BRIEF REPORT

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Retrospective Evaluation of Clinical and Follow-Up Outcomes in Primary Cutaneous CD30+ Lymphoproliferative Disorders

Primer Kutanöz CD30+ Lenfoproliferatif Hastalıklarda Klinik ve Takip Sonuçlarının Retrospektif Değerlendirilmesi

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Abstract

This study evaluated the demographic data, clinical characteristics, treatment approaches, and treatment responses of 43 patients with primary cutaneous CD30+ lymphoproliferative disorders. Lymphomatoid papulosis (LyP) was characterized by predominantly papular (94.1%) and generalized (70.6%) lesions, while primary cutaneous anaplastic large-cell lymphoma (pcALCL) presented with tumoral (77.8%) and solitary (77.8%) lesions (p<0.001). Common treatments for LyP included methotrexate (response rate: 78.5%), topical corticosteroids (response rate: 83.3%), and phototherapy (response rate: 85.8%), but relapse rates were high. In pcALCL, complete remission was achieved with all treatments, with no relapses after brentuximab vedotin (BV). Secondary malignancies were noted in 20.6% of LyP cases. Both LyP and pcALCL had a 100% 5-year disease-specific survival rate, although two LyP patients (5.9%) died of secondary malignancies. In conclusion, LyP and pcALCL are both indolent lymphomas, with LyP being more prone to relapse. BV is effective for resistant pcALCL. LyP patients need long-term monitoring due to the risk of secondary malignancies.

Keywords: Primary cutaneous CD30+ lymphoproliferative disorders, Lymphomatoid papulosis, Primary cutaneous anaplastic large-cell lymphoma

Öz

Bu çalışmada, primer kutanöz CD30+ lenfoproliferatif hastalık tanılı 43 hastanın demografik verileri, klinik özellikleri, aldığı tedaviler ve tedavi yanıtları incelendi. Lenfomatoid papülozis (LP), genellikle papüler (%94,1) ve generalize (%70,6) lezyonlarla karakterize iken; primer kutanöz anaplastik büyük hücreli lenfomada (pkABHL) sıklıkla tümoral (%77,8) ve soliter (%77,8) lezyonlar izlendi (p<0,001). LP'de en sık verilen tedaviler metotreksat (yanıt oranı: %78,5), topikal kortikosteroidler (yanıt oranı: %83,3) ve fototerapiydi (yanıt oranı: %85,8), ancak nüks oranları yüksekti. pkABHL hastalarında ise tüm tedavilerle tam remisyon sağlanmıştı ve brentuksimab vedotin (BV) tedavisinden sonra ise nüks izlenmedi. LP olgularının %20,6'sında sekonder maligniteler saptandı. LP ve pkABHL hastalarında 5 yıllık hastalığa özgü sağkalım oranı %100'dü, ancak LP hastalarının ikisi (%5,9) sekonder maligniteler nedeniyle hayatını kaybetti. Sonuç olarak, LP ve pkABHL indolent lenfomalardır; ancak LP'de nüks daha sık izlenmektedir. Dirençli pkABHL olgularında BV etkili bir tedavi seçeneğidir. LP hastalarında sekonder malignite riski nedeniyle uzun dönem takip gereklidir.

Anahtar Sözcükler: Primer kutanöz CD30+ lenfoproliferatif hastalıklar, Lenfomatoid papülozis, Primer kutanöz anaplastik büyük hücreli lenfoma

Introduction

Primary cutaneous CD30+ lymphoproliferative disorders (LPDs), 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

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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+ LPDs in the Ankara University Faculty of Medicine from January 2006 to July 2023. Ethical approval (no: 19-1190-17, date: 27.11.2017) was obtained from the Ankara University Faculty of Medicine, Clinical Research Ethics Committee, and informed consent was provided by all patients.

Diagnoses were 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 criteria of the European Organization of Research and Treatment of Cancer and the International Society for Cutaneous Lymphomas [4].

Histopathological examinations involved hematoxylin and eosin staining, with immunohistochemical testing performed using antibodies against CD2, CD3, CD4, CD5, CD7, CD8, CD20, and CD30 and additional tests for CD56, TIA-1, and cytotoxic markers anaplastic lymphoma kinase (ALK), perforin, and granzyme B as needed. Fluorescence in situ hybridization analyses were performed using an *IRF4-DUSP22* break-apart probe (Kreatech, Leica Biosystems, Deer Park, IL, USA) for the study of 6p25.3 rearrangement.

Treatment responses were categorized as complete response (CR), partial response, or no response. 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 appeared, was defined as self-healing. Survival data for overall survival (OS) and disease-specific survival (DSS) were recorded until July 1, 2023.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA) and statistical comparisons were made using chi-square tests, independent t-tests, and Mann-Whitney U tests with the significance threshold set at $p<0.05$.

Results

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). Patients with LyP 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 cases of LyP but only 11.1% of pcALCL cases ($p<0.001$). Extracutaneous involvement, specifically inguinal lymph node involvement, was observed in one pcALCL patient by fluorodeoxyglucose positron emission tomography-computed tomography. The demographic characteristics and clinical data of the patients are summarized in Table 1.

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.

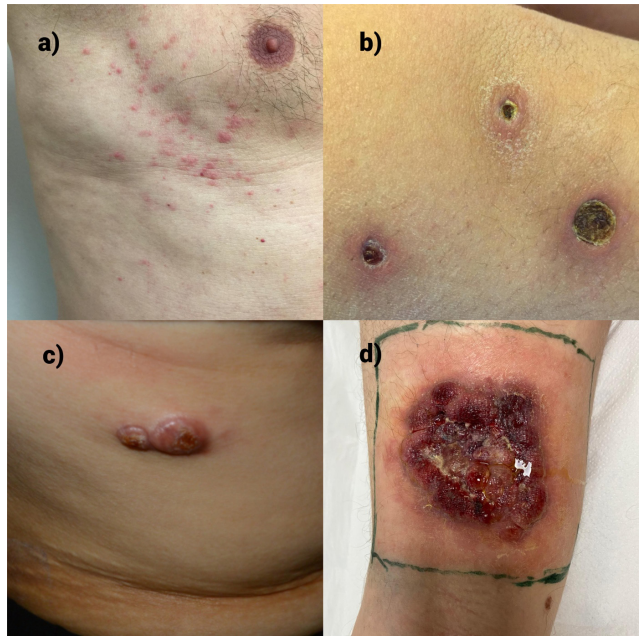

Figure 1. a) Papules on the trunk in a patient with LyP; (b) ulcerated papulonodular lesions covered by necrotic crusts in a patient with LyP; (c, d) ulcerated tumoral lesions in patients with pcALCL.

LyP: Lymphomatoid papulosis; pcALCL: primary cutaneous anaplastic large-cell lymphoma.

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.

Treatment and Treatment Responses

Treatment strategies for LyP included methotrexate, psoralen and ultraviolet A (PUVA) therapy, and topical corticosteroids (TCs). Methotrexate (<20 mg/week) had an overall response rate of 78.5%, while PUVA and TCs showed response rates of 85.8% and 83.3%, respectively. However, relapse rates for all treatments were high. For pcALCL, 2 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 (Tables 2 and 3).

Secondary Malignancies

Secondary lymphomas developed in 7 LyP patients (20.6%), including 4 cases of MF, with 2 of the patients in the early stages and 2 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).

Survival Outcomes

The mean follow-up duration for LyP patients was 52.3 months, with 16 patients alive with disease, 15 patients alive without disease, and 3 deaths (2 from secondary lymphomas, 1 from another cause). The mean follow-up duration 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⁺ LPDs, with generally favorable prognoses but differing in clinical presentation and histopathology [5]. In our study, the male-to-female ratio among LyP cases (1.41) was consistent with prior studies, while the ratio for pcALCL cases (0.8) was lower than expected [6]. The mean age at diagnosis for LyP was 48.4 years, while for pcALCL it was 54.5 years. These findings align with prior reports, although a few pediatric cases were observed in our study, which is unusual for these conditions [6,7,8,9,10,11].

Histologically, type A LyP lesions predominated, which is consistent with other studies [12], and we observed no type B

Table 1. Demographic characteristics and clinical findings of patients with primary cutaneous CD30⁺ lymphoproliferative disorders.

	LyP (n=34)	pcALCL (n=9)	p
Male/female ratio	23/11	4/5	0.257
Mean age at diagnosis, years, mean ± SD	48.4±18.69	54.5±24.23	0.415
Age at diagnosis, years <18 years old, n (%) >60 years old, n (%)	 2 (5.9) 8 (23.5)	 1 (11.1) 4 (44.4)	 0.515 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
Subjective symptoms Pruritus, n (%) Pain, n (%) Asymptomatic, n (%)	 18 (52.9) 2 (5.9) 12 (35.3)	 3 (33.3) 1 (11.1) 3 (33.3)	 0.457 0.515 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; pcALCL: primary cutaneous anaplastic large-cell lymphoma; SD: standard deviation.

Table 2. Treatments and treatment responses in patients with primary cutaneous CD30+ lymphoproliferative disorders.

	Partial remission, n (%)	Complete remission, n (%)	No response, n (%)	Relapse 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 (50)	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)	-	-
Peginterferon alfa-2a (n=4)	2 (50)	2 (50)	-	1 (50)
Systemic steroids (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)

*: Only for patients who achieved complete response; LyP: lymphomatoid papulosis; pcALCL: primary cutaneous anaplastic large-cell lymphoma.

Table 3. Distribution of sequential treatments with responses in patients with lymphomatoid papulosis (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)	-	-

PR: Partial remission; CR: complete remission; NR: no response.

lesions in our cohort. *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 they have been associated with an indolent clinical course in other settings [13,14,15].

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 our cases, though the high relapse rate indicates the need for ongoing management. Phototherapy, and especially PUVA, was effective in our cohort, with relapse rates consistent with the literature [3,16,17,18].

pcALCL treatment often involves radiotherapy or surgery for localized lesions, with chemotherapy and BV used for relapsed or advanced cases [3,19,20,21]. The use of BV in our study showed promising results, particularly in treatment-resistant cases. Relapse after BV was not observed in our cohort during a 3.5-year follow-up period, suggesting its potential as a viable treatment for resistant pcALCL.

The development of secondary malignancies, particularly MF, is a well-established risk in cases of LyP [22,23,24]. In our

study, 20.6% 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+ LPDs with favorable prognosis. Although treatment modalities often lead to remission, the chronic and recurrent nature of LyP and the risk of secondary malignancies necessitate ongoing management. pcALCL patients can benefit from localized treatments including 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.

Ethics

Ethics Committee Approval: Ethical approval (no: 19-1190-17, date: 27.11.2017) was obtained from the Ankara University Faculty of Medicine, Clinical Research Ethics Committee.

Informed Consent: Informed consent was provided by all patients. Patient consent was obtained for the photographs.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ş., A.T.A., İ.K.Y., A.H., I.K., A.K., A.B., B.N.A.; Concept: H.Ş., A.T.A., İ.K.Y., A.H., I.K., A.K., A.B., B.N.A.; Design: H.Ş., A.T.A., İ.K.Y., A.H., I.K., A.K., A.B., B.N.A.; Data Collection or Processing: H.Ş., A.T.A., İ.K.Y., A.H., I.K., A.K., A.B., B.N.A.; Analysis or Interpretation: H.Ş., A.T.A., İ.K.Y., A.H., I.K., A.K., A.B., B.N.A.; Literature Search: H.Ş., A.T.A., İ.K.Y., A.B., B.N.A.; Writing: H.Ş., A.T.A., İ.K.Y., A.B., B.N.A.

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