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Case Report

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-histchochemical 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 by reviewing 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.

RESUMO: Linfomas Cutâneos Primários são a segunda forma mais comum de linfomas extranodais, sendo os linfomas de células B, (CBCLs) representantes de 20 a 30% dos casos. O Linfoma Cutâneo Difuso de Grandes Células B, Tipo Perna (PCDLBCL-LT), representa o tipo mais agressivo de CBCLs. Na maioria dos casos, a apresentação clínica é caracterizada por placas ou tumores solitários, ora ulcerados, em uma ou ambas as pernas, de rápido crescimento. O diagnóstico é confirmado através do estudo histopatológico e imunohistoquímico. O tratamento é realizado por meio de quimioterapia e seu prognóstico é reservado com uma sobrevida de 50% a 60% em 05 anos. O objetivo deste trabalho é relatar um caso atendido de Linfoma Cutâneo Primário Difuso de Grandes Células B, Tipo Perna em um paciente de 75 anos, do sexo masculino com apresentação clínica clássica e desfecho desfavorável, realizar uma revisão bibliográfica do período de 2010 a 2020 na base de dados PUBMED sobre o assunto, dada sua raridade e agressividade ímpar. As informações foram obtidas através de revisão do prontuário, registro fotográfico e revisão da literatura. Por tudo isso, pode-se concluir a importância de estudos multidisciplinares, envolvendo Dermatologistas, Hematologistas, Oncologistas e Patologistas para que o diagnóstico e tratamento sejam instituídos o mais precoce possível, visto a raridade e agressividade do PCDLBCL-LT.

Palavras-chave: Linfoma; Linfoma cutâneo primário; Linfoma cutâneo de células B; Dermatologia.

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INTRODUCTION

Primary Cutaneous Lymphomas are the second most common type of extranodal lymphomas[1]. 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[2,3].

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)[1].

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[2,4], and their prognosis is excellent[1]. PCFCL is described as erythematous-violaceous plaques, nodules, or tumor formations of variable sizes that mainly affect the scalp, forehead, and trunk[2,4]. Meanwhile, the Large Cell Intravascular Lymphoma is clinically characterized by telangiectatic lesions or suggestive of panniculitis affecting the lower limbs and trunk[4]. 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[2]. The elementary lesion consists of a solitary mucocutaneous well-defined ulcer that develops quickly, affecting the oropharyngeal mucosa and gastrointestinal tract[2].

Finally, PCDLBCL-LT is the most aggressive type of BCLs, and it mainly targets older women according to studies[1,2,4]. In most cases, the clinical presentation is characterized by solitary or localized tumors and proliferates on one or both legs[1,2]. The diagnosis is confirmed through a histopathological and immunohistochemical analysis[4]. Treatment is performed by chemotherapy, and its prognosis is reserved, as it is worse when multiple ulcers are present and affect both limbs[3].

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.

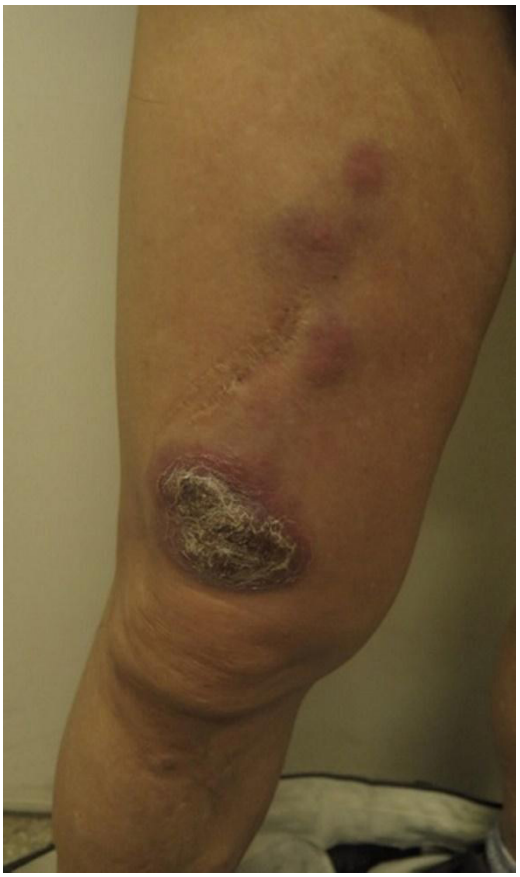

Figure 1. Violaceous tumor formation, with an erythematous, infiltrated, and keratotic base on the anterior right thigh and regular erythematous nodules following a lymphatic pathway.

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.

Marker	Result
CD79	Positive
CD45	Positive
CD20	Positive
MUM-1	Positive
PAX-5	Positive
Bcl-2	Negative
Ki-67	Positive in 80%

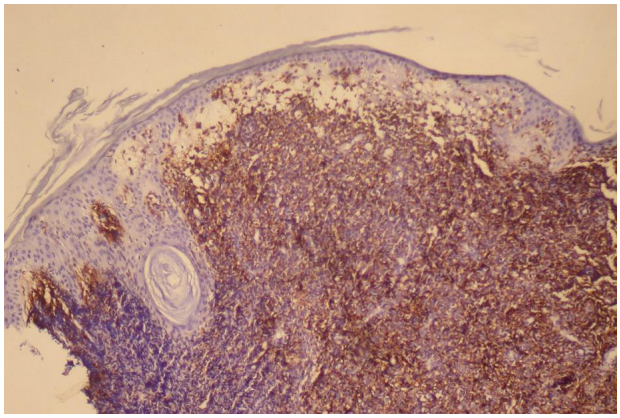

Figure 2. PCDLBCL-LT; The positive immunohistochemical for CD20 (100x).

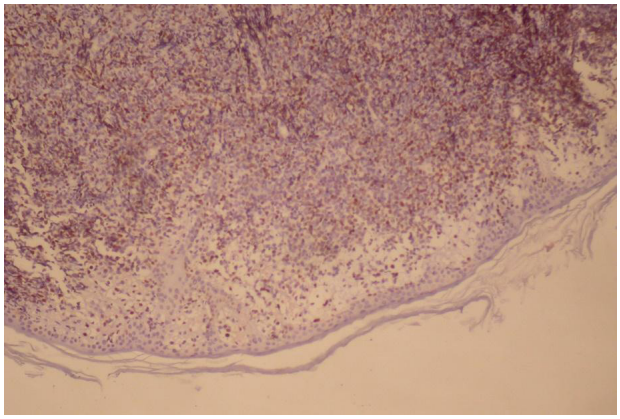

Figure 3. PCDLBCL-LT; The positive immunohistochemical for MUM-1 (100x).

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.

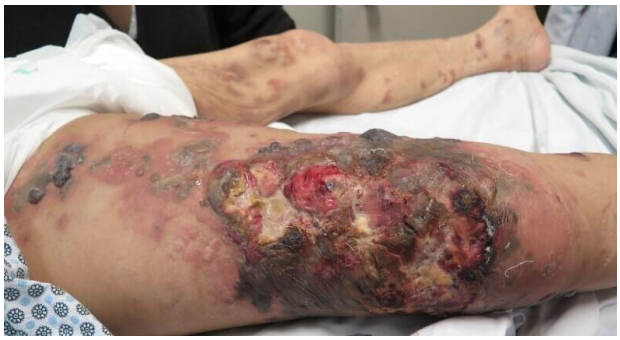

Figure 4. The ulcer is approximately 15 cm on the anterior surface of the right thigh and with erythematous-violaceous plaques, covered by infiltrates from intact brownish boils on the lower limbs.

DISCUSSION

Lymphomas are maligny 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[5].

These malign neoplasms are divided into two large groups: Hodgkin lymphomas (HL) and Non-Hodgkin lymphomas (NHL)[5]. 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[6]. 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[1,8].

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[9].

The primary cutaneous LNHs are even subclassified into two large heterogenous classes: T cell cutaneous lymphomas (TCCLs) and B cell cutaneous lymphomas (BCLs)[1]. The TCCLs represent the majority, from 75% to 80% of cases[2], as the BCLs constitute around 20 to 30% of primary cutaneous lymphomas[2,3].

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[10].

BCLs are classified into 5 types, according

to WHO-EORTC: Marginal Zone B Cell Cutaneous lymphoma, center-follicular B cell cutaneous lymphoma, intravascular cutaneous large B cell lymphoma, EBV+ mucocutaneous ulcer, and primary cutaneous diffuse large B-cell lymphoma, leg type[2,10].

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[1,2], 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.

B cell cutaneous lymphomas	Clinical signs	Histology	Immunohistochemical markers
PCMZL	Plaques, multifocal nodules on the arms and trunk	Small B cells with lymph plasmatic morphology or monocytoid plasmatic cells, monotype plasmatic cells, S reactive germinative center, and numerous T cells	CD20+/ CD79a+/ Bcl-2+ CD10-/ CD5-/ Bcl-6- Reactive Germinative Centers Bcl-6+ CD10+ Bcl-2+
PCFCL	Plaque, papules, nodules or solitary tumor, erythematous-violaceous on the head, neck, and trunk	The proliferation of the centrocytes and centroblasts on the dermis and subcutaneous with a diffused follicular pattern	CD20+/ CD79a+/ CD10+ Bcl-6+ Bcl-2-
Large Cell Intravascular Lymphomas	Telangiectatic plaques and hardened areas suggestive of paniculate or purple on the trunk or limbs	Dilated blood vessels in the dermis and subcutaneous tissue with large neoplastic cells confined inside the lit vessels	CD20+/ CD79a+ Bcl-6+/ Bcl-2+ CD10-
EBVMCU	Solitary mucocutaneous ulcer and very delimited to quick evolution in the oropharyngeal region and gastrointestinal tract	Large EBV cells of the Hodgkin type in a mixed inflammatory background	PAX-5+ CD20 with variable expression
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 type T Lymphomas	MUM-1+/ CD20+/Bcl-2+ Bcl-6+/MYC+ Genetic Mutations CD79b/ CARD 11/MYD 88

PCMZL: Marginal Zone B Cell Cutaneous Lymphoma; PCFCL Follicular Center B Cell Cutaneous Lymphoma; EBVMCU: EBV Positive Mucocutaneous Ulcer; PCDLBCL-LT: Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type. (WHO – EORTC 2018).

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.[2] 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[1,2]. In the immunohistochemical study, the majority displayed positivity for MUM - 1, PAX-5, CD20, Bcl - 2, Bcl-6, and MYC[1,2]. (Table 2)

The authors observed mutations activated genetically via NF - κB 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[13].

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[3]. The expression Bcl-2 and MUM-1 were not related to worse evolution[3,13].

The first-line treatment for PCDLBCL-LT is like systemic diffuse large cell lymphoma, employing combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone)[16]. 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%[11]. In single small lesions, exclusively cutaneous, radiotherapy can be considered[16].

Besides that, spontaneous remission of PCDLBCL - LT is extremely rare, as reported in very few cases in the literature[13,17]. 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[17].

CONCLUSION

Although genetic markers are essential tools, histological integration, immunophenotypic, genetic, and clinical data remain fundamental for a diagnostic conclusion[2].

It is essential to describe the clinical presentation of primary cutaneous diffuse large B-cell lymphoma, leg type, and its immunohistological findings to distinguish and identify it from the other types of primary B cell cutaneous lymphomas. Performing early differential diagnosis on the plaques and ulcers of the lower limbs is fundamental so that correct treatment is started quickly since it is a rare and aggressive pathology.

Therefore, a multidisciplinary approach collaborating with dermatologists, pathologists, hematologists, and oncologists has been crucial for defining new classifications, guaranteeing early diagnosis and treatment, and seeking to increase the survival rate of the patient[2].

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