Primary cutaneous diffuse large B-cell lymphoma, leg type mimicking subcutaneous panniculitis-like T-cell lymphoma in a COVID-19 setting: case report and review of literature

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Abstract

Primary cutaneous diffuse large B-cell lymphoma, leg type is a rare entity accounting for 4% of all primary cutaneous lymphomas whose clinical presentation encompasses a range of possibilities. COVID-19 has caused a delay in diagnosis of malignant neoplasms and consequently, this has resulted in poorer prognoses. A 62-year-old woman presented with two smooth-surfaced, mobile, well-circumscribed, oval, skin-colored nodules approximately one-cm in diameter with nonerythematous borders on the lower third of the left leg. Two months later, eleven nodules measuring between one and 1.5cm with erythematous halo, slight scaling, central erosion, and crusting had appeared. Histological study showed moderate pericapillary lymphocytic infiltration in the papillary and reticular dermis and prominent diffuse proliferation of medium to large cells in the subcutis. These exhibited irregular vesicular nuclei, a conspicuous solitary nucleolus of two to three small nucleoli, and three mitoses per high power field. Adipocytes were consistently encircled by neoplastic lymphocytes. Primary cutaneous diffuse large B-cell lymphoma, leg type is a high-grade lymphoma that can manifest as a diagnostic challenge and requires adequate immunohistochemistry and in situ hybridization studies for proper diagnosis, treatment, and prognosis.

Keywords: BCL2, cMYC, COVID-19, p63, primary cutaneous diffuse large B-cell lymphoma leg type, subcutaneous panniculitis-like T-cell lymphoma

Introduction

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), which most often affects elderly women, is a rare neoplasm composed of centroblasts and immunoblasts accounting for 4% of all primary cutaneous lymphomas and 20% of all primary cutaneous B-cell lymphomas [1]. Its presentation varies according to disease stage, appearing as irregular macules, solitary or multiple intact or ulcerating nodules or papules, converging plaques and tumors occupying large areas, and ulcers with infiltrated borders. Typically, the lesions are rapidly growing on one or both legs, with up to 15%–20% showing tumors on other parts of the body [2]. Owing to its rarity, multiple clinical presentations, and similarities with other types of cutaneous lymphomas (primary cutaneous follicle center lymphoma and Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly), a PCDLBCL-LT may be delayed [3-5]. It is essential to recognize its various clinical manifestations, histopathology, immunohistochemistry, and molecular profile to provide patients with appropriate treatment.

Case Synopsis

A 62-year-old woman with no systemic symptoms came in for consultation regarding two smooth-surfaced, mobile, well-circumscribed, oval, skin-colored nodules, approximately one cm in diameter, with nonerythematous borders on the lower third of

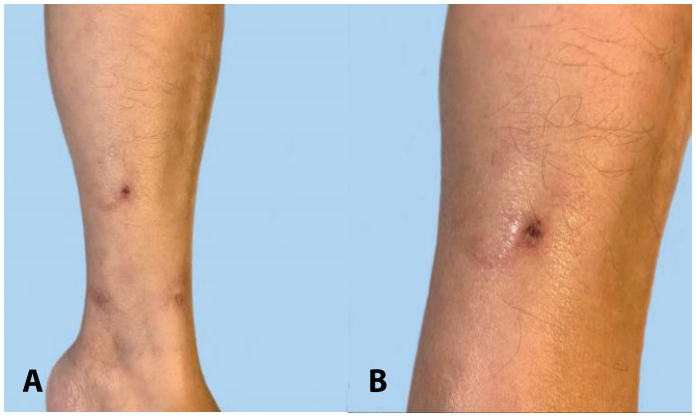

Figure 1. ***A)*** *Skin-colored nodular lesions approximately 1cm in diameter with nonerythematous borders in the lower third of the left leg.* ***B)*** *Nodular lesions measuring between one and 1.5cm with erythematous halo, slight scaling, centrally eroded, and scabbing.*

the left leg. Given the initial clinical suspicion of lipoma and the pandemic context of COVID-19, an observational management approach with reassurance to the patient was adopted. Two months later, eleven centrally eroded nodules, measuring between one and 1.5cm, with erythematous halo, slight scaling, and crusting had appeared (**Figure 1**). She had no palpable lymphadenopathy.

A biopsy was performed and the histological study showed variable pericapillary lymphocytic infiltration in the papillary and reticular dermis and a predominantly subcutaneous diffuse proliferation of medium to large cells with irregular vesicular nuclei. Solitary nuclei with two to three small nucleoli and three mitoses per HPF were observed (**Figure 2A**). Adipocytes were consistently encircled by neoplastic lymphocytes ("rimming"), a finding which led to the suspicion of subcutaneous panniculitis-like T-cell lymphoma (**Figure 2B**). Nevertheless, immunohistochemical and in situ hybridization studies showed negativity for CD56, CD3 (**Figure 3B**), CD30, CD4, CD8, CD10, and Epstein-Barr virus RNA chromogenic in situ hybridization. Positivity for CD20, BCL2, MUM1, p63 (**Figure 3A, C-E**), *cMYC* rearrangement (8%), and Ki67 (90%) was found, establishing a diagnosis of diffuse large B-cell lymphoma, leg type. A staging tomography, bone marrow biopsy, and laboratory tests were all found to be normal. The patient was classified as stage T2N0M0 and underwent six cycles of R-CHOP (rituximab-cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone) chemotherapy. She is currently in remission after the

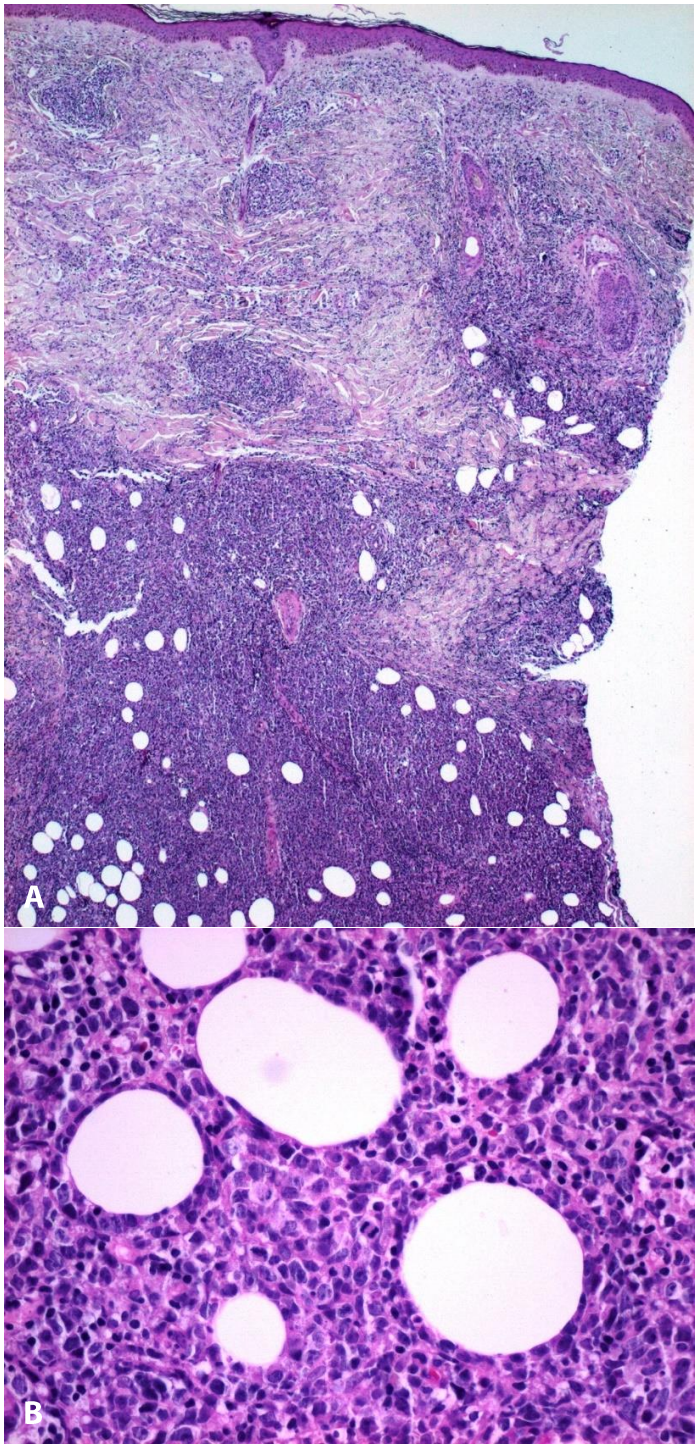

Figure 2. ***A)*** *The histological study showed skin with variable pericapillary lymphocytic infiltration in the papillary and reticular dermis, and prominent diffuse proliferation at the level of subcutaneous cellular tissue. H&E, 40×.* ***B)*** *Adipocytes were consistently encircled by neoplastic lymphocytes ("rimming"). H&E, 400×.*

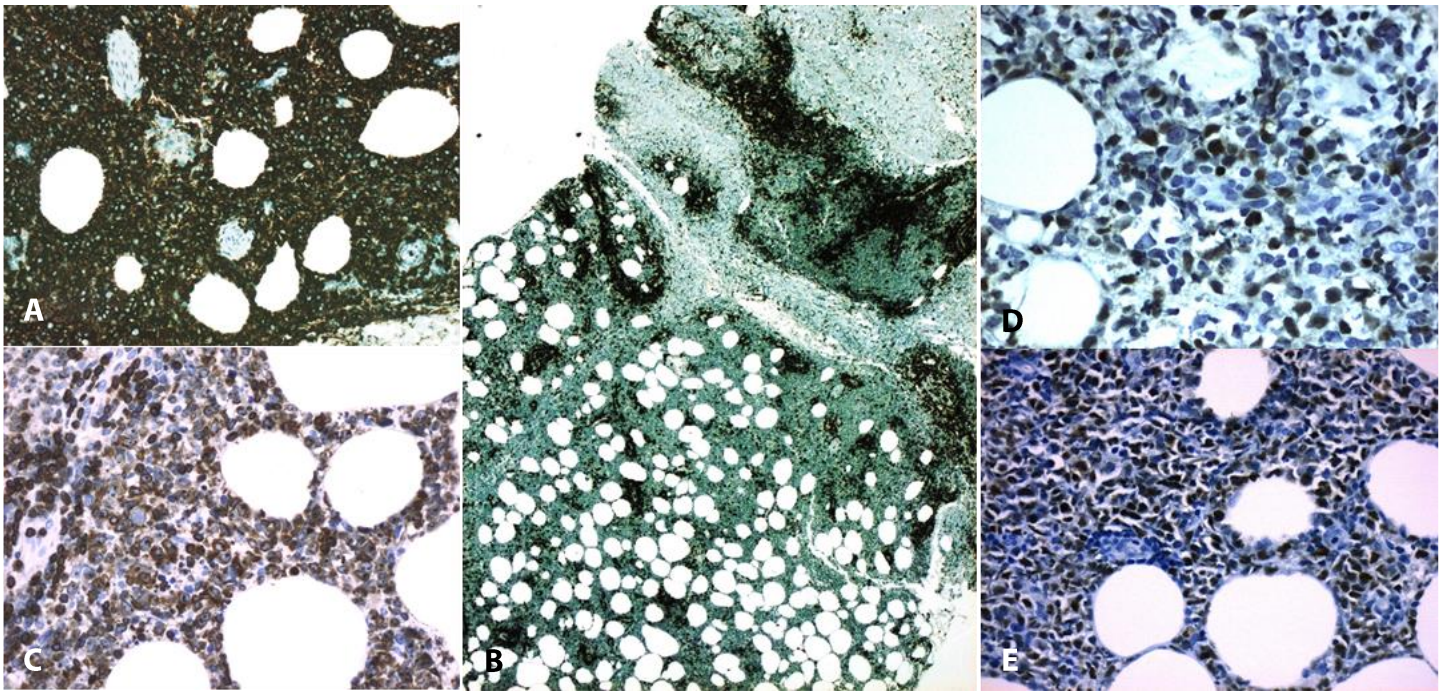

Figure 3. *Neoplastic lymphocytes were positive **A)** CD20, 200×, **B)** CD3 negative, 100×; **C)** BCL2, **D)** MUM1 and **E)** p63, 200×.*

sixth cycle and her trimestral follow-ups continue to be unremarkable 1.5 years after presentation.

Case Discussion

Primary cutaneous diffuse large B-cell lymphoma, leg type is an extranodal non-Hodgkin lymphoma that is part of the rare group of primary cutaneous lymphomas, according to the World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) classification system [6]. Primarily affecting women with an average age of 78 years [7], it accounts for 4% of primary cutaneous lymphomas and 20% of primary cutaneous B-cell lymphomas [1]. Diagnosis of this entity is a clinical challenge because its presentation can be a spectrum of dermatological lesions. Although ulcerating papules, nodules, or tumors in the lower third of the legs are its most frequent presentation, it can also manifest as flat and/or coalescing plaques, large ulcerations with infiltrated borders, irregular patches, annular lesions, verrucous nodules and plaque-like lesions, and widespread garland-like lesions with a reddish-blue multicolored rainbow-like pattern. Clinical features of cellulitis may be noted and papules and nodules may be distributed in a sporotrichoid pattern [2-15]. Lesions can be single or multiple, usually affecting one or both legs, although up to 15% may occur on other parts of the body, thus making the diagnosis even more difficult [1].

Because this malignant neoplasm has a poor prognosis but may go into remission with appropriate treatment [1], it is important to recognize its multiple clinical presentations to offer patients appropriate management. Our patient presented with initially underestimated small nodules considered to be likely benign. However, the nodules increase in number rapidly and exhibited significant morphological change resembling a more usual presentation of this rare type of lymphoma. It is important to recognize that the COVID-19 pandemic setting can influence the clinical decisions a physician may take, especially when it comes to early, benign-looking lesions.

Primary cutaneous diffuse large B-cell lymphoma, leg type typical histopathology is characterized by a diffuse infiltrate predominately in the dermis with variable extension into the subcutis., Monomorphic, large, atypical cells resembling centroblasts and immunoblasts in confluent sheets and frequent mitotic figures are noted [16]. The presence of neoplastic T lymphocytes forming a rim around

Table 1. *Primary cutaneous diffuse large B-cell lymphoma, leg type.*

Pearls	Reference
PCDLBCL-LT may present clinically in exceptional ways:	
-large ulcerations with infiltrated borders	[2]
-annular lesions	[2,14]
-verrucous nodules and plaque-like lesions	[10,13]
-widespread garland-like lesions	[11]
-lesions with reddish-blue multicolored rainbow-like pattern	[12]
-cellulitis-like lesions	[9,15]
-nodular lesions distributed in a sporotrichoid pattern	[15]
-fast growing dermatological lesions	[2,6]
Up to 15%–20% of PCDLBCL-LT may appear on other parts of the body	[2]
Rule out Epstein-Barr Virus-Positive Diffuse Large B-cell Lymphoma of the Elderly	[4,5]
Histological finding of "rimming of adipocytes by neoplastic lymphocytes" in PCDLBCL-LT and other lymphomas may simulate a subcutaneous panniculitis-like T-cell lymphoma	[17, this report]
BCL-2 expression and/or c-MYC rearrangement are poor prognosis markers	[18,19]
p63 is a diagnostic marker that can help differentiate between PCDLBCL-LT and PCFCL	[20]
In the context of COVID-19, PCDLBCL-LT is considered a high-risk primary cutaneous lymphoma	[23]

individual adipose cells (adipocyte rimming) in the subcutaneous lobes is considered a characteristic morphological factor of subcutaneous panniculitis-like T-cell lymphoma [17]. Lozzi et al. however, found "rimming of adipocytes by neoplastic lymphocytes" in a 45-case series of primary and secondary cutaneous B- and T-cell lymphomas and acute myeloid leukemia involving subcutaneous cell tissue. In our case, the prominent adipocyte rimming by neoplastic lymphocytes required consideration of subcutaneous panniculitis-like T-cell lymphoma, which was ruled out by our immunochemistry panel results. Such rimming should not be considered specific for subcutaneous panniculitis-like T-cell lymphoma [17], **Table 1**. Therefore, PCDLBCL-LT belongs to the lymphoma group that can present with a panniculitis-like histological pattern.

Besides the clinical challenge that PCDLBCL-LT imposes, an adequate immunohistochemical panel becomes a crucial tool to rule out other primary cutaneous large B-cell lymphomas such as primary cutaneous follicle center lymphoma, large cell. Menguy et al. performed immunohistochemistry and in situ hybridization studies in 44 cases of primary cutaneous B-cell lymphomas to assess how different markers can aid in the differential diagnosis and impact patients' prognosis. BCL2 and MUM1 positivity along with a high Ki67 (~86%) play a fundamental role as diagnostic features that support PCDLBCL-LT [18]. Furthermore, disease-specific and disease-free survival are negatively affected in patients with positive BCL2 expression and/or cMYC rearrangements [10,18,19]. Our patient's immunohistochemical and in situ hybridization studies granted her a poor prognosis in an already high-grade lymphoma. For this reason, it is imperative to conduct adequate diagnostic studies to provide patients with an accurate prognosis, treatment, and follow-up. The Epstein-Barr virus RNA chromogenic in situ hybridization negative result allowed us to confidently rule out Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly.

The *p63* gene is a member of the *p53* family in chromosome 3q27-28 whose function is to up-regulate *p53* targets and induce apoptosis. Mutations in *p63* have been described in different lymphomas such as non-Hodgkin, follicular, and diffuse large B-cell, even when its expression pattern is consistent in normal tissue. Robson et al. compared the diagnostic relevance of p63 expression in 30 PCDLBCL-LT and 34 primary cutaneous follicle center lymphoma (PCFCL) cases.

His results showed positive p63 expression in 70% of PCDLBCL-LT versus 12% of PCFCL cases [20]. There is also a significant association between p63 expression and a higher Ki67, which is particularly consistent with PCDLBCL-LT [20]. Therefore, p63 should be included in the immunohistochemical panel with the sole purpose of facilitating the differential diagnosis between PCDLBCL-LT and PCFCL until more studies can shine light on its impact in disease prognosis [20,21]. The biggest differential diagnostic challenge is between PCDLBCL-LT and PCFCL because of their possible histologic and genomic similarities. In our case, CD10 negativity, MUM1, BCL2, *cMYC* rearrangement, and p63 positivity favored PCDLBCL-LT as the final diagnosis [5].

The COVID-19 pandemic has caused a decrease in cancer screenings, diagnoses, and treatment because of people's fear of infection during a medical visit. This resulted in up to a 65.2% drop in new cancer diagnoses during April 2020, with breast, lung, colon, and melanoma being the most affected neoplasms according to data from the U.S. and England, [22]. Our case is a clear example of how decision-making by patients and even doctors may be biased, leading to a delay in diagnosis and inadequate follow-up, possibly affecting disease prognosis. COVID-19 has undoubtedly had a major impact even on the management of patients with primary cutaneous lymphomas. Primary cutaneous diffuse large B-cell lymphoma, leg type is classified as a high-risk malignant neoplasm among primary cutaneous lymphomas and the risks and benefits of follow-up and treatment could be discussed with the patient through telemedicine, avoiding as much as possible an increase in the risk of severe COVID-19 infection [23]. Decisions regarding the treatment of this type of lymphoma, should be assessed independently in each patient, according to their vaccine status, overall community-risk of infection and death-risk if infected.

Conclusion

As a rare primary cutaneous lymphoma with a poor prognosis and multiple clinical presentations, PCDLBCL-LT may be difficult to diagnose, thus delaying the start of treatment. Our case exemplifies the importance of knowing the classic and unusual lesions with which this type of lymphoma can present as well as the value of immunohistochemical and in situ hybridization studies to provide keys for optimal management. Primary cutaneous diffuse large B-cell lymphoma, leg type should always be considered regardless of the initial dermatological presentation of the lesions when clinical characteristics of advanced age, lower limb involvement, lesion ulceration, and rapid evolution are present.

Potential conflicts of interest

The authors declare no conflicts of interest.

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