Primary cutaneous diffuse large B-cell lymphoma, leg type – quick evolution and unfavorable outcome: case report

Linfoma cutâneo primário difuso de grandes células B, tipo perna – rápida evolução e desfecho desfavorável: relato de caso

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ABSTRACT: Primary cutaneous lymphomas are the second most common form of extranodal lymphomas, caused by B cell lymphomas (BCLs), representing 20 to 30% of cases. Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type (PCDLBCL-LT) represents the most aggressive type of BCLs. In most cases, the clinical presentation is characterized by single plaques or tumors, sometimes ulcerated and growing quickly on one or both legs. The diagnosis is confirmed through histopathological and immuno-histochemical studies. Treatment is carried out through chemotherapy, and its prognosis is reserved at a 50% to 60% survival rate in 5 years. The objective of this article is to report on a case of Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type in a 75-year-old male patient with a classical clinical presentation and unfavorable outcome and to perform a literary review on the subject from 2010 to 2020 in the PUBMED database, due to its rarity and unique aggressiveness. The data were obtained through the medical records, photographic records, and literature review. It has been possible to conclude the importance of multidisciplinary studies involving Dermatologists, Hematologists, Oncologists, and Pathologists so that the diagnosis and treatment are instituted as early as possible due to the rarity and aggressiveness of the PCDLBCL-LT.

Keywords: Lymphoma; Primary cutaneous lymphoma; Cutaneous B-cell lymphoma; Dermatology.
INTRODUCTION

Primary Cutaneous Lymphomas are the second most common type of extranodal lymphomas. 75% to 80% of the cases are cutaneous T-cell lymphomas (CTCLs) since the B-cell lymphomas constitute only around 20% to 30% of the cases of primary cutaneous lymphomas.

Primary Cutaneous B-cell Lymphomas (PCBCLs), according to the 2016 classification of WHO-EORTC (World Health Organization - European Organization for Research and Treatment of Cancer), are classified into 05 entities: Primary Cutaneous Marginal Zone B-Cell Lymphoma (PCMZL), Primary Cutaneous Follicle Center B-Cell Lymphoma (PCFCL), Large Cell Intravascular Lymphoma, EBV positive Mucocutaneous Ulcer (EBVMCU), Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type (PCDLBCL-LT).

Such BCLs present distinct dermatological characteristics. PCMZL is defined by multiple plaques or erythematous-violaceous nodules in the upper limbs and trunk, and they are most common among children and adolescents, and their prognosis is excellent. PCFCL is described as erythematous-violaceous plaques, nodules, or tumor formations of variable sizes that mainly affect the scalp, forehead, and trunk. Meanwhile, the Large Cell Intravascular Lymphoma is clinically characterized by telangiectatic lesions or suggestive of panniculitis affecting the lower limbs and trunk. And EBVMCU is distinguished from other clinical forms as it is a provisory entity, according to 2016 WHO classification, related to infection by EBV in immunosuppressed patients. The elementary lesion consists of a solitary mucocutaneous well-defined ulcer that develops quickly, affecting the oropharyngeal mucosa and gastrointestinal tract.

Finally, PCDLBCL-LT is the most aggressive type of BCLs, and it mainly targets older women according to studies. In most cases, the clinical presentation is characterized by solitary or localized tumors and proliferates on one or both legs. The diagnosis is confirmed through a histopathological and immunohistochemical analysis. Treatment is performed by chemotherapy, and its prognosis is reserved, as it is worse when multiple ulcers are present and affect both limbs.

CASE DESCRIPTION

The patient is a 75-year-old-retired male (he worked as an automobile mechanic), born in Japan and had lived in Campinas-SP for about 40 years. He presented a history of Diabetes Mellitus and Alzheimer’s Disease. He went to his first appointment at the Dermatology Clinic at PUC-Campinas-SP in April 2019. At that time, he referred to a progressively growing lesion and local pain in his right leg he had had for seven months. He denied systemic symptoms. He presented violaceous tumor formations in the dermatological exam, with an erythematous base, infiltrated, and a keratotic surface on the anterior surface of the right thigh and regular erythematous nodules following a lymphatic pathway.

Figure 1. Violaceous tumor formation, with an erythematous, infiltrated, and keratotic base on the anterior right thigh and regular erythematous nodules following a lymphatic pathway.

Cutaneous B Cell Lymphoma, Sporotrichosis, Cutaneous Leishmaniasis, Cutaneous Tuberculosis, and Pseudo lymphoma were proposed as diagnostic hypotheses based on the clinical condition. A biopsy was requested, evidenced in the anatomopathological report: ulcerated epidermis, dermis replaced by dense diffused lymphoid infiltrate, and focal necrose. The immunohistochemical study was positive for the CD79, CD45, CD20, MUM-1, PAX-5, and Ki-67 markers in around 80% of the slides and negative for Bcl-2.

Hence, the histological study evidenced diffused lymphocyte inflammatory infiltrates, added to the positivity of the characteristic immunohistochemical of type B lymphocytes, and the classical clinical condition of the patient that corroborated with the diagnosis of PCDLBCL-LT.
Table 1. Demonstration of the tested markers in the reported study tissue sample.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>CD79</td>
<td>Positive</td>
</tr>
<tr>
<td>CD45</td>
<td>Positive</td>
</tr>
<tr>
<td>CD20</td>
<td>Positive</td>
</tr>
<tr>
<td>MUM-1</td>
<td>Positive</td>
</tr>
<tr>
<td>PAX-5</td>
<td>Positive</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Negative</td>
</tr>
<tr>
<td>Ki-67</td>
<td>Positive in 80%</td>
</tr>
</tbody>
</table>

Three months later, after starting the scheduled chemotherapy, the patient presented worsening of the clinical condition and cutaneous lesions that affected over 70% of his lower right limb. On that occasion, he was hospitalized, and the diagnosis was confirmed as Deep Venous Thrombosis in the right lower limb through USG Doppler. He then presented acute respiratory insufficiency, evolving into his death.

DISCUSSION

Lymphomas are malign proliferated and originate from the clonal expansion of the lymphoid cells with genetic alterations in different stages of cellular differentiation, arising from diverse types of lymphomas.

These malign neoplasms are divided into two large groups: Hodgkin lymphomas (HL) and Non-Hodgkin lymphomas (NHL). The first one is a disturbance of B lymphocytes; they generally originate in the lymph nodes, characterized by neoplastic multinucleated cells named Reed-Sternberg cells. However, the second type is composed of a heterogeneous group of malign proliferative diseases that affect the lymphoid and other tissues. The skin is the second-most involved organ in LNH, corresponding to 18% of the cases and an incidence ranging from 0.3 to 1:100,000, just behind the gastrointestinal tract.

This way, the cutaneous LNHs can be separated into primary and secondary. The primary cases are manifested on the skin, without any evidence of extracutaneous disease when diagnosed, while the second type presents cutaneous and extracutaneous effects.

The primary cutaneous LNHs are even subclassified into two large heterogenous classes: T cell cutaneous lymphomas (TCCLs) and B cell cutaneous lymphomas (BCLs). The TCCLs represent the majority, from 75% to 80% of cases, as the BCLs constitute around 20 to 30% of primary cutaneous lymphomas.

These lymphoma groups have their own clinical, histological behavior, and prognoses, and they require a different type of treatment compared with morphologically similar nodal lymphomas that can involve the skin secondarily.

BCLs are classified into 5 types, according
The primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) is one of the most aggressive types of BCLs, and it is rare, as it represents around 20% of BCLs\(^2\), and it affects mainly women, 1.6 times more prevalent at an average age of 76 years old\(^{11}\).

### Table 2. B cell cutaneous lymphomas, immunological markers, and genetic mutations.

<table>
<thead>
<tr>
<th>B cell cutaneous lymphomas</th>
<th>Clinical signs</th>
<th>Histology</th>
<th>Immunohistochemical markers</th>
</tr>
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<tbody>
<tr>
<td>PCMZL</td>
<td>Plaque, papules, nodules or solitary tumor, erythematous-violaceous on the head, neck, and trunk</td>
<td>Dilated blood vessels in the dermis and subcutaneous tissue with large neoplastic cells confined inside the lid vessels</td>
<td>CD20+/ CD79a+/ CD10+/ Bcl-6+/ Bcl-2+/ Reactive Germinative Centers</td>
</tr>
<tr>
<td>PCFCL</td>
<td>Telangiectatic plaques and hardened areas suggestive of puriculate or purple on the trunk or limbs</td>
<td>Small B cells with lymph plasmatic morphology or monocytoid plasmatic cells, monotypic plasmatic cells, S reactive T cells</td>
<td>CD20+/ CD79a+/ Bcl-2+/ CD10-/ CD5-/ Bcl-6-/ Bcl-5-/ MYD88</td>
</tr>
</tbody>
</table>
| Large Cell Intravascular Lymphomas | Solitary mucocutaneous ulcer and very delimited to quick evolution in the oropharyngeal region and gastrointestinal tract | Monotone proliferation and dense infiltrate of the centroblast, immunoblast, and large centrocytes in the dermis and hypodermis. Epidermotropism can be present, simulating type T Lymphomas | MUM-1+ / CD20+/ Bcl-2+/ MYC+ /
Gene Mutations |
| EBVMCU                          | Solitary tumors or plaques or located sometimes as ulcerated, generally on a single lower limb | Large EBV cells of the Hodgkin type in a mixed inflammatory background | CD79b/ CARD11/ MYD88 88 |
| PCDLBCL-LT                      | Solitary tumors or plaques or located sometimes as ulcerated, generally on a single lower limb | Monotone proliferation and dense infiltrate of the centroblast, immunoblast, and large centrocytes in the dermis and hypodermis. Epidermotropism can be present, simulating T cell lymphomas | MUM-1+/ CD20+/ Bcl-2+ / MYC+ |

In most cases, the clinical presentation of PCDLBCL-LT is characterized by plaques or single or localized tumors, as ulcerated, generally located on a lower single limb, exceptionally on both legs, growing quickly\(^2,12\). In about 15% of the cases, it affects distinct anatomical regions.\(^7\) It rarely can be present in the lymph nodes, central nervous system, bone, and other entails\(^13,14\).

The histology of PCDLBCL-LT displays monotone proliferation and dense infiltrates of the centroblasts, immunoblasts, and large centrocytes in the dermis and subcutaneous tissue; mitosis figures are frequent, and epidermotropism can be present, simulating T cell lymphomas\(^12\). In the immunohistochemical study, the majority displayed positivity for MUM - 1, PAX-5, CD20, Bcl - 2, Bcl-6, and MYC\(^13\). (Table 2)

The authors observed mutations activated genetically via NF - kB in PCDLBCL-LT, including CD79B, CARD11, and the mutation of MYD88, as this last one was the most prevalent\(^15\). Besides that, the MYD88 mutation can be used as a diagnostic resource for differentiating PCDLBCL-LT from primary follicular center B cell cutaneous lymphoma\(^2,15\). The diagnosis of different CBLCs is a challenge, as the clinical correlation, histology, immunohistochemical, and genetics are extremely important\(^1,2\). The most significant difficulty is differentiating between the PCDLBCL-LT and PCFCL subtypes due to the histological and clinical characteristics in common\(^2,13\). The increased positivity of the MUM-1 and Bcl-2 Markers favor the diagnosis of PCDLBCL-LT and the increased aggressiveness and quick evolution. Although up to 10% of PCDLBCL-LT do not display the Bcl-2 or MUM-1 coloration, careful clinical-pathological correlation is necessary for a definite diagnosis\(^3\).

The prognosis is reserved for a 5-year survival rate estimated as around 56%\(^2\); yet some characteristics,
when present, make the prognosis even worse, such as the clinical condition of multiple ulcers and when both limbs are affected. The expression Bcl-2 and MUM-1 were not related to worse evolution.

The first-line treatment for PCDLBCL-LT is like systemic diffuse large cell lymphoma, employing combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). The systemic use, isolated or combined with chemotherapy, using anti-CD20 antibody has demonstrated favorable results, increasing the survival rate to five years by around 65%-75%. In single small lesions, exclusively cutaneous, radiotherapy can be considered.

Besides that, spontaneous remission of PCDLBCL-LT is extremely rare, as reported in very few cases in the literature. The etiology of such an episode is unknown. It was described as a probable result of the immunological system to bacterial or viral infections or traumatic causes, including biopsies, apoptosis, or a specific condition of the microenvironmental tumor.

Information about the authors: Fernanda Blasques de Faria: caring for patients at the PUC Campinas Dermatology Clinic; following the same patients in their Hospitalization. Collected medical literature data for the last ten years on this subject to prepare this manuscript. Isabela Espargolla Santos: Collaborated on collecting medical literature data for the last ten years on this subject to prepare this text. Made photographic records of the patient. Amilcar Castro de Mattos: performed anatomicopathological and immunohistochemical analyses of the cutaneous biopsy specimens; participated in the discussion for diagnostic confirmation through immunomarkers and pathological clinical correlation. He also prepared the photographic records of the slides. Elaine Cristina Faria Abrhoa Machado: she contributed to the clinical discussion and medical literature data collection; as well as correction and improvement of the manuscript. Livia Matida Gontijo: she contributed to the diagnostic and clinical handling of the patient during his hospitalization; as well as correction and improvement of the manuscript.

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