Original Investigation
Orijinal Araştırma

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Evaluation of clinical and follow-up outcomes in primary cutaneous B-cell lymphomas: A single-center retrospective study from 2006 to 2022

Primer kutanöz B-hücreli lenfomalarda klinik ve takip sonuçlarının değerlendirilmesi: 2006-2022 yılları arası tek merkezli retrospektif çalışma

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Abstract

Background and Design: Primary cutaneous B-cell lymphomas (PCBCLs) have not been well characterized due to their relatively low incidence and heterogeneous clinical features.
Materials and Methods: Data of 29 patients with primary cutaneous marginal zone lymphoma (PCMZL) (n=18), primary cutaneous follicle center B-cell lymphoma (PCFCL) (n=7), and primary cutaneous diffuse large B-cell lymphoma-leg type (PCDLBCL-LT) (n=4) who were followed and treated at Ankara University Faculty of Medicine between 2006 and 2022 were retrospectively evaluated. Clinical characteristics, treatment modalities, and outcomes of all patients were analyzed.
Results: Our study supports the data that there are geographical differences in the distribution of B-cell lymphomas and that PCMZL is predominant in Asian countries compared to Europe. The mean age at the time of diagnosis in the PCDLBCL-LT group was significantly older than the indolent PCBCL group (p=0.022). The lesion size was predominantly less than 2 cm in PCMZL, between 2 and 5 cm in PCFCL, and larger than 5 cm in the PCDLBCL-LT group (p=0.006). While skin-directed treatments were the most common approach in the PCMZL and PCFCL groups, multi-agent chemotherapy was the preferred treatment in the PCDLBCL-LT group (p=0.003 and p=0.001, respectively). No significant correlation was found between age, gender, clinical features of the lesion, cutaneous lymphoma international prognostic index score, stage and treatment modalities, recurrence, and overall survival. The World Health Organization and European Organization for Research and Treatment of Cancer classification of cutaneous lymphoma remains the primary guideline for understanding the clinical behavior and prognostic parameters of this heterogeneous patient group.
Conclusion: Given the relative rarity of these types of lymphoma, our patient collective provides an additional value to the existing literature.
Keywords: Cutaneous lymphoma, B-cell lymphoma, primary cutaneous marginal zone lymphoma, primary cutaneous follicle center B-cell lymphoma, primary cutaneous diffuse large B-cell lymphoma, leg type

Öz

Amaç: Primer kutanöz B-hücreli lenfomalar (PKBHL), nispeten düşük insidansları ve heterojen klinik özellikleri nedeniyle iyi karakterize edilememiştir.
Gereç ve Yöntem: 2006-2022 yılları arasında Ankara Üniversitesi Tıp Fakültesi'nde takip ve tedavi edilen primer kutanöz marjinal zon lenfoma (PKMZL) (n=18), primer kutanöz folikül merkez hücreli lenfoma (PKFMHL) (n=7) ve primer kutanöz diffüz büyük B-hücreli lenfoma-bacak tipi (PKDBBHL-BT) (n=4) olan 29 hastanın verileri retrospektif olarak incelendi. Tüm hastaların klinik özellikleri, tedavi yöntemleri ve sonuçları analiz edildi.
Bulgular: Çalışmamız B-hücreli lenfomaların dağılımında coğrafi farklılıklar olduğu ve PKMZL'nin Avrupa'ya kıyasla Asya ülkelerinde baskın olduğu verisini desteklemektedir. PKDBBHL-BT grubunun tanı anındaki ortalama yaşı, indolent PKBHL grubundan anlamlı olarak daha ileri bulunmuştur (p=0,022). Lezyon boyutu PKMZL'de çoğunlukla 2 cm'den küçük, PKFMHL'de 2-5 cm arasında ve PKDBBHL-BT grubunda 5 cm'den büyük saptanmıştır (p=0,006). PKMZL ve PKFMHL gruplarında çoğunlukla deriye yönelik tedaviler kullanılırken, PKDBBHL-BT grubunda

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çok ajanlı kemoterapi sıklıkla tercih edilmiştir (sırasıyla; p=0,003 ve p=0,001). Yaş, cinsiyet, lezyonun klinik özellikleri, kutanöz lenfoma uluslararası prognostik indeks skoru, evre ve tedavi modaliteleri ile nüks ve genel sağkalım arasında anlamlı bir ilişki saptanmamıştır. Dünya Sağlık Örgütü ve Avrupa Kanser Araştırma ve Tedavi Örgütü kutanöz lenfoma sınıflandırması, bu heterojen hasta grubunda klinik davranışı ve prognostik parametreleri anlamak için halen birincil kılavuz olmaya devam etmektedir.

Sonuç: Bu tür lenfomaların görece nadirliği göz önüne alındığında, hasta serimiz mevcut literatüre ek bir değer katmaktadır.

Anahtar Kelimeler: Kutanöz lenfoma, B-hücreli lenfoma, primer kutanöz marjinal zon lenfoma, primer kutanöz folikül merkez hücreli lenfoma, primer kutanöz diffüz büyük B-hücreli lenfoma, bacak tipi

Introduction

The different types of primary cutaneous B-cell lymphomas (PCBCL) are mature B-cell neoplasms that tend to grow on the skin. They have different biological and clinical features than their nodal counterparts. PCBCL tend to have a more indolent course, with a lower propensity for dissemination, and are generally associated with a more favorable prognosis. PCBCL are less common than cutaneous T-cell lymphomas and account for 20-25% of all cutaneous lymphomas[1,2]. The incidence of CBCL has been increasing and is approximately 4 per million persons in the United States, as per data from the Surveillance, Epidemiology, and End Results registry[3].

Primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center B-cell lymphoma (PCFCL), primary cutaneous diffuse large B-cell lymphoma-leg type (PCDLBCL-LT), and intravascular large B-cell lymphoma (IVLBCL) are examples of PCBCL. The World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) revised its consensus classification in September 2018, incorporating Epstein-Barr virus-positive mucocutaneous ulcer as a newly recognized provisional entity within the PCBCL group. The PCMZL section was also updated, and two different subtypes were defined according to the presence or absence of class-swiched immunoglobulin heavy chains. About 75% of the cases are heavy chain class-switched, meaning they express immunoglobulin G (IgG), IgA, and/or IgD. These cases look a lot like reactive B-cell proliferations, which are also called pseudolymphomas, both in terms of how they look and how they are treated. IgM-positive cases, on the other hand, behave more like MALT lymphomas and may have a worse overall prognosis with a higher risk of spreading outside of the skin[4,5].

Each type of CBCL presents with a distinct clinical manifestation, immunopathology, and requires a tailored management strategy. PCMZL and PCFCL are recognized as indolent lymphomas, while PCDLBCL-LT and IVLBCL have a more aggressive course. The overall survival at 5 years has been 99%, 95%, 72%, and 56% for PCMZL, PCFCL, IVLBCL, and PCDLBCL-LT, respectively[4].

The tumor type, prognosis, localization, size, patient's age, and comorbidities should all be considered when determining the appropriate treatment approach. Conservative skin-directed therapies such as surgical excision, topical and intralesional steroids, or radiotherapy (RT) can manage most patients with indolent lymphoma, but multiagent chemotherapy is typically required for PCDLBCL-LT[6].

The aim of our study was to analyze data to enhance practical understanding of the clinical presentation, management, and treatment outcomes among patients with PCBCL.

Materials and Methods

We conducted a retrospective review of 29 PCBCL patients diagnosed at Ankara University Faculty of Medicine between January 2006 and 2022. Patients were eligible for inclusion if they exhibited no evidence of extracutaneous or distant nodal spread present at the time of diagnosis. The cases were confirmed histologically and immunohistochemically as CBCL by pathologists and were classified according to the WHO-EORTC classification scheme.

The collected data included age at diagnosis, gender, time to diagnosis, clinical features such as size, number, and localization of lesions, laboratory test results, computed tomography (CT) and/or positron emission tomography (PET)/CT imaging findings, bone marrow biopsy results, type of treatment administered, response to treatment, time to relapse or progression, status at last follow-up, and survival outcomes.

The patients were staged using the International Society for Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (ISCL/EORTC) modified tumor-node-metastasis (TNM) staging system for primary cutaneous lymphomas other than mycosis fungoides/Sezary syndrome. We classified solitary lesions as T1 disease, regional skin involvement as T2 disease, and generalized skin lesions as T3 disease. We calculated the cutaneous lymphoma international prognostic index (CLIPi) by taking into account the serum lactate dehydrogenase (LDH) level, lesion morphology, and number of lesions.

The sections were stained with hematoxylin and eosin for routine histopathologic evaluation. Detailed immunophenotypic analysis was performed using a broad panel of monoclonal antibodies, including CD-3, CD-10, CD-20, CD-21, BCL-2, BCL-6, PAX-5, MUM-1, and Ki-67.

The study was approved by the Ankara University Institutional Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki (approval number: İ08-517-22, date: 22.09.2022). The patients in this manuscript have given written informed consent for the publication of their case details, including clinical and dermatoscopic photographs.

Statistical Analysis

The SPSS version 11.5 software was used for data analysis. We used the mean/standard deviation and median (minimum-maximum) for quantitative variables and the number of patients (percentage) for qualitative variables. The Shapiro-Wilk test checked the normality assumption as the first step of the statistical analysis, while the Levene test checked the homogeneity of variance. We used the Analysis of Variance (ANOVA) test to compare the three dependent groups with a normal distribution, and the Kruskal-Wallis test when the assumption did not hold true. If there was a statistically significant difference between the three groups, we applied Bonferroni analysis to identify the difference between the two groups. The Fisher's exact test was used to test the relationship between categorical variables when the sample size assumption (expected value >5) was not met. The Kaplan-Meier method was used for the overall survival curve of the patients. Factors affecting relapse and survival were analyzed by Cox regression analysis. The statistical significance level was taken as 0.05.

Results

The 2018 WHO/EORTC classification classified 29 patients (14 male and 15 female) as follows: 18 had PCMZL (62.1%), 7 had PCFCL (24.1%), and 4 had PCBCL-LT (13.8%). The mean follow-up period for the 29 patients was 7.03 years (range, 1-16). The median age at diagnosis of the patients in the PCDLBCL-LT group was significantly older than the other two groups (p=0.022).

Most patients with PCBCL presented with cutaneous nodules, papules, or plaques involving the trunk (n=10; 34.5%), including 7 with PCMZL, 1 with PCFCL, and 2 with PCDLBCL-LT. After the trunk lesions, face and scalp lesions were the next most common (n=9, 31%; 6 PCMZL, 2 PCFCL, and 1 PCDLBCL-LT), followed by upper extremity (n=8, 27.6%; 4 PCMZL, 4 PCFCL) and lower extremity lesions (n=2, 6.9%; 1 PCMZL, and 1 PCDLBCL-LT).

The lesion size was mostly between 2 and 5 cm in the PCFCL group, less than 2 cm in the PCMZL group, and larger than 5 cm in the PCDLBCL-LT group (p=0,006). While 3 (42.8%) patients in the PCFCL group, 11 (61.1%) patients in the PCMZL group, and 2 (50%) patients in the PCDLBCL-LT group had solitary lesions, the remaining patients had multiple lesions.

The clinical and dermatoscopic features of the patients are illustrated in Figure 1. The histopathological and immunophenotypic characteristics of the PCMZL lesion, PCFCL lesion, and PCDLBCL-LT lesion are presented in Figures 2-4, respectively.

Pruritus was present at diagnosis in 52% of the indolent PCBCL patients, whereas all PCDLBCL-LT patients were asymptomatic.

A bone marrow biopsy was performed in 6 patients in the PCFCL group, 14 patients in the PCMZL group, and all patients in the PCDLBCL-LT group.

The preferred imaging modalities for evaluating systemic involvement were CT and PET/CT.

According to ISCL/EORTC TNM modified staging, all cases were N_0M_0 at presentation, with 16 stage T1 (55.2%), 12 stage T2 (41.4%), and 1 stage T3 (3.4%) disease.

Based on the CLIPi score, 9 (31%) patients were classified as low risk, 16 (55.2%) as intermediate risk, and 4 (13.8%) as high risk.

Patient characteristics and clinical findings are summarized in Table 1.

Surgical excision of the lesion, topical and intralesional corticosteroids (ILCS), systemic interferon-alpha (IFN-α), RT, rituximab (RTX), or multi-agent chemotherapy (RTX, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP), methotrexate, cytarabine, and lenalinomide) were the first-line treatments. Excluding 1 patient who refused treatment, 24 of 28 patients (85.7%) responded completely to the initial treatment, and 4 patients showed a partial response.

Primary treatment modalities according to histopathologic subtype are listed in Table 2. While skin-directed therapies were used more frequently in the PCMZL and PCFCL groups, multi-agent chemotherapy was mostly preferred in the PCDLBCL-LT group (p=0.003 and p=0.001, respectively). All patients in the PCFCL group had a complete response to initial treatment, but one patient had a cutaneous relapse after IFN-α and RTX treatment, and a complete response was achieved with RTX. Another patient in the same group had recurrent skin lesions after RT that completely regressed with RTX.

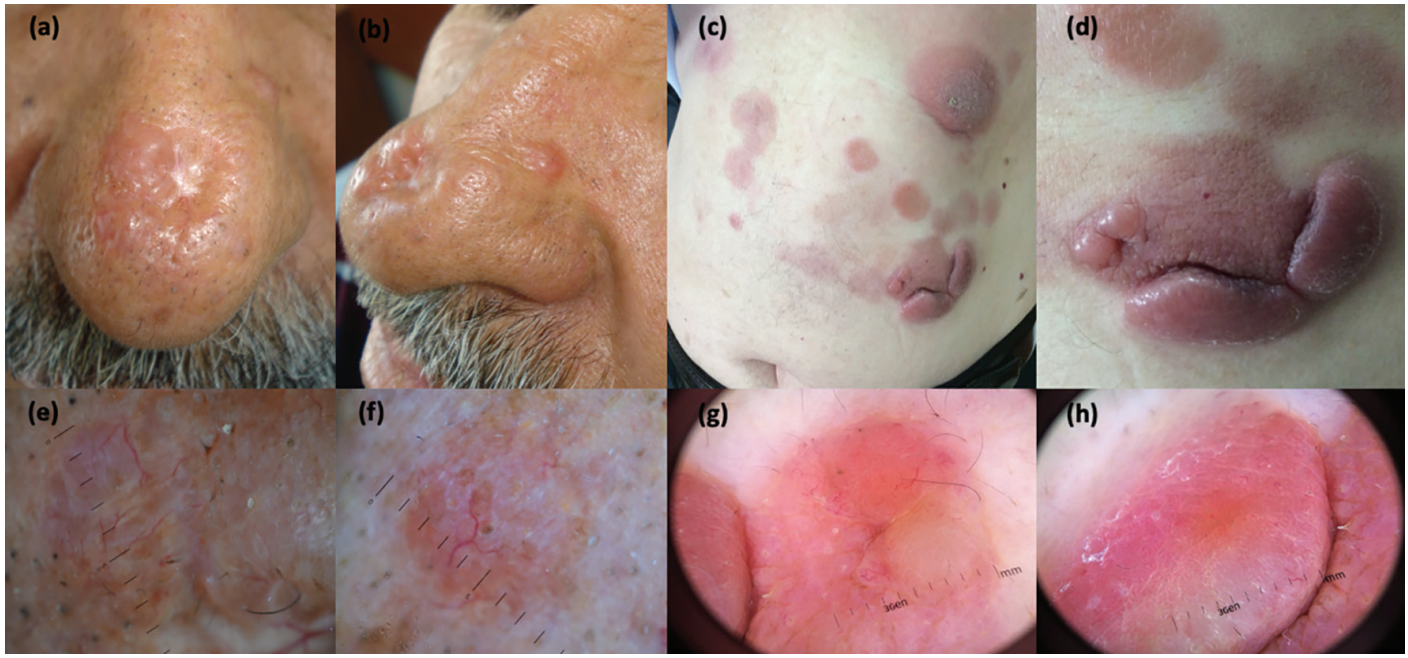

Figure 1. The clinical and dermatoscopic features of the patients. **(a, b)** A patient with PCMZL presented with multiple papulonodular skin-colored lesions on the nose. The depressed portion at the tip was the site of a previous biopsy containing scar tissue. **(c, d)** A patient with primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) presented with disseminated, erythematous, indurated plaques and tumors on the trunk. **(e, f)** Dermatoscopic examination of the PCMZL lesions reveals a salmon-to-orange colored background with numerous fine, irregular-linear vessels and branched vessels that are not present on the skin around the lesion. **(g, h)** Dermatoscopic examination of the PCDLBCL-LT lesions shows a pink-salmon-colored background with fine, irregular-linear vessels, as well as perifollicular yellow-white halos and scales

PCMZL: Primary cutaneous marginal zone lymphoma, PCDLBCL-LT: Primary cutaneous diffuse large B-cell lymphoma, leg type

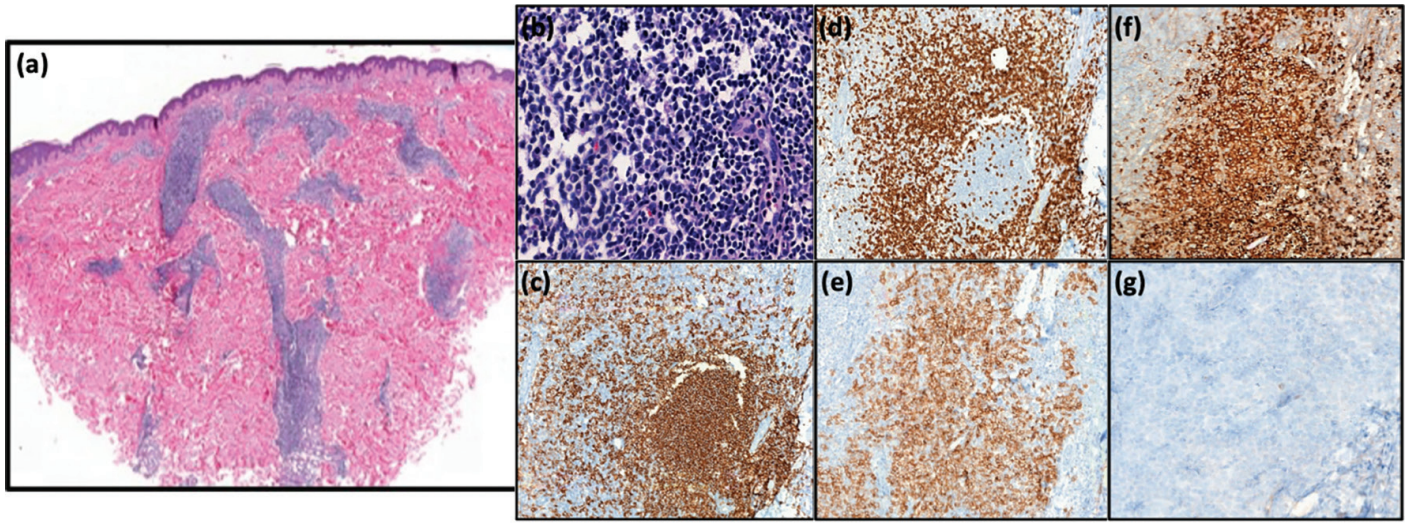

Figure 2. Histopathological and immunophenotypic characteristics of the PCMZL lesion. **(a, b)** Skin biopsy revealed dermal nodular lymphoid infiltration with monotonous, small-medium-sized atypical cells H&E, (x40), (x400). **(c)** The nodular lymphoid infiltration was diffusely positive with CD20-positive B lymphocytes (x200). **(d)** CD3-positive reactive T-lymphocytes were seen scattered in the lymphoid infiltration (x200). **(e-g)** Kappa monotypic plasma cells have been determined, establishing the neoplastic nature of this dermal lymphoid infiltration, CD38 (x200), kappa (x200), and lambda (x200), respectively.

PCMZL: Primary cutaneous marginal zone lymphoma, H&E: Hematoxylin and eosin

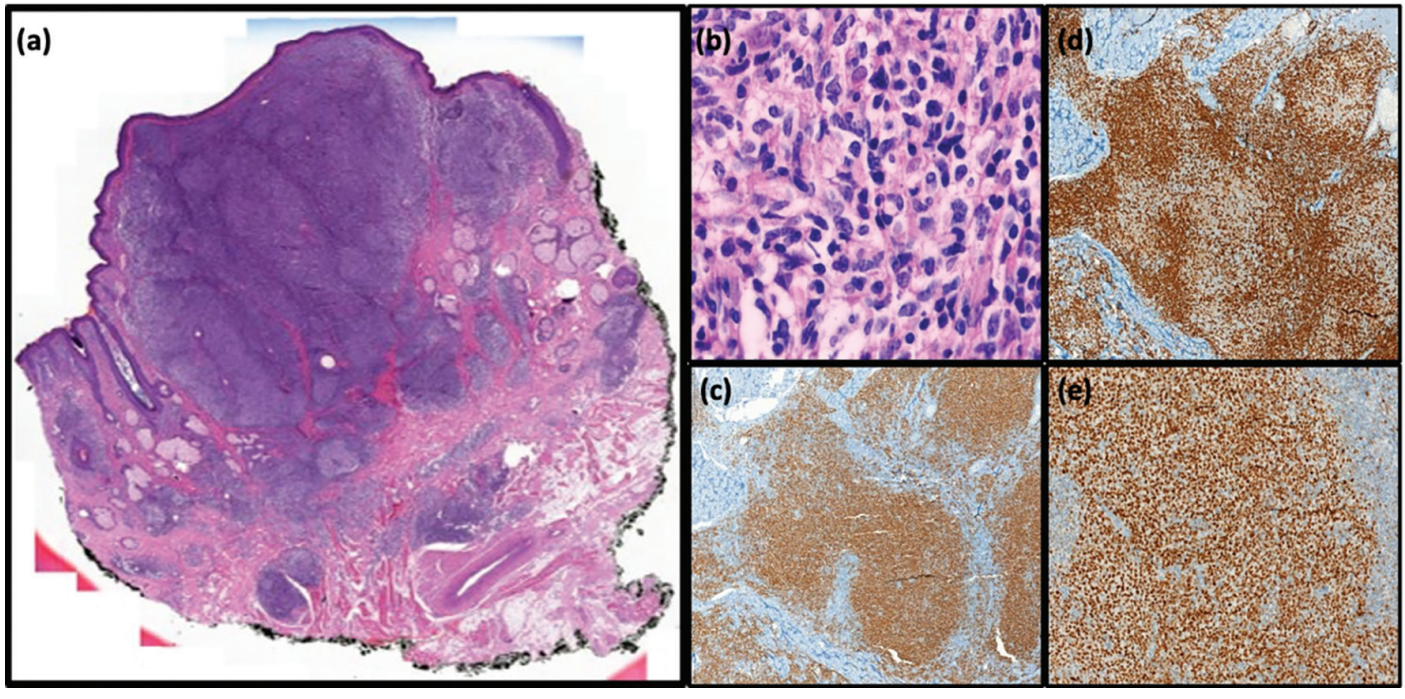

Figure 3. Histopathological and immunophenotypic characteristics of the PCFCL lesion. **(a, b)** The skin biopsy revealed a dermal monotonous nodular lymphoid infiltration, accompanied by small-medium-sized atypical cells, as indicated by H&E (x40) and (x400). **(c)** The nodular lymphoid infiltration was diffusely positive with CD20-positive B lymphocytes (x100). **(d)** CD3-positive reactive T-lymphocytes were accompanying atypical B lymphocytes (x200). **(e)** Atypical lymphocytes were BCL-6 positive, showing the germinal center phenotype (x200)

PCFCL: Primary cutaneous follicle center B-cell lymphoma, H&E: Hematoxylin and eosin, BCL: B-cell lymphoma

Three patients in the PCMZL group achieved a complete cure through re-excision, while six patients (33.3%) experienced cutaneous relapse. One patient developed a recurrence after ILCS, but achieved a complete response with surgical excision. One patient, who developed recurrence after a partial response to ILCS and IFN-α, achieved a complete response with RT. Following a complete response to RT and chemotherapy, one patient developed a relapse and responded completely to RTX.

Three patients (16.6%) in the PCMZL group exhibited progression to diffuse large B-cell lymphoma (DLBCL). Below, we provide a summary

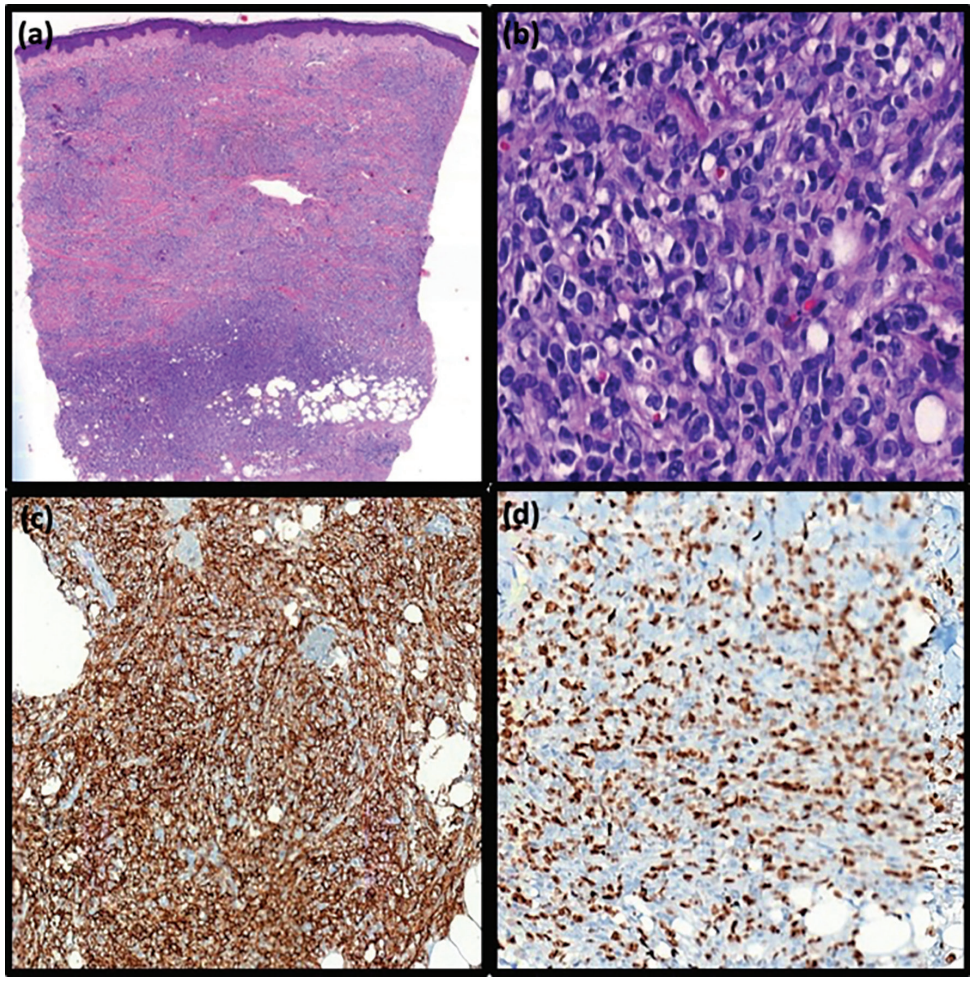

Figure 4. Histopathological and immunophenotypic characteristics of the PCDLBCL-LT lesion. **(a, b)** Skin biopsy showed diffusely infiltrating dermal large, pleomorphic, atypical lymphoid cells H&E, (x40), (x400). **(c)** The lymhoid infiltration was diffusely positive with CD20-positive B lymphocytes (x400). **(d)** Ki-67 showed the high proliferation rate of these atypical lymphocytes (x200)

PCDLBCL-LT: Primary cutaneous diffuse large B-cell lymphoma-leg type, H&E: Hematoxylin and eosin

of the characteristics of patients who progress to DLBCL, taking into account the relatively low prevalence of this condition.

The first patient was a 65-year-old male who presented with a papulonodular lesion on the nose for a period of three years (Figure 1a, b). A skin biopsy of the lesion showed small to medium-sized lymphocytic infiltration in the form of nodules filling the dermis. The immunophenotypic and molecular results were also consistent with the PCMZL. Complete blood count, LDH, and B2-microglobulin levels were within the normal range, but the bone marrow biopsy revealed focal involvement. The patient presented with paraplegia after a two-year period without follow-up or treatment, and a biopsy of the spinal mass revealed progression to DLBCL. He died of lymphoma four years after the initial diagnosis.

The second patient was a 57-year-old female who had been diagnosed with PCMZL two years after presenting with a 2x3 cm itchy plaque on the back. Histopathology revealed diffuse dermal and subepidermal infiltration of atypical B lymphocytes, characterized by necrosis. The immunophenotypic and molecular results align with PCMZL. CT, blood tests, and bone marrow biopsy were normal. After six cycles of RTX, the lesions recurred, and a new skin biopsy showed progression to DLBCL. The patient remains alive, having undergone chemotherapy.

The last patient was a 79-year-old female who was diagnosed with PCMZL six months after presenting with an asymptomatic 4x5 cm nodule on the back. The pathological report revealed morphological, immunophenotypic, and molecular findings consistent with PCMZL. CT, blood tests, and bone marrow biopsy were normal. We treated the lesion with total surgical excision. One year later, the patient presented with nasal obstruction, and a biopsy of the nasal sinus mass was compatible with progression to DLBCL. Consequently, treatment with zilovertamab vedotin and R-CHP (rituximab-cyclophosphamide, doxorubicin, prednisone) was initiated, but the patient developed pulmonary thromboembolism. She is currently receiving treatment with tafasitamab in combination with lenalidomide, and she is responding well.

In the PCDLBCL-LT group, all patients received multi-agent chemotherapy, and 1 patient received concurrent RT.

At the last visit, all patients in the PCFCL group were alive. One patient (5.5%) in the PCMZL group died because of progression to DLBCL. In the PCDLBCL-LT group, two (50%) patients with a partial response to chemotherapy died of lymphoma. The mean survival time was found to be 14.50±1.13 months. However, due to the small number of fatalities,

Table 1. Patient characteristics and clinical manifestations by PCBCL subtype

Characteristic		PCFCL, (n=7)	PCMZL, (n=18)	PCDLBCL-LT, (n=4)	p
Age, years	Mean ± SD	59.14±14.66	55.78±16.64	78.25±8.34	**0.046***
	Median (min.-max.)	58.00 (35.00-76.00)	55.50 (23.00-81.00)	79.50 (68.00-86.00)	
Gender, n (%)	Female	6 (85.7)	7 (38.9)	2 (50.0)	0.150
	Male	1 (14.3)	11 (61.1)	2 (50.0)	
Age at diagnosis	Mean ± SD	49.14±11.77	49.33±16.85	73.50±9.47	**0.022***
	Median (min-max)	49.00 (31.00-67.00)	50.50 (17.00-77.00)	74.50 (61.00-84.00)	
Time to diagnosis (mo)	Mean ± SD	29.43±20.16	16.11±20.06	6.75±3.77	0.130
	Median (min.-max.)	24.00 (2.00-60.00)	7.00 (2.00-84.00)	6.00 (3.00-12.00)	
Mean follow-up (years)		10	6.38	4.75	
Localization, n (%)	Face	2 (28.6)	5 (27.8)	1 (25.0)	0.511
	Scalp	0 (0.0)	1 (5.6)	0 (0.0)	
	Trunk	1 (14.3)	7 (38.8)	2 (50.0)	
	Lower extremity	0 (0.0)	1 (5.6)	1 (25.0)	
	Upper extremity	4 (57.1)	4 (22.2)	0 (0.0)	
Lesion character, n (%)	Nodule	5 (71.4)	6 (33.3)	2 (50.0)	0.234
	Other	2 (28.6)	12 (66.7)	2 (50.0)	
Lesion size (cm), n (%)	<2	2 (28.5)	11 (61.1)	0 (0.0)	**0.006***
	2-5	5 (71.4)	6 (33.3)	1 (25)	
	>5	0 (0.0)	1 (5.5)	3 (75)	
Lesion number	Mean ± SD	2.71±1.89	2.11±1.60	3.00±3.37	0.691
	Median (min.-max.)	2.00 (1.00-5.00)	1.00 (1.00-5.00)	1.50 (1.00-8.00)	
Pruritus, n (%)	Yes	5 (71.4)	8 (44.4)	0 (0.0)	0.104
	No	2 (28.6)	10 (55.6)	4 (100)	
Stage, n (%)	T1	3 (28.6)	11 (61.1)	2 (50)	0.535
	T2	3 (42.8)	7 (38.9)	2 (50)	
	T3	1 (14.3)	0 (0.0)	0 (0.0)	
CLIPi score	0 (low)	1 (14.3)	7 (38.9)	1 (25)	0.420
	1 (intermediate)	4 (57.1)	10 (55.6)	2 (50)	
	2 and 3 (high)	2 (28.6)	1 (5.5)	1 (25)	
Initial treatment response, n (%)	Partial	0 (0)	2 (11.8)	2 (50)	0.123
	Complete	7 (100)	15 (88.2)	2 (50)	
Relapse, n (%)	Yes	2 (28.6)	9 (50)	0 (0)	0.161
	No	5 (71.4)	9 (50)	4 (100)	
Time to relapse (mo)		16	41.7	0	
Status at last follow-up	Alive	7 (100)	16 (88.9)	2 (50)	0.126
	Died of lymphoma	0 (0)	1 (5.5)	2 (50)	
	Died of other cause	0 (0)	1 (5.5)	0 (0)	
Survival	Overall survival	100	88.9	50	
	Disease-specific survival	100	94.4	50	

SD: Standard deviation, Min.: Minimum, Max.: Maximum, PCBCL: Primary cutaneous B-cell lymphomas, PCFCL: Primary cutaneous follicle center B-cell lymphoma, PCDLBCL-LT: Primary cutaneous diffuse large B-cell lymphoma-leg type, CLIPi: Cutaneous lymphoma international prognostic index

the median survival time was not determined. The overall survival curve is shown in Figure 5.

We assessed factors affecting survival and relapse through Cox regression analysis, but found no variable to be a significant risk factor.

We found no significant association between age, gender, lesion character, size, number, CLIPi score, stage, and treatment modalities with overall survival and relapse (Table 3, 4).

Discussion

PCBCLs are rare non-Hodgkin lymphomas that arise in the skin and have subtypes with heterogeneous clinical features. The WHO-EORTC 2018 update lists the following primary cutaneous lymphomas in order of frequency: PCFCL (12%), PCMZL (9%), PCDLBCL-LT (4%), IVLBCL (less than 1%), and EBV+ mucocutaneous ulcer (less than 1%)[4]. Wu et al.[7] found geographical differences in the distribution of B-cell lymphomas between Asian and European countries. In our study, PCMZL cases were more common than PCFCL, similar to other Asian countries. It is thought that the higher rate of marginal zone lymphoma in Asian countries may be because of more common environmental factors like viral and bacterial infections. This is because MZL is linked to chronic antigenic stimulation of B-cells.

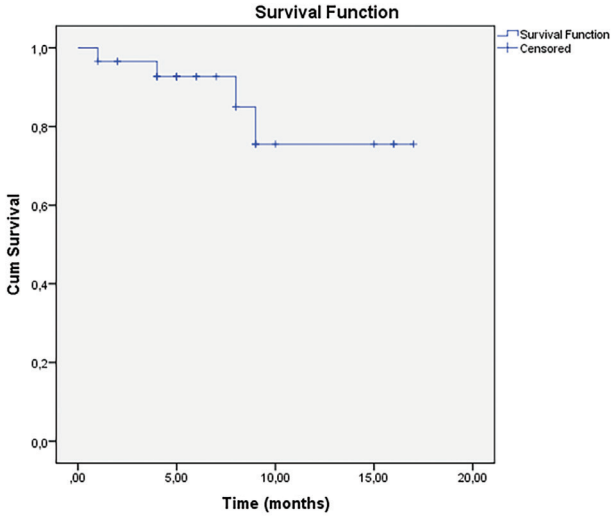

Figure 5. Overall survival curve of the study

Males are more likely to have these subtypes than females, with the median age at diagnosis for PCMZL being 55 and for PCFCL being 60 years. PCDLBCL-LT primarily affects elderly patients, with a median age of diagnosis ranging from 70 to 82 years and a female predominance[8]. Similarly, our findings revealed a significantly older mean age at diagnosis among PCDLBCL-LT patients compared to the other two groups. However, we observed a female predominance in the PCFCL group, while the number of male and female patients was equal in the PCDLBCL-LT group.

The tumor microenvironment is thought to play a part in the skin site tropism seen in CBCLs, and studies have shown that survival rates vary depending on where the lesion is located. A population-based study reported lesions localizing to the upper extremity (31%), trunk (27%), and face (27%) in PCMZL, head/neck (37%), face (33%), and trunk (19%) in PCFCL, and lower extremity (29%), head/neck (22%), and face (22% in PCDLBCL-LT, respectively. The authors agree that PCDLBCL-LT usually shows up on the leg, but they say that when body surface

Table 2. Primary treatment modalities according to histopathologic subtype

Primary treatment modalities	PCFCL, (n=7)	PCMZL, (n=18)	PCDLBCL-LT, (n=4)	p
Skin-directed therapy	1 (14.3)	13 (72.2)	0 (0)	**0.003***
IFN-α	2 (28.6)	1 (5.6)	0 (0)	0.178
RT	2 (28.6)	2 (11.1)	1 (25)	0.483
Rituximab	2 (28.6)	2 (11.1)	0 (0)	0.442
Chemotherapy	1 (14.3)	1 (5.6)	4 (100)	**0.001***

A p-value of <0.05 was considered statistically significant. PCFCL: Primary cutaneous follicle center B-cell lymphoma, PCMZL: Primary cutaneous marginal zone lymphoma, PCDLBCL-LT: Primary cutaneous diffuse large B-cell lymphoma-leg type, IFN-α: Interferon-alpha, RT: Radiotherapy

Table 3. Cox regression analysis of independent prognostic factors for overall survival

Factor (reference)		p	HR	CI for HR
Age		0.081	1.109	0.987-1.245
Gender (female)	Male	0.467	2.328	0.239-22.714
Lesion (nodule)	Other	0.341	52.068	0.015-177901.649
Biggest lesion size		0.774	0.938	0.604-1.455
Lesion number		0.208	0.442	0.124-1.577
CLIPi score (0)	1	0.079	0.124	0.012-1.278
	2	0.991	-	-
	3	0.997	-	-
Stage (T1)	T2/T3	0.309	0.303	0.030-3.018
Skin directed therapy (yes)	No	0.338	54.657	0.015-196866.796
IFN (yes)	No	0.527	31.559	0.001-1387392.790
RT (yes)	No	0.546	0.496	0.051-4.820
Rituximab (yes)	No	0.566	27.183	0.001-2121819.049
CT (yes)	No	0.238	0.301	0.041-2.206

HR: Hazard ratio, CI: Confidence interval, CLIPi: Cutaneous lymphoma international prognostic index, IFN: Interferon, RT: Radiotherapy, CT: Computed tomography

Table 4. Cox regression analysis of independent prognostic factors for relapse

Factor (reference)		p	HR	CI for HR
Age (<60)	60≤	0.810	0.001	0.000-1.5E+22
Gender (female)	Male	1,000	1,000	0.136-7.328
Lesion (nodule)	Other	0.104	3138.375	0.191-51444737.49
Biggest lesion size (<2)	2-5	0.615	3960443.969	0.000-1.94E+32
	>5	0.942	76,185	0.000-4.06E+52
Lesion number (1)	1<	0.315	0.026	0.000-31.66
CLIPi score (0 & 1)	2 & 3	-	-	-
Stage (T1)	T2/T3	-	-	-
Skin directed therapy (yes)	No	0.957	4,982	0.000-1.11E+26
IFN (yes)	No	0.883	6287.136	0.000-1.94E+54
RT (yes)	No	0.816	0.001	0.000-4.46E+22
Rituximab (yes)	No	-	-	-
CT (yes)	No	0.077	14631339714.456	0.082-2.62E+21

HR: Hazard ratio, CI: Confidence interval, CLIPi: Cutaneous lymphoma international prognostic index, IFN: Interferon, RT: Radiotherapy, CT: Computed tomography

area is taken into account, PCDLBCL-LT really does tend to show up on the face and head/neck rather than the leg[9]. Our findings diverged from the literature, as we observed that lesions were most frequently localized in the upper extremities among PCFCL patients and in the trunk among PCMZL and PCDLBCL-LT patients.

PCBCL lesions are usually asymptomatic, but local symptoms such as pruritus or pain may be seen. Olszewska-Szopa et al.[10] reported that approximately half of the indolent PCBCL patients had local symptoms at the time of diagnosis. In our study, pruritus was present in 52% of the patients in the indolent group.

Due to the clinical and pathological heterogeneity of cutaneous lymphomas, the TNM staging system provides solely anatomical information regarding the extent of disease and offers limited prognostic value in CBCL[11]. The WHO-EORTC cutaneous lymphoma classification is the most important tool for figuring out how these different groups of patients will behave and what their prognostic factors are[4]. The International Extranodal Lymphoma Study Group identified three independent prognostic factors (elevated LDH level, more than two skin lesions, and nodular lesions) among patients with indolent PCBCL. These factors were combined to form the CLIPi score. Patients were then stratified into three risk groups: Score 0, low risk; score 1, intermediate risk; score 2 and 3, high risk, with a 5-year progression-free survival of 91%, 64%, and 48%, respectively. Because the vast majority of relapses were confined to the skin, the CLIPi cannot be used to stratify patients' overall survival risk[12]. We did not find any association between survival and relapse and clinical characteristics such as stage or CLIPi score in our patients. We support adding extra prognostic information, like biological or molecular markers, to the TNM classification so that a full picture of the prognosis and choice of treatment can be made.

Cutaneous relapse after treatment is very frequent in PCMZL and occurs in approximately 50% of patients. It is also common in PCFCL (30%) and is usually adjacent to previous areas of involvement[1]. Transformation of PCMZL and PCFCL into DLBCL or another type of high-grade lymphoma is possible and has a negative impact on prognosis[13]. Similarly, cutaneous relapses were common in our patient group. A patient with PCMZL who progressed to DLBCL was the only one to die in the indolent lymphoma group.

The management of patients with CBCL requires a multidisciplinary approach involving dermatologists, pathologists, hemato-oncologists, and radiation oncologists. Treatment recommendations are mostly based on small retrospective studies because there are no randomized controlled trials available. Indolent PCBCL patients with solitary or relatively few skin lesions may be effectively managed with surgical excision, ILCS, and local radiation therapy, while single-agent RTX may be employed for patients with more extensive skin involvement. However, a direct comparison of local therapies with intravenous RTX has not yet been performed. Porkert et al.[14] treated 26 patients with indolent PCBCL with 4 cycles of RTX 375 mg/m^2 once weekly and found that it appears to be a safe treatment option both for multifocal or recurrent disease and in patients with single lesions in distinct anatomical locations where local therapy is less favorable. IFN-α has been utilized intralesionally or systemically in indolent CBCL with favorable response rates and tolerability, despite lacking FDA approval for this indication[15].

Treatment of patients with PCDLBCL-LT is similar to systemic DLBCL, and chemotherapy with or without radiation therapy is considered standard front-line therapy. RT alone remains a good palliative option for patients with comorbidities and localized disease. Lenalidomide, ibrutinib, and immune checkpoint inhibitors might offer a viable therapeutic option in cases of refractory PCDLBCL-LT[5].

Study Limitations

Limitations of the study include its retrospective design, small sample size, and lack of a standardized treatment approach. Nevertheless, considering the relative rarity of these lymphoma types, our patient cohort of 29 cases contributes additional value to the existing knowledge.

Conclusion

Our findings suggest geographical disparities in the distribution of B-cell lymphomas, with PCMZL predominating in Asian countries compared to European regions. Our study's clinical features of PCBCL generally

align with existing literature, albeit with notable differences such as a higher predilection for upper extremities and trunk involvement, as well as a female predominance in PCFCL cases. We observed frequent relapses despite all treatment modalities yielding high overall response rates. We recommend the integration of additional prognostic factors, including biological and molecular markers, alongside TNM staging to better predict survival and relapse. Excellent long-term survival underscores the indolent nature of PCFCL and PCMZL, contrasting with the more aggressive course of PCDLBCL-LT.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University Institutional Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki (approval number: İ08-517-22, date: 22.09.2022).

Informed Consent: The patients in this manuscript have given written informed consent for the publication of their case details, including clinical and dermatoscopic photographs.

Authorship Contributions

Concept: H.Ş., H.M.E.M., D.D.K., B.N.A., Design: H.Ş., H.M.E.M., D.D.K., B.N.A., Data Collection or Processing: H.M.E.M., D.D.K., I.K., A.O.H., A.K., Analysis or Interpretation: H.Ş., H.M.E.M., B.N.A., Literature Search: H.M.E.M., Writing: H.M.E.M., B.N.A.

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