

Carol Avila, MD¹, Hector Arreaza, MD¹,
Michelle Rivera, MD².

Rio Bravo Family Medicine Residency Program¹
Dermatology at Washington Hospital Center²

Case Presentation

A 95-year-old Hispanic male with a history of T2DM and CKD was referred to dermatology for a rapidly progressing skin rash on the left shin ongoing for 3 months. He denied any systemic symptoms. He was initially diagnosed with eczema and received a 2-week course of topical steroids, which was ineffective.

Examination revealed **violaceous nodules and coalescing plaques extending through the whole length of the left shin**, the left lower calf, and the posterior ankle. General examination, including lymph node examination, was unremarkable.

The **differential diagnoses** included: **Cutaneous T-cell Lymphoma deep fungal infection, and Necrobiosis Lipoidica**. Periodic acid-Schiff stain with diastase was negative, excluding deep fungal infection. The absence of evidence of Necrobiosis Lipoidica on further assessment excluded the diagnosis.

Microscopic examination of the lesion revealed sheets of **large mononuclear lymphoid cells** filling the dermis with few interspersed **CD3 positive** cells and negative CD20 stains for B cells. The cells were also positive for **CD45 and CD79a**. The cells were negative for CD56, CD117, CD34, CD30, CD1a, S100, pan-cytokeratin, cytokeratin 20, and Melan-A. Further immunohistochemistry revealed that the cells are positive for **BCL2, BCL6 (partial), FOX-P1, CD10 (partial)**, and negative for C-MYC, MUM1, and cyclin D-1. Epstein-Barr virus (EBV)-encoded RNA 1 (EBER-1) in situ hybridization was negative for Epstein-Barr mRNA.

Positron emission tomography (PET) and computed tomography (CT) scan demonstrated **high uptake in the left leg** and a large hypermetabolic lymph node in the left pelvis. **In the absence of other areas of systemic involvement, and with the skin of the legs being the main area affected, the diagnosis of Primary Cutaneous Diffuse B Cell Lymphoma, Leg type was made.**

The patient was treated with four doses of **rituximab** followed by clinical evaluation for cancer responsiveness. Follow-up with a multidisciplinary team of specialists, including primary care physician, oncologist, and dermatologist was established.

CD20 Negative Primary Cutaneous Diffuse Large B Cell Lymphoma, Leg Type with rapidly progressing skin lesions.



March



April



June



June

Discussion

The updated World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) consensus classification recognizes **five forms of Primary Cutaneous B cell Lymphomas**: Primary Cutaneous Marginal Zone B cell Lymphoma (PCMZL), Primary Cutaneous Follicle Center Cell Lymphoma (PCFCL), and Primary Cutaneous Diffuse Large B Cell Lymphoma, Leg Type (PCDLBCL-LT).^{1,2}

Primary Cutaneous Diffuse Large B Cell Lymphoma, Leg Type (PCDLBCL-LT) is a rare **non-Hodgkin's lymphoma (NHL)** that usually presents in the **skin of the legs as violaceous, indurated plaques or nodules without evidence of internal or nodal involvement** at the time of initial presentation.^{3,4,5,6,7,8,9,10,11} However, 10-20% of cases present with lesions outside the legs and spread to extracutaneous sites such as lymph nodes, bone marrow, and central nervous system.^{1,2,3,4,7,8,9}

PCDLBCL-LT is **aggressive, disseminates to extracutaneous sites (46%), has the worst prognosis (5-year survival, 30-50%)** among Primary Cutaneous B cell Lymphomas, the median age of occurrence is 70s, and has a slightly higher predominance in females.^{2,3,4,5,6,7,8,9}

Histologically, similar to our findings in this case report, PCDLBCL-LT appears as a diffuse population of **large cells (centroblasts and immunoblasts) with interspersed mature reactive T lymphocytes**.^{3,4,5,6} A large retrospective multicenter study described the clinicopathologic features of PCDLBCL-LT in 60 patients showing neoplastic cells that expressed B cell markers in every patient (CD20 positive) and were negative for CD3.³

CD20-negative non-Hodgkin's Lymphoma (NHL), such as PCDLBCL-LT presented in this report, is a **rare type (1-2%) of NHL**.^{5,10,12} CD20-negative B cell lymphomas are significant because they are more aggressive, associated with extranodal involvement, and decreased responsiveness to monoclonal antibodies (e.g. rituximab).^{10,12}

Rituximab is a CD20 monoclonal antibody that destroys B cell malignancies through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). It is combined with cyclophosphamide, doxorubicin, oncovin/vincristine, and prednisone (R-CHOP) as the **gold standard for treating PCDLBCL-LT**.^{2,3,4,5,6,7,10} Radiotherapy would be the therapeutic option for patients that are unable to receive the standard therapy. **In CD20-negative PCDLBCL-LT, pathologists and clinicians face a diagnostic challenge because of the absence of CD20 markers**. In such cases, the diagnosis can be established through immunohistochemical detection of other specific markers. For instance, in cases of CD20 negative lymphoma, flow cytometric analysis can detect positivity for CD19, CD79a, CD5, and CD10.^{2,4,10,12} CD20 negativity also poses therapeutic difficulties, making treatment with rituximab less effective.¹⁰

PCDLBCL-LT strongly expresses **BCL2, IRF4/MUM1, and MYC** (65-80% of cases).^{3,4,5,7,8,12,13} The immunohistochemistry of our patient's specimen was positive for BCL2, partially positive for BCL6, but negative for C-MYC and MUM1.^{5,10,13}

Similar to the case presented in this report, patients with loco-regional extracutaneous involvement were still considered a primary skin disease because they primarily involved the limbs and showed histological features of leg-type B cell lymphoma.⁴

This report also demonstrates a **rapid and dramatic progression of the cutaneous lesions**. The patient lesions progressed dramatically over three months, as shown in Figures (March) and (April). Figure (June) demonstrates the patient's skin lesions on presentation to the dermatologist. This report also serves to highlight that a **multidisciplinary approach is a cornerstone of diagnosing PCDLBCL-LT**. Careful clinical evaluation and investigations are imperative for timely diagnosis and appropriate treatment. Oncologists should undertake a thorough assessment to exclude systemic involvement, bearing in mind that borderline cases can show primary cutaneous and systemic DLBCL features, such as the case presented in this report.

References

1. WHO. (2017) "Primary Cutaneous Lymphomas: The 2018 Update of the WHO-EORTC Classification." *Annals of the New York Academy of Sciences*, 1411, 104-110. doi:10.1111/anaj.14111
2. Thomas, Y., DeMaio, H., & Meehan, W. (2017) Primary cutaneous large B-cell lymphoma. *Mayo Clinic Proceedings*, 92(1), 202-203. doi:10.1016/j.mcp.2016.11.008
3. Minkov, E., Rajak, M., Vargha, A., Somayesi, F., Hristova, L., Dinev, S., Ermen, S., Tomchev, J., Donchev, K., and M. P. Dimitrova, G., Dinev, S., Letichev, S., Dimitrova, M., Zov, P., Zhuravskiy, J., & Papanov, T. (2021) Primary cutaneous diffuse large B-cell lymphoma: leg type: clinicopathologic features and prognostic analysis in 60 cases. *Annals of Hematology*, 100(1), 105-114. doi:10.1007/s00125-020-1900-9
4. Minkov, E., Somayesi, F., Hristova, L., Dinev, S., Ermen, S., Tomchev, J., Donchev, K., and M. P. Dimitrova, G., Dinev, S., Letichev, S., Dimitrova, M., Zov, P., Zhuravskiy, J., & Papanov, T. (2021) Primary cutaneous diffuse large B-cell lymphoma: leg type: clinicopathologic features and prognostic analysis in 60 cases. *Annals of Hematology*, 100(1), 105-114. doi:10.1007/s00125-020-1900-9
5. Minkov, E., Somayesi, F., Hristova, L., Dinev, S., Ermen, S., Tomchev, J., Donchev, K., and M. P. Dimitrova, G., Dinev, S., Letichev, S., Dimitrova, M., Zov, P., Zhuravskiy, J., & Papanov, T. (2021) Primary cutaneous diffuse large B-cell lymphoma: leg type: clinicopathologic features and prognostic analysis in 60 cases. *Annals of Hematology*, 100(1), 105-114. doi:10.1007/s00125-020-1900-9
6. Long, V., Liang, M., Wu, L., Li, S., & Li, J. (2020) Two distinctive cases of primary cutaneous diffuse large B-cell lymphoma (leg type) involving orbita and nose. *Journal of Cutaneous Medicine and Surgery*, 46(1), 1-4. doi:10.1177/1077224219881111
7. Papanov, H., & Gueorgieva, P. (2017) A literature review on Primary Cutaneous B-cell lymphoma. *Balkan Journal of Dermatology*, 4(2), 146-157. doi:10.1515/bjod-2017-0011
8. Li, S., Li, J., & Li, J. (2017) Diagnosis and treatment of CD20-negative B cell lymphoma. *Biotherapy Research*, 5, 1-11. doi:10.1016/j.bior.2017.03.001
9. Minkov, E., Somayesi, F., Hristova, L., Dinev, S., Ermen, S., Tomchev, J., Donchev, K., and M. P. Dimitrova, G., Dinev, S., Letichev, S., Dimitrova, M., Zov, P., Zhuravskiy, J., & Papanov, T. (2021) Primary cutaneous diffuse large B-cell lymphoma: leg type: clinicopathologic features and prognostic analysis in 60 cases. *Annals of Hematology*, 100(1), 105-114. doi:10.1007/s00125-020-1900-9
10. Minkov, E., Somayesi, F., Hristova, L., Dinev, S., Ermen, S., Tomchev, J., Donchev, K., and M. P. Dimitrova, G., Dinev, S., Letichev, S., Dimitrova, M., Zov, P., Zhuravskiy, J., & Papanov, T. (2021) Primary cutaneous diffuse large B-cell lymphoma: leg type: clinicopathologic features and prognostic analysis in 60 cases. *Annals of Hematology*, 100(1), 105-114. doi:10.1007/s00125-020-1900-9
11. Minkov, E., Somayesi, F., Hristova, L., Dinev, S., Ermen, S., Tomchev, J., Donchev, K., and M. P. Dimitrova, G., Dinev, S., Letichev, S., Dimitrova, M., Zov, P., Zhuravskiy, J., & Papanov, T. (2021) Primary cutaneous diffuse large B-cell lymphoma: leg type: clinicopathologic features and prognostic analysis in 60 cases. *Annals of Hematology*, 100(1), 105-114. doi:10.1007/s00125-020-1900-9
12. Minkov, E., Somayesi, F., Hristova, L., Dinev, S., Ermen, S., Tomchev, J., Donchev, K., and M. P. Dimitrova, G., Dinev, S., Letichev, S., Dimitrova, M., Zov, P., Zhuravskiy, J., & Papanov, T. (2021) Primary cutaneous diffuse large B-cell lymphoma: leg type: clinicopathologic features and prognostic analysis in 60 cases. *Annals of Hematology*, 100(1), 105-114. doi:10.1007/s00125-020-1900-9
13. Minkov, E., Somayesi, F., Hristova, L., Dinev, S., Ermen, S., Tomchev, J., Donchev, K., and M. P. Dimitrova, G., Dinev, S., Letichev, S., Dimitrova, M., Zov, P., Zhuravskiy, J., & Papanov, T. (2021) Primary cutaneous diffuse large B-cell lymphoma: leg type: clinicopathologic features and prognostic analysis in 60 cases. *Annals of Hematology*, 100(1), 105-114. doi:10.1007/s00125-020-1900-9

