A rare case of primary cutaneous follicle center lymphoma presenting as facial nodules

Dinar Chieko Triesayuningtyas, MD [1,2]
Menul Ayu Umborowati, MD [1,2*]
Bagus Haryo Kusumaputra, MD [1,2]
Maylita Sari, MD [1,2]
Irmadita Citrashanty, MD [1,2]
Diah Mira Indramaya, MD [1,2]
Muhammad Yulianto Listiawan, MD, PhD [1,2]
Sawitri Sawitri, MD [1,2]

1. Department of Dermatology Venereology and Aesthetic, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
2. Department of Dermatology Venereology and Aesthetic, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Corresponding author:
Menul Ayu Umborowati, MD,
Department of Dermatology Venereology and Aesthetic, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
Postal code: 60132
Email: menulayu@gmail.com

Received: 24 May 2025
Accepted: 23 August 2025

Primary Cutaneous Follicle Center Lymphoma (PCFCL) is a rare subtype of Non-Hodgkin Lymphoma that primarily affects the skin without systemic involvement. It often mimic other dermatologic conditions, leading to diagnostic challenges. We report the case of a 54-year-old male who presented with multiple facial lumps persisting for 1.5 years, progressively increasing in size and number, particularly on the cheeks. The lesions were pruritic and worsened with sweating and fish consumption, but there was no associated pain or numbness. Initial evaluation excluded leprosy based on the absence of clinical signs and negative acid-fast bacilli on skin slit smear. Treatment with topical corticosteroids and antihistamines was ineffective. Histopathological examination initially suggested granuloma faciale; however, immunohistochemistry confirmed the diagnosis of PCFCL, demonstrating positivity for CD20, Ki67 (50%), CD21, CD10, CD23, and BCL-6, and negativity for BCL-2 and CD5. The patient was referred for chemotherapy and completed four of six planned cycles but discontinued treatment due to adverse effects. Notably, clinical improvement was observed after three sessions, and no signs of relapse were detected after six months after therapy discontinuation. This case underscores the importance of considering PCFCL in the differential diagnosis of persistent facial lesions and highlights the critical role of histopathological and immunohistochemical analyses in establishing an accurate diagnosis. Early recognition and a multidisciplinary approach involving dermatologists, pathologists, and oncologists are essential for effective management. Patient adherence and close follow-up also significantly contribute to favorable long-term outcomes in PCFCL.

Keywords: B-cell, immunohistochemistry, lymphoma, non-Hodgkin

Iran J Dermatol 2025; 28: 299-305

DOI: 10.22034/ijd.2025.523604.2028

INTRODUCTION

Primary cutaneous lymphomas are non-Hodgkin lymphomas (NHL) that originate from hematodermic precursor neoplasms (plasmacytoid dendritic cell neoplasms) and malignant clonal transformation of resident or skin-homing T or B cells [1]. Primary cutaneous lymphomas consist of several types, including Sézary syndrome, mycosis fungoides, and primary cutaneous CD30+ lymphoma, which are the subtypes of cutaneous lymphomas. Additionally,

Please cite this article as: Triesayuningtyas DC, Umborowati MA, Kusumaputra BH, Sari M, Citrashanty I, Indramaya DM, Listiawan MY, Sawitri S. A rare case of primary cutaneous follicle center lymphoma presenting as facial nodules. Iran J Dermatol. 2025; 28(4): 299-305.

primary cutaneous follicle center lymphoma (PCFCL), primary cutaneous marginal zone lymphoma (PCMZL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), and intravascular cutaneous B-cell lymphoma represent the most common B-cell lymphomas. Approximately 90% of all cutaneous lymphomas fall into these seven categories [1]. Primary cutaneous B-cell lymphomas (CBCLs) account for 20% to 25% of primary cutaneous lymphomas. The most frequent CBCL is PCFCL, comprising 34.6% to 49.3% of CBCL cases [2]. Epidemiological data on CBCL and PCFCL in Indonesia are limited. however, the Indonesian Ministry of Health reported a lymphoma prevalence of 0.06% in 2013 [3]. A study of NHL patients at the National Referral Hospital in Indonesia found that B-cell lymphomas accounted for 90.6% of cases, with diffuse large B-cell lymphoma (DLBCL) being the most common subtype (68.8%) [4].

Primary CBCLs are uncommon but critical diagnostic entities in dermatology that require precise histopathologic diagnosis and comprehensive evaluation to rule out systemic involvement [5]. The prognosis, immunophenotyping, histology, and clinical presentation of cutaneous lymphomas vary significantly. The indolent subtypes include PCMZL and PCFCL whereas the PCDLBCL-LT exhibits intermediate to aggressive clinical behavior [1]. Multidisciplinary teams- comprising dermatologists, dermatopathologists, pathologists, hemato-oncologists, as well as diagnostic and radiation oncologists-are ideally suited to manage patients with all types of cutaneous lymphoma [2]. This study presents the diagnostic challenge of a 54-year-old man with PCFCL on the face. The patient provided formal consent authorizing the use of his medical information and photographs for publication.

CASE PRESENTATION

A 54-year-old man presented with multiple lumps on his face that had developed over the past 1.5 years. The lesions initially appeared as small nodules on his cheeks but gradually increased in both size and number. The patient reported occasional itching of the lumps, particularly when sweating or after eating fish, which prompted him to scratch the affected areas. He denied any numbness or pain. There were no systemic symptoms such as fever, respiratory infections, or joint pain. He also reported no family history of similar conditions, leprosy, cancer, or autoimmune diseases.

The patient had previously visited several healthcare providers. At the local health center, he was treated with anti-itch medications and topical corticosteroids; however, his condition did not improve. He was later referred to Sidoarjo Regional Hospital, where an initial suspicion of leprosy prompted further evaluations. A skin slit smear test was performed, which was negative for acid-fast bacilli. He was then referred to Dr. Soetomo General Academic Hospital for further investigation. The patient was examined

Figure 1. Clinical presentation on the first visit revealed multiple erythematous nodules on the patient's face.

in the leprosy division, but leprosy was ruled out based on the absence of clinical signs and a negative acid-fast bacillli result from the skin slit smear.

Based on the physical examination shown in Figure 1, multiple well-demarcated erythematous nodules were observed on the face. The nodules were soft to firm in consistency, immobile, and non-tender, with diameters ranging from 1 to 3 cm. There was no tenderness, pus, ulceration, or lymphadenopathy. No lesions were present on the other parts of the body. The differential diagnoses included granuloma faciale, sarcoidosis, cutaneous lymphoma, discoid lupus erythematosus, and erythema elevatum diutinum. A skin biopsy was performed using a 4 mm punch on one of the lesions. Initial histopathological findings suggested granuloma faciale (Figure 2); however, immunohistochemistry (IHC) was recommended by the pathologist for confirmation.

Immunohistochemistry revealed positive staining for CD20, with a Ki67 proliferation index of 50%. The CD3 was also positive but exhibited a normal pattern. These findings indicate that the IHC did not support a diagnosis of granuloma faciale. The pathologist recommended further IHC analysis to rule out the differential diagnoses,including reactive follicular hyperplasia (RFH) and PCFCL.

The histopathology and IHC analysis process was quite lengthy, requiring a total duration of two months in this case. While awaiting the completion of the analysis results, the patient was treated for granuloma faciale with desoximethasone 0.25% cream applied twice daily to the facial lesions. Symptomatic therapy included cetirizine 10mg once daily for pruritus and a moisturizer cream applied twice daily. additionally, natrium fusidate 2% cream was administered twice daily to the wound resulting from the punch biopsy. The lumps showed no improvement throughout the course of therapy.

The second IHC examination revealed positive results for CD21, CD10, CD23, and BCL-6, confirming the diagnosis of PCFCL. The absence of BCL-2 and CD5 expression ruled out more aggressive lymphomas. The IHC results are presented in Figure 3. A second review of the histopathological features also supported the diagnosis of PCFCL. The patient was referred to the Oncology-Internal Medicine Department for systemic treatment.

Blood tests showed normal kidney and liver function. There were no comorbidities such as HIV, hepatitis B, and hepatitis C. radiological examinations were within normal limits, and no metastatic lesions were detected in the lungs and bones. The patient was also referred to Cardiology for hypertension management, and Coronary CT Angiography (CCTA) was performed for screening purposes. The CCTA revealed minimal, non-obstructive coronary artery disease. The patient was also assessed for suspected ischemic cardiomyopathy, and due to a high-risk cardiac condition, the standard CHOP regimen (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) was deemed unsafe. Consequently, an alternative regimen, CEOP (Cyclophosphamide,

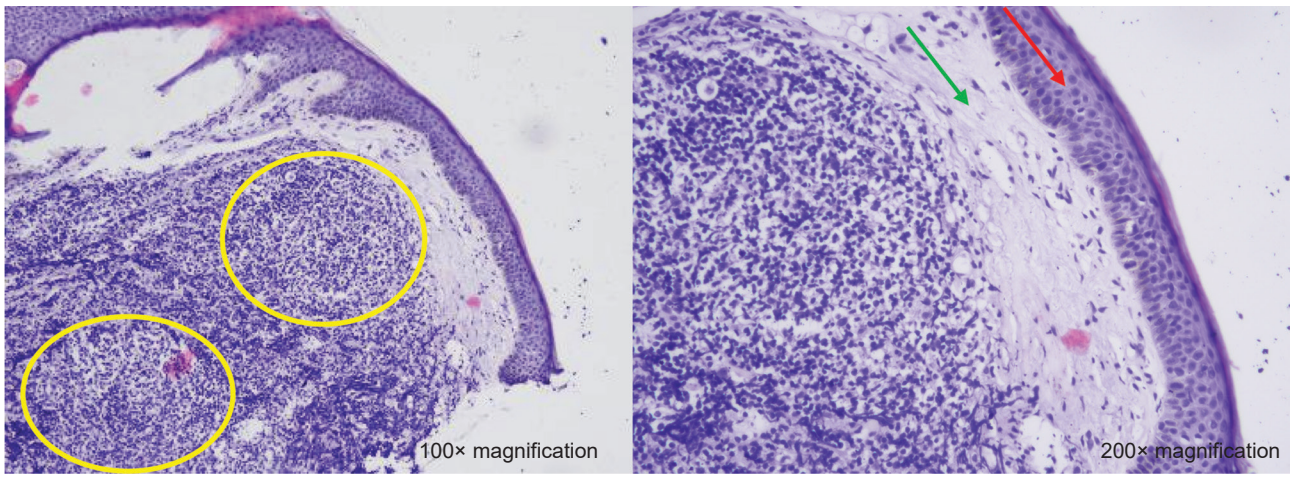

Figure 2. Histopathological analysis revealed epidermal atrophy, and shortened rete ridges (red arrow), with a grenz zone beneath the epidermis (green arrow). A dense infiltrate of lymphocytes was observed extending from the superficial to the deep dermis, exhibiting both follicular lymphoid (yellow circle) and diffuse growth patterns.

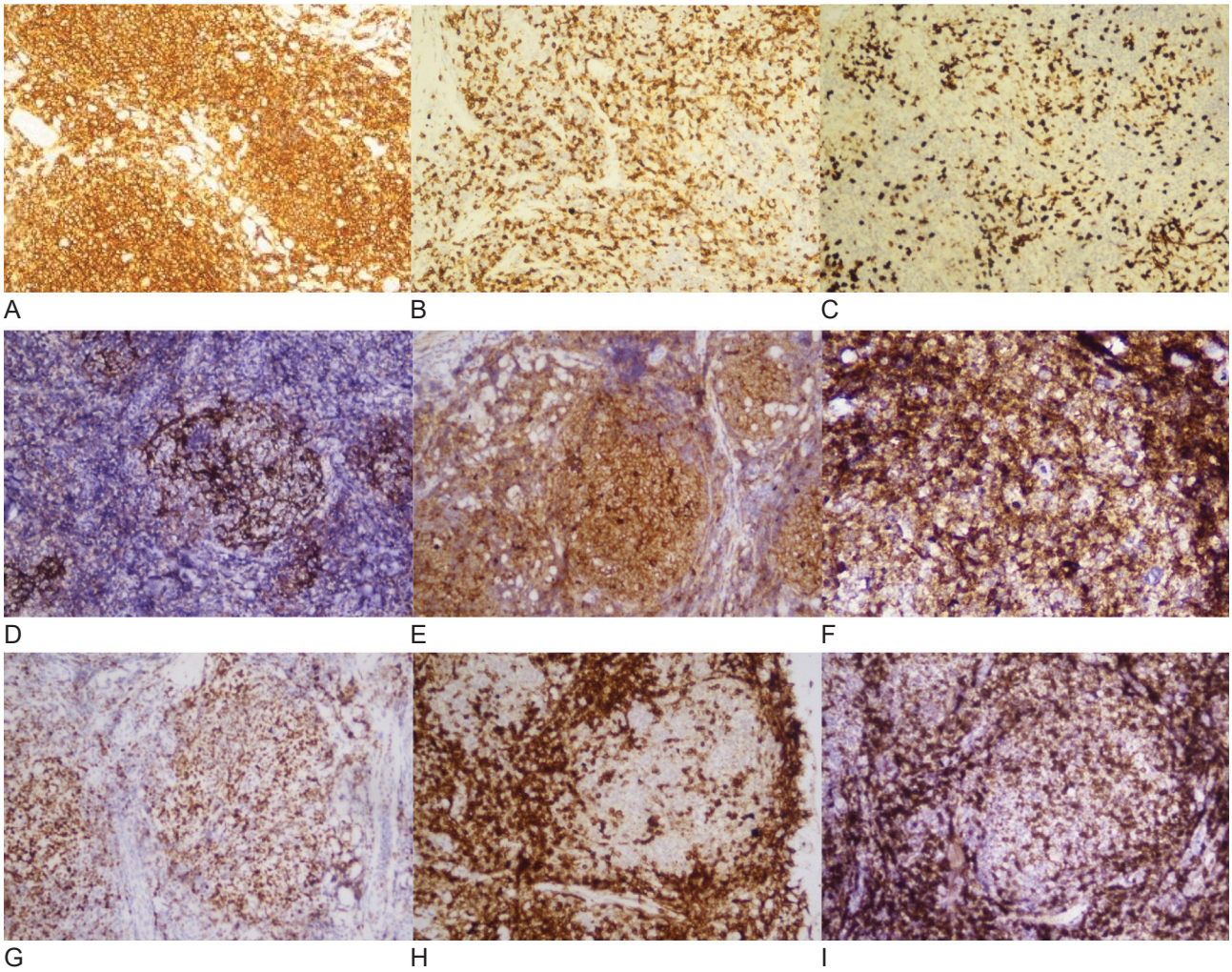

Figure 3. Immunohistochemistry examination revealed the following: (A) CD20 positivity forming a nodular pattern, including some cells outside the follicles; (B) CD3 positivity with a normal distribution pattern, (C) Ki67 showing a 50% proliferation index, (D) CD21 positivity in partially disrupted follicular dendritic cell cytoplasm, (E) CD10 positivity on the tumor cell membrane; (F) CD23 positivity on the tumor cell membrane; (G) BCL-6 positivity in the nuclei of B lymphocytes with a nodular pattern; (H) BCL-2 negativity in the tumor cell nuclei; and (I) CD5 negativity on the tumor cell membrane. All images were captured at 200x magnification.

Etoposide, Vincristine, and Prednisone), was initiated. The patient completed four out of six planned chemotherapy cycles but discontinued the treatment due to significant side effects that temporarily impaired his ability to work, including nausea, fatigue, and weakness on both legs. Despite this, clinical improvement was observed after three chemotherapy sessions, with a reduction in the size and number of lesions. Six months after discontinuing therapy, the patient remained free of relapse, with no new lesions detected.

DISCUSSION

PCFCL is the most common subtype of CBCL which primarily affects the skin and is characterized by the clonal proliferation of centrocytes and centroblasts [1,2]. The current WHO classification recognizes three main types of CBCLs: PCFCL, PCMZL, and PCDLBCL-LT [6,7].

Recent research has advanced the understanding of the pathogenesis of CBCL, despite the rarity of its subtypes. A key finding is the role of aberrant somatic hypermutation, in which enzyme activation-induced deaminase activity leads to mutations in oncogene-containing regions, contributing to lymphomagenesis. Genetic studies have revealed distinct molecular differences among CBCL subtypes: PCFCL exhibits a germinal center B-cell profile, whereas PCDLBCL-LT aligns with an activated B-cell profile. Prognostic differences are associated with apoptosis-related gene

expression, with PCFCL favoring an anti-tumoral immune response, whereas PCDLBCL-LT activates apoptotic pathways [1].

The development of CBCL has been associated with several risk factors, including chronic antigenic stimulation and infections caused by viruses such as hepatitis C, human herpesvirus (HHV), and Epstein-Barr virus. These infectious agents may contribute to lymphomagenesis by inducing prolonged immune activation and genetic alterations in B-cells. In PCMZL, bacterial infections such as *Helicobacter pylori* and *Borrelia burgdorferi* have also been implicated, potentially promoting lymphoma development through persistent immune stimulation. However, studies investigating these associations have produced contradictory results, suggesting that while infections and chronic inflammation may play a role, other genetic and environmental factors likely contribute to CBCL pathogenesis [1,5]. The patient in this study had no history of the aforementioned infections, as determined through clinical history and supporting examinations.

PCFCL primarily affects middle-aged and older adults, with a median age at diagnosis of approximately 58 years. Epidemiological data indicate a male predominance, with adult males being nearly twice as likely to develop the disease compared to females [1,5,8]. This aligns with the presented case of a 54-year-old man, which falls within the expected age range and supports the observed gender distribution in PCFCL. Although individual cases may vary, these trends provide valuable insight into the typical demographic profile of PCFCL patients.

The PCFCL subtype often presents as solitary or grouped, firm, painless, erythematous plaques or tumors. PCFCL is typically found on the head and trunk andrarely on the leg [1]. Its clinical presentation can be mistaken for other dermatologic conditions such as granuloma faciale, sarcoidosis, or leprosy, which was initially suspected in this case. The diagnosis of CBCL may be clinically suspected based on morphology, location, and history; however the definitive diagnosis depends on histopathology. Essential components of the histopathologic diagnosis of CBCL include an adequate biopsy (punch, incisional, or excisional) performed by dermatologist, an appropriate immunophenotyping panel (CD3, CD20, CD10, BCL-2, BCL-6, IRF4/MUM1, CD21) ordered by the pathologist and a review by a dermatopathologist with expertise in CBCL. Additional examinations can be useful, such as CD23, IgM, IgG, IgA and IgD for suspected PCMZL, as well as Ki67, EBER, IgM, IgD, FOXP1, and MYC for suspected or to rule out PCDLBCL-LT [5].

Histopathological examination of PCFCL typically reveals a dense lymphoid infiltrate in the dermis with a follicular growth pattern, separated from the epidermis by a grenz zone [9]. In the presented case, the histological findings align with these characteristics, showing epidermal atrophy and shortened rete ridges, with a well-defined Grenz zone beneath the epidermis. Additionally, the presence of a dense lymphocytic infiltrate extending from the superficial to the deep dermis, exhibiting both follicular lymphoid and diffuse growth patterns, is consistent with PCFCL histopathology. These features help differentiate PCFCL from other inflammatory dermatoses. IHC is critical for distinguishing PCFCL from other cutaneous lymphomas and secondary skin involvement by a systemic lymphoma [1,10]. In this case, positive markers such as CD20, CD10, CD21, and BCL-6, along with a Ki67 proliferation index of 50%, were consistent with PCFCL. Negative results for BCL-2 and CD5 helped exclude more aggressive lymphomas, such as PCDLBCL-LT [11].

RFH is one of the differential diagnoses in this case [7,12]. Due to its histologic similarities- particularly the presence of numerous reactive follicles with an irregular architecture- RFH can be difficult to distinguish from PCFCL. However, RFH typically exhibits a well-organized follicular structure with polarized centrocytes and centroblasts, confined BCL-6+ cells confined within CD21+ and CD23+ follicular dendritic networks, and a polyclonal B-cell population. Clinically, RFH tends to resolve spontaneously, whereas PCFCL persists [11]. In this case, histopathologic analysis revealed a dense lymphoid infiltrate with both follicular and diffuse growth patterns. Immunohistochemical findings confirmed the diagnosis of PCFCL, effectively ruling out RFH.

Immunohistochemical markers are essential for characterizing the cellular origin and behavior of lymphomas, including PCFCL. It arises from germinal center B-cells, which explains the positivity for markers associated with B-cell lineage and germinal center activity. CD19, CD20, CD22, and CD79a

are pan-B-cell markers involved in B-cell receptor signaling and differentiation, confirming the B-cell origin of PCFCL. PAX-5, a transcription factor critical in B-cell malignancies, is also expressed in PCFCL [1,11,13]. Additionally, BCL-6 and CD10 serves as markers of germinal center B-cells, further supporting the neoplasm's origin from follicle center cells. CD21, a marker for follicular dendritic cells, highlights the presence of follicular structures within the infiltrate, reinforcing the diagnosis of PCFCL [11,14]. Ki-67, a proliferation marker, aids in assessing tumor cell growth; its expression in PCFCL reflects the active proliferation of malignant B-cells. Ki67 expression in PCFCL is variable but typically exceeds 30% [2,11].

PCFCL typically lacks expression of markers associated with more aggressive B-cell lymphomas. BCL-2, an anti-apoptotic protein, is usually negative or weakly expressed in PCFCL [2,5,11]. This finding distinguishes PCFCL from systemic follicular lymphoma, in which BCL-2 is often strongly positive due to the t(14;18) translocation [2,11]. MUM-1, FOX-P1, and cytoplasmic immunoglobulin are markers of post-germinal center or activated B-cells, characteristic of more aggressive lymphomas such as PCDLBCL-LT [5,10,11]. The absence of these markers in PCFCL supports its classification as an indolent lymphoma with a favorable prognosis, as even a low expression of the PCDLBCL-LT marker FOXP1 is independently linked to a worse prognosis [1,11,15].

A systemic evaluation of CBCL is essential to confirm its primary cutaneous origin and to exclude systemic involvement, as the diagnosis of primary CBCL requires the absence of extracutaneous disease at the time of diagnosis. Since no definitive histopathologic or immunohistochemical features can differentiate primary from secondary cutaneous B-cell lymphomas, a comprehensive clinical assessment- including imaging and laboratory tests- is necessary [5]. In this case, the patient underwent a thorough systemic evaluation, which confirmed normal kidney and liver function and showed no evidence of infection. Radiological examinations revealed no involvement of other organs. These findings confirm the absence of systemic lymphoma, supporting the diagnosis of primary cutaneous lymphoma.

Treatment options for PCFCL include radiotherapy, surgical excision, and systemic therapy for more extensive disease. The choice of treatment depends on the extent and severity of the disease, as well as patient comorbidities. For solitary or localized lesions, first-line treatments include local radiotherapy or surgical excision, with alternatives such as intralesional interferon-alpha (IFN-α) or Rituximab. In cases of multifocal disease, a "wait-and-see" approach is often preferred due to the indolent nature of PCFCL, although local radiotherapy or intravenous Rituximab may be used if intervention is necessary. Systemic chemotherapy, such as R-CVP (Rituximab, cyclophosphamide, vincristine, prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), are reserved for more extensive cases or extracutaneous involvement [1,5].

Systemic therapy was necessary due to the presence of multifocal lesions in this patient. The oncology department scheduled chemotherapy using the CHOP regimen. However, the cardiotoxic drug doxorubicin, a standard component of the CHOP regimen, could not be administered because of the patient's underlying heart disease [16]. Therefore, an alternative CEOP regimen, which replaces doxorubicin with etoposide, was used. Although the patient did not complete the full six cycles, significant improvement was observed after four cycles, with no evidence of relapse during the six-month follow-up following the discontinuation of therapy.

The prognosis for PCFCL is generally excellent, with a five-year survival rate exceeding 95%. Although relapses occur in approximately 30% of cases, they do not typically indicate a worse outcome and can be effectively managed with radiotherapy [1,5]. Studies have shown that R-CEOP is associated with significantly poorer four-year progression-free, overall, and disease-specific survival compared to R-CHOP in systemic diffuse large B-cell lymphoma [17]. In this case, the patient completed only four out of six planned chemotherapy cycles but showed clinical improvement after three sessions, with no signs of relapse six months after discontinuation. These findings align with the generally favorable course of PCFCL and reinforce the indolent nature of the disease. However, incomplete chemotherapy with the alternative CEOP regimen may affect the prognosis and recurrence rates. Patient education is crucial in these cases to encourage adherence to therapy and regular follow-up, as early detection of relapse can prevent disease progression.

CONCLUSION

This case underscores the importance of recognizing the clinical and histopathological features of PCFCL. Accurate diagnosis, achieved through a combination of clinical evaluation, histopathology, and IHC is crucial to distinguish PCFCL from other cutaneous conditions. A multidisciplinary approach involving dermatology, pathology, oncology, and other related specialties ensures optimal patient outcomes. Additionally, patient education and adherence to therapy are critical for preventing relapse and improving long-term prognosis.

Ethical consideration

Written authorization for the use or disclosure of medical information and photographs was obtained from the patient.

Acknowledgements

The authors gratefully thank the patient and Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, for providing the resources used in this case report.

Authors contributions

DCT: data collection, clinical evaluation and management of the patient, and manuscript writing; **MAU, BHK, MS, IC**: clinical evaluation and management of the patient, manuscript writing, and project supervision; **DMI, MYL, S**: clinical evaluation and management of the patient, and project supervision.

Funding source

The authors did not receive funding from any organization for the submitted work.

Conflict of interest: None declared.

REFERENCES

1. Bagot M, Stadler R. Cutaneous lymphoma. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al., editors. Fitzpatrick's Dermatology 9th Edition. New York: McGraw Hill; 2019.
2. Blanchard M, Hoetzenecker W, Blanchard G, et al. What is new about primary cutaneous B cell lymphomas. Ital J Dermatol Venereol. 2023;158(3):205–16.
3. Kementerian Kesehatan Republik Indonesia. Data dan Kondisi Penyakit Limfoma di Indonesia. Jakarta: Pusat Data dan Informasi Kementerian Kesehatan RI; 2015.
4. Harahap AS, Ham MF, Kurniawan A, et al. Fifteen years of non-hodgkin lymphoma in an Indonesian National Referral Hospital: epidemiologic trends and diagnostic challenges. JCO Global Oncol. 2024;(10):e2400346.
5. Goyal N, O'Leary D, Carter JB, et al. A practical review of the presentation, diagnosis, and management of cutaneous B-Cell lymphomas. Dermatol Clin. 2023;41(1):187–208.
6. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720–48.
7. Lucioni M, Fraticelli S, Neri G, et al. Primary cutaneous B-Cell lymphoma: an update on pathologic and molecular features. Hemato. 2022;3(2):318–40.
8. Villasenor-Park J, Chung J, et al. Cutaneous B-Cell lymphomas. Hematol Oncol Clin North Am. 2024;38(5):1111–31.
9. Al Harbi SM, Al Natour S, Al Saif NM, et al. Primary cutaneous follicle center lymphoma presenting as a solitary nodule on the forearm of an adolescent girl: a case report and literature review. Clin Cosmet Investig Dermatol. 2023;16:167–72.
10. Hristov AC, Tejasvi T, Wilcox RA. Cutaneous B-cell lymphomas: 2021 update on diagnosis, risk-stratification, and management. Am J Hematol. 2020;95(10):1209–13.
11. Skala SL, Hristov B, Hristov AC. Primary cutaneous follicle center lymphoma. Arch Pathol Lab Med. 2018;142(11):1313–21.
12. Bátai B, Kiss L, Varga L, et al. Profiling of copy number alterations using low-coverage whole-genome sequencing informs differential diagnosis and prognosis in primary cutaneous follicle center lymphoma. Mod Pathol. 2024;37(5):100465.
13. Krenitsky A, Klager S, Hatch L, et al. Update in diagnosis and management of primary cutaneous B-Cell lymphomas. Am J Clin Dermatol. 2022;23(5):689–706.
14. Oschlies I, Wehkamp U. Cutaneous B cell lymphomas: standards in diagnostic and clinical work-up. Hints, pitfalls and recent advances. Histopathology. 2022;80(1):184–95.
15. Senff NJ, Hoefnagel JJ, Jansen PM, et al. Reclassification of 300 primary cutaneous B-cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: Comparison with previous classifications and identification of prognostic markers. J Clin Oncol. 2007;25(12):1581–7.
16. Rihackova E, Rihacek M, Vyskocilova M, et al. Revisiting treatment-related cardiotoxicity in patients with malignant lymphoma—a review and prospects for the future. Front Cardiovasc Med. 2023;10:1243531.
17. Puckrin R, Ghosh S, Peters A, et al. Inferior outcomes with R-CEOP for patients with DLBCL and cardiovascular comorbidities. Leuk Lymphoma. 2022;63(3):583–90.