node involvement, was observed in one pcALCL patient with [^{18}F] FDG-PET/CT. The demographic characteristics and clinical data are summarized in Table 1.

2. Histopathological and Immunophenotypic Features

Histologically, LyP was predominantly type A (67.6%), followed by type C (23.5%), type E (5.9%), and type D (2.9%). No type B lesions were observed. Both LyP and pcALCL were negative for ALK expression. CD56 positivity was found in 27.3% of LyP cases. Cytotoxic markers were detected in 1 of 7 LyP patients and 2 of 5 pcALCL patients. *DUSP22* rearrangements were identified in 2 of 4 pcALCL cases.

3. Treatment and Treatment Responses

Treatment strategies for LyP included methotrexate, psoralen and ultraviolet A (PUVA) therapy, and topical corticosteroids (TC). Methotrexate (<20 mg/week) had an overall response rate of 78.5%, while PUVA and TC showed response rates of 85.8% and 91.6%, respectively. However, relapse rates for all treatments were high. For pcALCL, two patients treated with brentuximab vedotin (BV) achieved CR. One of these patients who received BV treatment had lymph node involvement, while the other patient experienced relapses following treatment with radiotherapy, CHOP, and ESHAP protocols (Table 2, 3).

4. Secondary Malignancies

Secondary lymphomas developed in 7 LyP patients (20.5%), including four cases of MF with two patients in the early stages and the other two in advanced stages. One patient developed Hodgkin lymphoma, one patient had pcALCL, and another had non-Hodgkin lymphoma (Burkitt lymphoma). No significant associations were found between the occurrence of secondary lymphoma and patient demographics or LyP subtypes ($p>0.05$).

5. Survival Outcomes

The mean follow-up for LyP patients was 52.3 months, with 16 patients alive with disease, 15 without disease, and 3 deaths (2 from secondary lymphomas, 1 from another cause). The mean follow-up for pcALCL patients was 54.1 months. One patient died from septic shock, and 7 were alive without disease. The 5-year DSS rates were 100% for both LyP and pcALCL. The 5-year OS rates were 90.9% for LyP and 83.3% for pcALCL.

DISCUSSION

LyP and pcALCL are distinct entities within the spectrum of primary cutaneous CD30+ LPD, with generally favorable prognoses but differing in clinical presentation and histopathology [5]. In our study, the male-to-female ratio in LyP (1.41) was consistent with prior studies, while the ratio for pcALCL (0.8) was lower than expected [6]. The mean age at diagnosis for LyP was 48.4 years, and for pcALCL, 54.5 years. These findings align with prior reports, although a few pediatric cases were observed, which is unusual for these conditions [6-11].

Histologically, type A LyP lesions predominated, which is consistent with other studies, though we observed no type B lesions in our cohort [12]. *DUSP22* rearrangements were found in two pcALCL cases, a finding that aligns with the literature, as these rearrangements are more common in pcALCL compared to LyP. The prognostic significance of *DUSP22* rearrangements in pcALCL remains unclear but has been associated with an indolent clinical course in other settings [13-15].

Treatment for LyP typically involves a watch-and-wait approach for limited lesions, with phototherapy and methotrexate providing effective treatment for generalized cases [3]. Methotrexate was effective in 78.5% of cases, though the high relapse rate indicates the need for ongoing management. Phototherapy, especially PUVA, was effective in our cohort, with relapse rates consistent with the literature [3, 16-18].

pcALCL treatment often involves radiotherapy or surgery for localized lesions, with chemotherapy and BV used for relapsed or advanced cases [3, 19-21]. The use of BV in our study showed promising results, particularly in treatment-resistant cases. The relapse for BV was not observed in our cohort during a 3.5-year follow-up, suggesting its potential as a viable treatment for resistant pcALCL.

The development of secondary malignancies, particularly MF, is a well-established risk in LyP patients [22-24]. In our study, 20.5% of LyP patients developed secondary lymphomas, underscoring the need for vigilant long-term follow-up. No significant associations were found between demographic factors or LyP subtype and the occurrence of secondary malignancies.

CONCLUSION

LyP and pcALCL are distinct primary cutaneous CD30+ LPD with favorable prognosis. Although treatment modalities often lead to remission, the chronic-recurrent nature of LyP and the risk of secondary malignancies necessitate ongoing management. pcALCL patients can benefit from localized treatments like surgery and radiotherapy, with BV emerging as a promising option for resistant cases. Future research should focus on

identifying factors that influence relapse and secondary malignancy risk to refine treatment and follow-up strategies.

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Table 1. Demographic characteristics, clinical findings of the patients with primary cutaneous CD30+ LPD

	LyP (n=34)	**pcALCL (n=9)**	**p**
Male/Female ratio	23/11	4/5	0.257
Mean age of diagnosis (years) (mean ± SD)	48.4 ± 18.69	54.5 ± 24.23	0.415
Age at diagnosis (years)			
<18 years old, n (%)	2 (5.9)	1 (11.1)	0.515
>60 years old, n (%)	8 (23.5)	4 (44.4)	0.237
Type of skin lesions, n (%)	Papule 32 (94.1) Plaque 10 (29.4) Nodule 9 (26.5) Papulonodular 8 (23.5) Tumor 2 (5.9)	Papule 2 (22.2) Plaque 1 (11.1) Nodule 2 (22.2) Papulonodular 1 (11.1) Tumor 7 (77.8)	**< 0.001**
Distribution of lesions, n (%)	Head-neck 5 (14.7) Trunk 16 (47.1) Upper extremity 18 (52.9) Lower extremity 18 (52.9)	Head-neck 3 (33.3) Trunk 1 (11.1) Upper extremity 2 (22.2) Lower extremity 4 (44.5)	0.199
Lesion pattern, n (%)	Generalized 24 (70.6) Localized 9 (26.5) Solitary 1 (2.9)	Generalized 1 (11.1) Localized 1 (11.1) Solitary 7 (77.8)	**< 0.001**
<u>Subjective symptoms</u>			
Pruritus, n (%)	18 (52.9)	3 (33.3)	0.457
Pain, n (%)	2 (5.9)	1 (11.1)	0.515
Asymptomatic, n (%)	12 (35.3)	3 (33.3)	1.000
Ulcer, n (%)	6 (17.6)	2/5 (40)	0.268
Self healing, n (%)	34 (100)	1 (11.1)	**< 0.001**
Extracutaneous disease, n (%)	-	1 (11.1)	0.209

LyP: lymphomatoid papulosis, n: Number of patients, pcALCL: primary cutaneous anaplastic large cell lymphoma SD: Standard deviation

Table 2. Treatments and treatment responses in primary cutaneous CD30+ LPD patients

	Partial remission n (%)	**Complete remission n (%)**	**No response n (%)**	**Relaps after treatment* n (%)**
LyP patients (n=34)				
Methotrexate (n=14)	3 (21.4)	8 (57.1)	3 (21.4)	6 (75)
Topical corticosteroids (n=12)	4 (33.3)	6 (58.3)	2 (16.7)	5 (83.3)
Phototherapy (n=7)	3 (42.9)	3 (42.9)	1 (14.3)	2 (66.7)
Follow-up without treatment (n=7)	6 (85.7)	1 (14.3)	-	1 (100)
Peginterferon alfa-2a (n=4)	2 (50)	2 (50)	-	1 (50)
Systemic steroid (n=3)	1 (33.3)	1 (33.3)	1 (33.3)	1 (100)
Intralesional interferon alfa-2a (n=1)	-	1 (100)	-	-
Surgical excision (n=1)	-	1 (100)	-	1 (100)
pcALCL patients (n=9)				
Local radiotherapy (n=5)	-	5 (100)	-	2 (40)
Surgical excision (n=4)	-	4 (100)	-	1 (25)
Brentuximab vedotin (n=2)	-	2 (100)	-	-
Multi-agent chemotherapy (n=2)		2 (100)	-	2 (100)

LyP: lymphomatoid papulosis, n: Number of patients, pcALCL: primary cutaneous anaplastic large cell lymphoma, * Only for patients who achieved CR

Table 3. The distribution of sequential treatments with responses in LyP patients (n=34)

	Initial Treatments	Second Treatments	Third Treatments
Methotrexate (n=14)	n=11 (PR:2, CR:6, NR:3)	n=1 (CR:1)	n=2 (PR:1, CR:1)
Topical corticosteroids (n=12)	n=12 (PR:4, CR:6, NR:2)	-	-
Phototherapy (n=7)	n=4 (PR:1, CR:3)	n=2 (PR:1, NR:1)	n=1 (PR:1)
Follow-up without treatment (n=7)	n=5 (PR:4, CR:1)	n=2 (PR:2)	-
Peginterferon alfa-2a (n=4)	-	n=4 (PR:2, CR:2)	-
Systemic steroid (n=3)	n=1 (PR:1)	n=2 (CR:1, NR:1)	-
Intralesional interferon alfa-2a (n=1)	-	n=1 (CR:1)	-
Surgical excision (n=1)	n=1 (CR:1)	-	-

n: Number of patients, PR: Partial remission, CR: Complete remission, NR: No response

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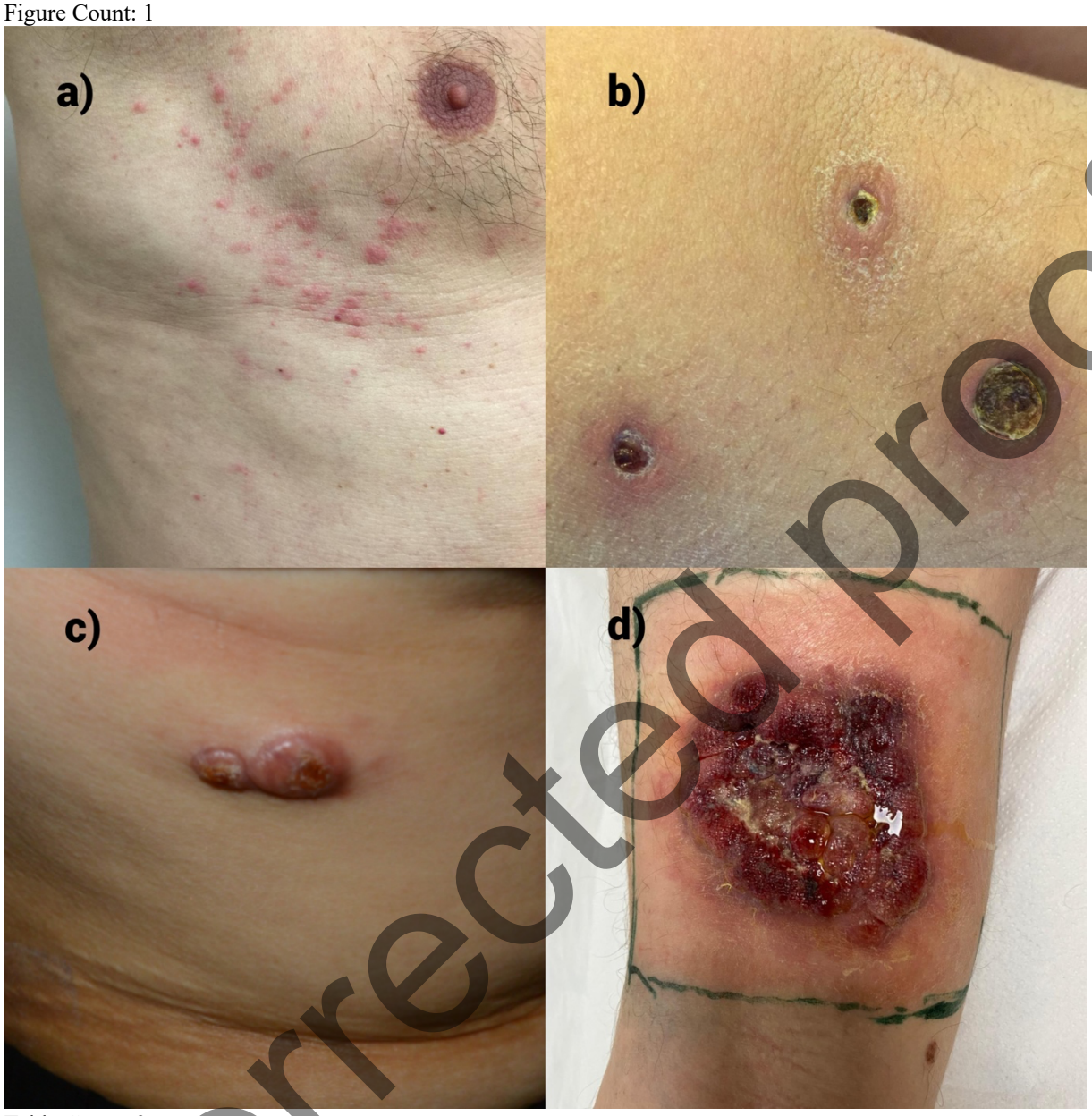

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