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Case Report

CD20 Negative Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type with Rapidly Progressing Skin Lesions

Dalya M. M. Abdelmaged[1], Carol A. Avila[2], Abubaker A MohamedSharif[3], and Isra Bdraldein Salih Mohammed[3]*

[1]Faculty of Medicine, Al Neelain University, Khartoum, Sudan
[2]Universidad de Carabobo, Valencia, Venezuela
[3]Faculty of Medicine, University of Khartoum, Khartoum, Sudan
ORCID:
Isra Bdraldein Salih Mohammed: https://orcid.org/0000-0003-0655-3653

Abstract

A 95-year-old man came with violaceous nodular skin lesions of the left shin. The lesions were not painful or pruritic but progressed rapidly over the 3 months. Fever, night sweats, weight loss, and other systemic symptoms were absent. Shave biopsy of the lesion revealed the cells negative for CD20 but positive for *BCL2, BCL6, FOX-P1*, and *CD10*. PET/CT showed high uptake in the left leg and a sizeable hypermetabolic lymph node in the left pelvis. The patient was started on rituximab treatment as a single agent. This report highlights some of the diagnostic and treatment difficulties in CD20 negative lymphomas and the importance of a multidisciplinary approach in those cases.

Keywords: diffuse large B-cell lymphoma, leg type (DLBCL-LT), primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), positron emission tomography/computed tomography (PET/CT), cluster of differentiation (*CD*), B-cell lymphoma 2 (*BCL2*), B-cell lymphoma 6 (*BCL6*), Forkhead box P1 (*FOX-P1*), c-myelocytomatosis oncogene product (*C-MYC*), multiple myeloma oncogene 1 (*MUM1*), Epstein-Barr virus (EBV)-encoded RNA 1 (*EBER-1*)

Corresponding Author: Isra Bdraldein Salih Mohammed; email: Israbdr1995@gmail.com

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1. Background

This is a case of an uncommon and bellicose subtype of non-Hodgkin lymphoma (1). Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), mainly affects the legs with a median age of onset of 70 (2). However, 10–20% of cases present with lesions outside the legs and spread to extracutaneous locations like lymph nodes, bone marrow, and the central nervous system (2).

It is essential to recognize that the cases presenting with loco-regional extracutaneous disassociating can still be deemed primary skin diseases, since they primarily

involve the skin, and if they demonstrate histological features of PCDLBCL-LT. Borderline cases, such as the one presented in this report, highlight a ceaseless spectrum between cutaneous and systemic B-cell lymphoma. Clinicians should consider this principle when diagnosing PCDLBCL-LT in patients who come with skin lesions and local nodal involvement, such as the patient described in this report.

It is also important to recognize that PCDLBCL-LT is aggressive and can present with extensive and rapidly progressing lesions, which can be demonstrated by the lesions shown in this case report (1). This is an important feature that, when observed, should lead clinicians to consider a diagnosis of cutaneous B-cell Lymphoma. Clinicians are urged to adopt a multidisciplinary approach in diagnosing and treating patients with PCDLBCL-LT. Primary care physicians, oncologists, and dermatologists should work together to promptly diagnose cases that present with vague skin signs, especially in the initial stages of the disease.

2. Case Presentation:

A 95-year-old male with a history of diabetes mellitus, chronic kidney disease, and chronic anemia was referred to a dermatologist for a rash. The rash was non-pruritic and non-painful, had been rapidly progressing for 3 months before consulting the dermatologist, and mainly involved the left shin. He had no fever, chills, weight loss, night sweats, or other systemic complaints. Before referral, his primary care physician diagnosed him with eczema and treated the rash with a 2-week course of topical steroids, which were ineffective. His previous medical history was negative for lymphoma and other malignancies. However, he had a history of anemia for 10 years due to chronic kidney failure. Examination revealed violaceous nodules and coalescing plaques extending through the whole length of the left shin, the left lower calf, and posterior ankle. The right posterior ankle also showed a few solitary lesions. The lesions spared his torso, arms, thighs, and face. The general examination, including lymph node examination, was unremarkable.

Based on the appearance of the lesions, the dermatologist suspected T-cell lymphoma and performed a shave biopsy. However, the pathologist suspected B-cell lymphoma, despite the cells being negative for CD20. Further consultations and immunohistochemistry showed cells positive for *BCL2, BCL6* (partial), *FOX-P1*, *CD10* (partial), and negative for *C-MYC, MUM1, and cyclin D-1*, confirming a diagnosis of B-cell lymphoma.

In the absence of a reported history of systemic lymphoma, the presumptive diagnosis was primary cutaneous diffuse large B-cell lymphoma. The patient was forwarded to an

oncologist for further assessment to exclude systemic involvement. The patient underwent a detailed workup and positron emission tomography (PET)/computed tomography (CT), which disclosed high absorbency in the left leg and a hypermetabolic lymph node in the left pelvis. It did not demonstrate other systemic involvement. Because the skin is the main organ affected, and the legs are the primary areas of involvement, with the absence of systemic spread, the diagnosis of PCDLBCL-LT was established. The patient was started on rituximab, and he is being followed up by a multidisciplinary team that includes a dermatologist, oncologist, nephrologist, and primary care physician.

3. Investigations

A shave biopsy of the lesion in the left shin was performed. Microscopic examination of the sample disclosed 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, CD-117, CD34, CD30, CD1a, S100, pan-cytokeratin, cytokeratin 20, and Melan-A. Because the immunohistochemical panel did not fully characterize the tumor, additional immunostains were performed. Further immunohistochemistry disclosed 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.

PET/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. Further blood tests showed raised LDH (345 U/L; reference range 140–280), decreased GFR (32 mL/min/1.72m2), hemoglobin (10.1 g/dL), RBC (3.2x10∧6/uL), and lymphocytes (13.1%).

4. Antibodies Used in Flow Cytometry with Dilution:

Flow cytometry analysis was performed on the patient's skin biopsy sample using the following antibodies: anti-*CD20*-APC (BioLegend, catalogue number 302307, 1:100 dilution), anti-*CD5*-PE (BD Biosciences, catalogue number 555352, 1:50 dilution), anti-*CD10*-FITC (BioLegend, catalogue number 312206, 1:50 dilution), anti-*BCL2*-PE-Cy7 (BD Biosciences, catalogue number 560971, 1:100 dilution), anti-*BCL6*-APC-Cy7 (BioLegend,

catalogue number 353212, 1:50 dilution), and anti-*MUM1*-PerCP-Cy5.5 (BioLegend, catalogue number 359603, 1:100 dilution) (3, 4).

Isotype controls were used to assess non-specific binding. Samples were analyzed using a BD FACSCanto II flow cytometer (BD Biosciences) and data were processed using FlowJo software (TreeStar, Inc.) (5).

5. Differential Diagnoses

Cutaneous T-Cell Lymphoma was the primary differential diagnosis because of the violaceous nodular appearance of the skin lesions. However, it was excluded by performing immunohistochemistry, which revealed B-cell markers and only a few scattered *CD3*-positive cells (T cells).

Other differential diagnoses included deep fungal infection and necrobiosis lipoidica. Because the patient has diabetes, he was at risk for both the conditions. Periodic acid-Schiff stain with diastase was negative, which excluded deep fungal infection. The absence of evidence of necrobiosis lipoidica on further assessment excluded the diagnosis.

6. Treatment

The patient's oncologist proposed treatment using rituximab (Rituxan) as a single agent. This recommendation was made based on the patient's age and comorbidities, which make him ineligible for further treatments. The patient will be treated with four doses of rituximab followed by clinical evaluation for the cancer responsiveness. Wound care for bruises that developed in the lesions will also be performed. Follow-up with a multidisciplinary team of specialists, including primary care physician, oncologist, dermatologist, and nephrologist, was established.

7. Discussion

The updated World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) consensus categorization recognizes five forms of primary cutaneous B-cell lymphomas: Primary Cutaneous Marginal Zone Lymphoma (PCMZL), Primary Cutaneous Follicle Center Lymphoma (PCFCL), PCDLBCL-LT, Epstein-Barr virus-positive mucocutaneous ulcer, and intravascular large B-cell lymphoma (6).

PCDLBCL-LT is a rare non-Hodgkin's lymphoma (NHL) (1/300,000 incidence) that usually presents in the skin of the legs without extracutaneous involvement at the time of initial presentation (1). PCDLBCL-LT is aggressive, disseminates to extracutaneous locations (45%), and has the worst prognosis (5-year survival, 50–60%) among primary cutaneous B-cell lymphomas (6). Histologically, similar to our findings in this case report, PCDLBCL-LT appears as a diffuse population of large cells with interspersed mature reactive T lymphocytes (7).

The CD20-negative non-Hodgkin's Lymphoma (NHL), such as PCDLBCL-LT presented in this report, is a rare type (1-2%) of NHL (5). CD20, a tetra-transmembrane glycosylated phosphoprotein, is encoded by the *MS4A1* gene on chromosome 11q12.2. It plays a role in the differentiation, maturation, and activation of B-cells through intracellular phosphorylation (8). It is absent on early pro-B-cells, plasmablasts, and plasma cells and found on late pro-B-cells through memory B-cells (8). Genetic mutations of *MS4A1* are the proposed underlying mechanism of the CD20-negative PCDLBCL-LT (8). CD20-negative B-cell lymphomas are significant because they are more aggressive, associated with extranodal involvement, and decreased responsiveness to rituximab (8). Rituximab is a CD20 monoclonal antibody that destroys B-cell malignancies through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) (8). It is combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as the gold standard for treating PCDLBCL-LT (8). In CD20-negative PCDLBCL-LT, pathologists and clinicians face a diagnostic dilemma 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* (8). CD20 negativity also poses therapeutic difficulties, making treatment with rituximab less effective.

PCDLBCL-LT strongly expresses *BCL2*, IRF4/*MUM1*, and MYC (65-80% of cases) (6). The immunohistochemistry of our patient's specimen was positive for *BCL2*, partially positive for *BCL6*, but negative for *C-MYC and MUM1*. In a study that examined the skin biopsies of 23 patients with DLBCL-LT for specific genetic alterations, most cases (96%) exhibited genetic mutations, with 52% showing multiple alterations (9). *BCL6* split was found in 6/23 patients, while *BCL2* and *MYC* splits were noticed in 1/23 and 3/23 cases, respectively (9). Other mutations detected included *CDKN2A* deletion (5/23) and *p.L265P MYD88* mutation (14/23) (9).

In contrast to other primary cutaneous B-cell lymphoma subtypes, PCDLBCL-LT usually harbors a common genetic profile with their nodal counterparts (9). Similar to the

case presented in this report, cases with loco-regional extracutaneous involvement were still considered as a primary skin disease because they primarily involved the limbs and showed histological features of leg-type B-cell lymphoma (9). Such borderline cases, like the one presented in this report, underline a continuous spectrum between cutaneous and systemic B-cell lymphoma (9). This should be considered when diagnosing cases with PCDLBCL-LT.

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 (1) and (2). Figure (3) 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 both primary cutaneous and systemic DLBCL features such as the case presented in this report.

8. Learning Points

1. A continuous spectrum exists between cutaneous and systemic B-cell lymphoma that clinicians should consider when diagnosing cases with loco-regional extracutaneous manifestations.

2. A multidisciplinary team approach should be adopted to achieve prompt diagnosis in rare and complex cases like CD20 negative PCDLBCL-LT.

3. The gold standard treatment for PCDLBCL-LT is rituximab which acts by targeting CD20 on the surfaces of B-cells. CD20 negative PCDLBCL-LT poses treatment dilemmas because of the absence of CD20.

4. Cutaneous manifestations of PCDLBCL-LT can be rapidly progressive over a short period and can also resemble benign dermatologic conditions in the early stages.

Conflict of Interests

There are no conflict of interests.

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