Lymphoproliferative processes of the skin Part 1 - Primary cutaneous B-cell lymphomas
Processos linfoproliferativos da pele. Parte 1 - Linfomas cutâneos de células B

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Abstract: Primary cutaneous B-cell lymphomas comprise a group of malignant neoplasms originated from the B-cell lymphoid lineage, of the non-Hodgkin type. The diagnostic routine of cutaneous B-cell lymphoproliferative processes consists of a skin biopsy for histopathological, immunohistochemical and gene rearrangement analysis. The classification of primary cutaneous lymphomas is still controversial. The currently most usual classifications are those proposed by the World Health Organization (WHO) and by the European Organization for Research and Treatment of Cancer (EORTC). The recently proposed WHO-EORTC consensus classification should replace them. However, despite recent progress in this field, there are still controversies and difficulties, mainly regarding the diagnosis and classification of cutaneous B-cell lymphomas.
Keywords: B-lymphocytes; Lymphoma, B-cell; Lymphoma, non-Hodgkin; Skin neoplasms; Lymphoproliferative disorders

Resumo: *Os linfomas cutâneos primários de células B pertencem ao grupo das neoplasias malignas originadas de linfócitos B, do tipo não-Hodgkin. A rotina diagnóstica nos processos linfoproliferativos de células B é realizada pela biópsia da pele lesada para a análise histopatológica, imuno-histoquímica e pesquisa do rearranjo gênico. A classificação dos linfomas cutâneos primários vem sendo discutida nos últimos anos; as usualmente utilizadas são as propostas pela World Health Organization - WHO e pela European Organization for Research and Treatment of Cancer - EORTC. A recente classificação consensual proposta por WHO-EORTC deverá substituí-las. Entretanto, apesar dos recentes progressos, ainda existem controvérsias e dificuldades quanto à classificação, ao diagnóstico e ao tratamento dos linfomas cutâneos primários de células B.*
Palavras-chave: Linfócitos B; Linfoma de células B; Linfoma não Hodgkin; Neoplasias cutâneas; Transtornos linfoproliferativos

INTRODUCTION

Primary cutaneous lymphomas can originate from T, B or NK lymphocytes.[1,2] To understand primary cutaneous lymphomas, knowledge of the skin as an immune organ is necessary – it is a large organ and a barrier system between the organism and the external environment, taking active part in the immune responses and inflammatory reactions. The cell population involved in these responses consists mainly of keratinocytes, Langerhans cells, dermal dendrocytes, T-lymphocytes, polymorphonuclear leukocytes, mast cells and endothelial cells.[3] T-lymphocytes are produced in the bone marrow and undergo differentiation in the thymus. After maturation, they constantly circulate in the naïve form (virgin, not exposed to antigens) in blood and peripheral lymphoid organs. When T lymphocytes are presented, in the lymph nodes, to antigens coming from the skin (effector lymphocytes, memory lymphocytes) they express markers on their surface, which turns them into "participants" of the immune system of this organ. B-lymphocytes do not belong to the skin cell population under physiological conditions, but they are produced and matured in the bone marrow, remaining in the peripheral lymphoid organs and tissues (spleen, lymph nodes and mucosa), as well as in the bone marrow. In response to antigenic stimuli (at distance), the B-lymphocytes can migrate to other organs.[3]

To understand the lymphoproliferative disorders of the B-cells, it is important to know some con-

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cepts about the differentiation of the B-lymphocytes. This process comprises an initial phase, named antigen-independent, which occurs in the fetal liver and in the fetal and adult bone marrow, and an antigen-dependent phase, which takes place in peripheral lymphoid organs. During the first stage (antigen-independent), the Ig genes undergo a gene rearrangement V(D)J of the variable (V), diversity (D) and junction (J) segments, by means of somatic recombination, producing immature B-cells that are able to migrate to the spleen. In the spleen, part of the lymphocytes will constitute the native follicular B-cells, and another subpopulation will originate the cells of the marginal zone. During the second maturation phase, the recognition of a "T-dependent antigen" triggers the formation of a germinal center and the corresponding transition of naïve follicular B-cells to effector cells. The germinal center is a complex cell microenvironment, composed of B-lymphocytes (centroblasts, centrocytes), follicular dendritic cells and antigen-dependent T-lymphocytes, and it generates high-affinity humoral responses. These changes are due to activation of the somatic hypermutation process, affecting the V segment, and to the change in Ig class by recombination, replacing the constant μ region. Later on, some of the memory cells and the long-lived plasma cells come to reside in the B zones of the peripheral lymphoid organs, while others re-circulate or migrate to the bone marrow. The marginal-zone B-cells located in the lymphoid organs with a high antigenic influx play an important role in the response to T-independent antigens and intervene in the initial phase of the response to T-dependent antigens (capture, processing and antigenic introduction), rapidly differentiating into short-lived plasma cells.[3-8]

All cells express molecules (antigens) that identify them, either on their surface or inside. Many of these molecules, named CD (cluster of differentiation), are identified by monoclonal or polyclonal antibodies. Based on the development of antibodies to recognize these molecules, it was possible to study the role of the T/NK and B-lymphocytes in both physiological and neoplastic processes, and to classify the lymphomas, which are clonal proliferations of theses cells in their several stages of differentiation.

Lymphomas are initially divided into two large groups: Hodgkin and non-Hodgkin. Hodgkin lymphomas affect mainly cervical lymph nodes in adults. Their absolute incidence does not seem to have changed, as opposed to the evident increased incidence of non-Hodgkin lymphomas.[9,10] The latter are further divided into two groups: nodal and extranodal. Nodal non-Hodgkin lymphomas affect primarily the lymph node. The primary cutaneous lymphomas belong to the group of extranodal non-Hodgkin lymphomas, which primarily involve other sites, different from the lymph nodes. Skin is the second location of extranodal involvement, corresponding to 25% of all extranodal non-Hodgkin lymphomas, following the gastrointestinal tract.[11] The primary cutaneous lymphomas differ significantly from the equivalent nodal forms with regard to their clinical behavior and prognosis.[12]

In the past, cutaneous lymphomas were not recognized as a condition, but rather as a secondary skin involvement by nodal lymphoma. Initially, only mycosis fungoides, a cutaneous T-cell lymphoma, was recognized as a primary form of cutaneous lymphoma. The first reports of non-mycosis fungoides primary cutaneous lymphomas were published in the 1960's and 1970's. Based on the immunophenotypic characteristics of neoplastic cells, in the late 1970's, lymphomas were divided into two large groups, T-cell and B-cell, according to their origin.[13,14] In the 1980's and 1990's the concept of primary and secondary cutaneous lymphomas was introduced, and thereafter several classifications were proposed.[15-17] Recently, the World Health Organization – WHO and the European Organization for Research and Treatment of Cancer – EORTC proposed a consensus classification for cutaneous lymphomas, encompassing histopathological, immunohistochemical, molecular and clinical aspects.

The diagnostic confirmation of cutaneous lymphoma is not easy. The tests considered as the "golden standard" are histopathology and immunohistochemistry. The diagnosis of this neoplasm is usually suggested by experienced pathologists by means of cytomorphological evaluation and by the disposition of the infiltrate architectural arrangement. Currently, to classify lymphomas it is indispensable to perform an immunohistochemical study, with an antibody panel that is rationalized according to the histological findings. Initially, this study aims to discriminate whether the infiltrate is composed of B or T/NK lymphocytes. Secondarily, it will help to classify into two large groups (B and T/NK). On rare occasions, the immunohistochemical study has diagnostic power. It is also important to distinguish between the phenotypes of the cells of interest (neoplastic cells) and those of the reactive infiltrate (reactive inflammatory cells). The panel used to mark the T-cells consists mainly of anti-CD3 and CD45RO antibodies; for NK cells, anti-CD16 and CD56; and, for B cells, anti-CD19, CD20, CD79a and CD10. T-lymphocytes are CD3+ and, when they are memory cells, they are also CD45RO+. NK lymphocytes are CD3-,CD16+ and CD56+. B-lymphocytes are CD3-, CD19+, CD20+ and CD79a+. The B-lymphocytes of the germinal center are CD19+, CD20+, CD79a+ and CD10+, where-

as the B-lymphocytes of the marginal zone are CD19+, CD20+, CD79a+ and CD10-. The plasma cells are usually CD19-, CD20- and CD79a+. Other complementary markers are important aids for diagnosis or classification, such as CD21, CD23, ALK, EMA, CD4, CD8, besides the molecules related to apoptosis, such as bcl-2, bcl-6, and the cell proliferation marker Ki-67.[3,11]

CUTANEOUS B-CELL LYMPHOMAS

The annual incidence of B-cell lymphomas, including nodal and extranodal lymphomas, is extremely variable. In the US, the incidence is approximately 15 per 100,000 inhabitants, in China 1.2 per 100,000 inhabitants. South America, Africa and Japan present intermediary incidences. The primary cutaneous B-cell lymphomas represent approximately 20-25% of all primary cutaneous lymphomas.[11] According to a study of the EORTC, primary cutaneous B-cell lymphomas show a discreet prevalence of the male sex, in the ratio of 2:1, and affect individuals with a mean age of 59 years. Cutaneous B-cell lymphomas present clinically in a monotonous form, in most cases as papules or nodules, differently from cutaneous T-cell lymphomas.[18] In order to characterize a lymphoma as primary cutaneous, it is necessary that only the skin is affected and that there is no evidence of systemic involvement upon the initial evaluation.14 The etiopathogenis of cutaneous B-cell lymphomas is unknown. Attempts are being made to understand them concerning the differentiation process of B-cells, as reviewed above. It has been reported that the neoplastic cells exhibit mutations in the VH genes that remind of antigenic selection processes of the germinal centers; however, recent studies have demonstrated the existence of possible somatic hypermutation processes in the marginal-zone cells in the absence of germinal center formation. It is currently believed that cutaneous B-cell lymphomas may originate from germinal center lymphocytes, their descendants or from the marginal zone, which are chronically activated and stimulated by antigens.[19-21] In Europe, a frequent association with Borrelia burgdorferi infection is reported, but this does not occur in the US, and has not been observed in Brazil either.[18,22-24]

Classification

The classification of lymphomas has been discussed and modified over the last decades. Currently, the classifications usually employed for cutaneous lymphomas are those proposed by WHO and EORTC.[25] The first of them, an update of the Revised European-American Lymphoid Neoplasm Classification – REAL, combines histological, immunophenotypic and genetic criteria and is widely adopted by pathologists and the most commonly used in the US.[26] The EORTC classification is based on a combination of clinical, histological, immunophenotypic and genetic criteria and is usually preferred by dermatologists and clinical oncologists; it is the most commonly used in Europe.[9]

The recent WHO-EORTC consensus classification for primary cutaneous B-cell lymphomas divides them into two large groups according to their clinical behavior, either indolent or intermediary (Chart 1).[27] In this article we will describe the cutaneous B-cell lymphomas with regard to their clinical, histological and immunohistochemical characteristics according to the WHO-EORTC classification for primary cutaneous lymphomas.

Diagnostic aspects

Clinical history and physical examination collaborate in the diagnosis of primary cutaneous B-cell lymphomas. Confirmation, however, is obtained essentially by the histological and immunohistochemical studies (Figures 1 and 2).[28,29] Both the histological and the immunohistochemical studies are performed on a fragment of skin biopsy. Currently, the immunohistochemical examination may be done in formaldehyde-fixed and paraffin-embedded specimens, due to the development of antibodies and techniques capable of revealing antigens present in tissues processed in this manner.[30,31] The search for a rearrangement of the immunoglobulin heavy chain gene and for genetic alterations by means of molecular biology techniques has been described as an important aid in the diagnosis of lymphoproliferative processes. The search for a rearrangement in the immunoglobulin gene is currently also performed in formaldehyde-fixed and paraffin-embedded specimens.[32-34]

CHART 1: WHO-EORTC classifications for primary cutaneous B-cell lymphomas

Indolent clinical behavior

- Primary cutaneous marginal-zone B-cell lymphoma
- Primary cutaneous follicle-center lymphoma

Intermediate clinical behavior

- Primary cutaneous diffuse large B-cell lymphoma, leg-type
- Primary cutaneous diffuse large B-cell lymphoma, other
- Primary cutaneous intravascular large B-cell lym phoma

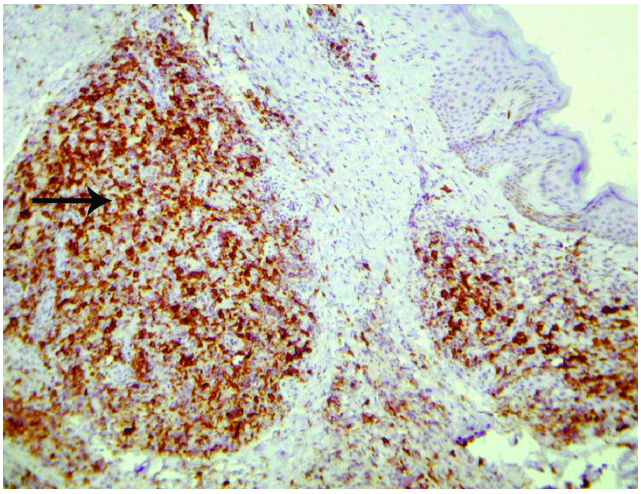

FIGURE 1: Primary cutaneous marginal-zone B-cell lymphoma, CD 20+ in the neoplastic cells (arrow) (x100)

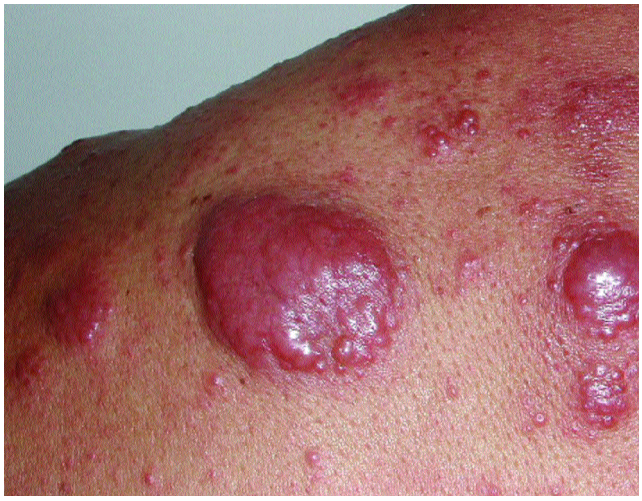

FIGURE 3: Primary cutaneous follicular center B-cell lymphoma. Papules and nodules in the dorsal region

Clinical aspects

By and large, the primary cutaneous B-cell lymphomas clinically present as papules, plaques or nodules.[35] Their coloration can vary from erythematous to purple. The lesions could be solitary or multiple, disseminated or grouped in a region of the body, rarely presenting ulceration or necrosis (Figure 3). As for their localization, they may affect any region of the skin, although some subtypes show areas of predilection (Figure 4). Chart 2 presents a list of the main clinical characteristics of primary cutaneous B-cell lymphomas, according to the recent WHO-EORTC classification of primary cutaneous lymphomas.[31, 36-41]

Histological aspects

A histological study using hematoxylin-eosin (HE) staining enables identifying neoplastic lymphocyte proliferation. The presence of the normal collagen band in the superficial dermis, called Grenz zone, separating the epidermis from the dermal lymphoid infiltrate, is a common finding in cutaneous B-cell lymphomas.[1] Epidermotropism, the migration of lymphocytes to the epidermis, frequent in T-cell lymphomas, is rare in B-cell lymphomas.[2,17] The lymphocytic infiltrate described in cutaneous B-cell lymphomas is usually dense, asymmetric, nodular or diffuse, and often tends to be more intense in the deep

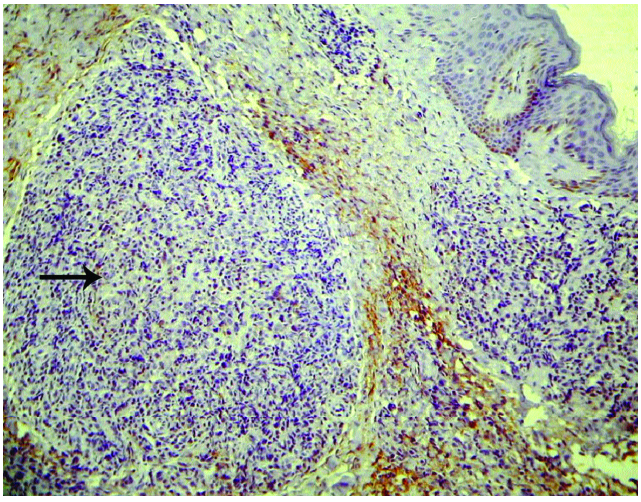

FIGURE 2: Primary cutaneous marginal-zone B-cell lymphoma, CD 10- in the neoplastic cells (arrow) (x100)

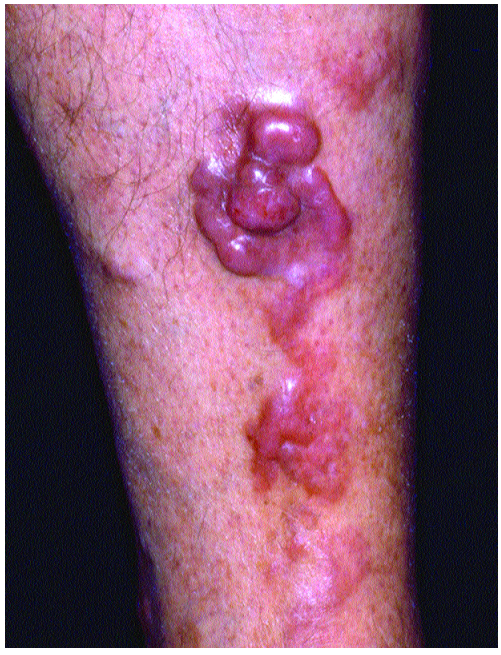

FIGURE 4: Primary cutaneous diffuse large B-cell lymphoma, on the leg

CHART 2: Clinical, histological and immunohistochemical profile of cutaneous lymphomas according to the WHO-EORTC classification for primary cutaneous lymphomas

Primary cutaneous marginal-zone B-cell lymphoma [27,55]

- **Clinical characteristics – It usually presents as a papule, plaque or nodule; single or, more frequently, multiple grouped lesions; with a predilection for the trunk or limbs, mainly the upper limbs. Immunocytoma and the follicular lymphoid hyperplasia with monotypic plasma cells, as well as the rare cases of plasmocytoma non-associated with multiple myeloma (extramedullary plasmocytoma of the skin), are included in this group.**
- **Histology – It presents a diffuse, nodular or perivascular and periadnexal area-forming lymphocyte infiltrate, affecting the dermis down to the subcutaneous tissue. A "reverse pattern" to the one observed in the germinal centers of the lymphoid follicles is described for the lymphocyte infiltrate of the marginal-zone lymphoma: it presents with a darker center formed by small lymphocytes, circumscribed by a lighter area formed by medium-size cells and abundant cytoplasm, resembling centrocyte. Reactive germinal centers are frequently present. The cell infiltrate of the interfollicular areas may be composed of small lymphocytes, plasma cells, lymphoplasmocytoid cells, monocytes, eosinophils and, occasionally, blasts.**
- **Immunohistochemistry – Neoplastic cells are CD20+, CD79a+, bcl-2+, CD10-, CD5- and bcl-6-. Yet, reactive germinal centers are frequently bcl-6+, CD10+ and bcl-2- (Figures 1 and 2).**
- **Genetic characteristics – Monoclonality is observed in the gene rearrangement for the immunoglobulin heavy chain (IgH). Chromosome translocations involving IgH and other genes have been demonstrated, they however do not constitute markers of this group.**
- **Prognosis – Case series demonstrate a 100% survival over five years.**
- **Treatment – Single lesions are treated with radiotherapy or surgical excision. When an association with Borrelia burgdorferi infection is demonstrated, the initial use of systemic antibiotics is recommended. In multiple lesions, chlorambucil, subcutaneous or intralesional interferon alpha, and systemic or intralesional monoclonal anti-CD20 antibody are indicated. If frequent relapses occur, topical or intralesional steroids is indicated.**

Primary cutaneous follicle center lymphoma [17,27,31,56]

- **Clinical characteristics – It presents a predilection for the head (scalp and frontal region) and trunk. The lymphoma described in the past as Crosti lymphoma or reticulohistiocytoma of the dorsum, usually a nodule or plaque, corresponds to the primary cutaneous follicular center-cell lymphoma. (Figure 3)**
- **Histology – It is characterized by a diffuse and/or follicular growth pattern, formed by neoplastic center cells and centroblasts, besides immunoblasts, small lymphocytes, histiocytes, eosinophils and plasma cells. Mitosis figures can be frequent. Reactive lymphoid follicles reminding of germinal centers may be present, frequently making the differential diagnosis with pseudolymphomas difficult.**
- **Immunohistochemistry – Regarding the follicular pattern, the neoplastic cells are CD20+, CD79a+, CD10+ and bcl-6+. CD10 expression is usually negative in the diffuse pattern. They are CD5-, CD43- and bcl-2- (rarely positive) (Figures 6 and 7).**
- **Genetic characteristics – Monoclonality in the gene rearrangement for the immunoglobulin heavy chain was demonstrated. Somatic hypermutation of the light and heavy chain genes was observed. Inactivation of suppressor genes such as p15 and p16 is described in 10-30% of the cases. There is no association with the t(14;18) translocation.**
- **Prognosis – The follicular pattern suggests a better prognosis, with 95% survival over five years. The diffuse growth pattern and positivity for bcl-2 are related to a less favorable prognosis.**
- **Treatment – Radiotherapy is the treatment of choice. Surgical excision of small lesions may be indicated. In very large skin lesions and in extracutaneous disease, chemotherapy is indicated. Recently the use of intralesional or systemic anti-CD20 antibody was demonstrated to be effective.**

Primary cutaneous diffuse large B-cell lymphoma, leg-type [27,33]

- **Clinical characteristics – It affects the lower limbs, frequently only one limb, rarely bilaterally. It affects mainly the elderly and particularly females. The lesions may be solitary or multiple grouped (Figure 4).**
- **Histology – It presents a dense infiltrate of large cells in the dermis and subcutaneous tissue, formed by centroblasts, immunoblasts and large centrocytes. Epidermotropism simulating T-cell lymphoma may be present, and mitosis figures are frequent (Figure 5).**
- **Immunohistochemistry – The neoplastic cells are CD20+, CD 79a+, bcl-2+ and bcl-6+ in most cases. They are frequently CD10-.**
- **Genetic characteristics – Monoclonality is observed in the gene rearrangement for heavy chain immunoglobulin (IgH). Although intense expression of bcl-2 occurs frequently, no t(14;18) translocation is observed.**
- **Prognosis – Five-year survival was demonstrated in 36 to 100% of cases. Multiple lesions and/or involvement of both lower limbs provide a poorer prognosis.**
- **Treatment – The indicated treatment is the same as in diffuse systemic large-cell lymphoma, that is, chemotherapy. In small single and exclusively cutaneous lesions, radiotherapy can be considered. Systemic use of the anti-CD20 antibody, alone or in association with chemotherapy, demonstrated to give favorable results.**

Primary cutaneous diffuse large B-cell lymphoma, other [27]

- **Clinical characteristics – It presents clinical characteristics that are similar to the group of marginal-zone and fol-**

Continua

QUADRO 2: Perfil clínico, histológico e imuno-histoquímico dos linfomas cutâneos, segundo a classificação WHO-EORTC para os linfomas cutâneos primários

licular centrocytes primary B-cell lymphoma, affecting the head, neck, trunk and lower limbs. In this group, rare cases are included, which do not meet the classification criteria for primary follicular center cell lymphoma, nor for diffuse primary cutaneous large B-cell lymphoma, leg-type. In general, these cases correspond to diffuse large B-cell lymphomas, anaplastic variant, plasma cell variant, B-cell lymphoma rich in T-cells variant, or even systemic lymphomas with skin involvement.

Primary cutaneous intravascular large B-cell lymphoma[27]

- **Clínica - Clinical characteristics – It is characterized by telangiectasic lesions, plaques or hardened areas that are tender, suggesting panniculitis or purpura, involving the trunk and lower limbs. It can also affect the central nervous system and lungs.**
- **Histology – It presents a great number of dilated blood vessels in the dermis and subcutaneous tissue, with the presence of large neoplastic lymphoid cells confined to the lumen of venules, capillaries and arterioles.**
- **Immunohistochemistry –The neoplastic cells are CD20+, CD79a+, bcl-2+, bcl-6+, and frequently CD10-.**
- **Prognosis – It is reserved in cases with associated extracutaneous involvement (three-year survival in 22% of cases) with a more favorable prognosis for exclusively cutaneous lesions (three-year survival in 56% of cases).**
- **Treatment – Systemic chemotherapy.**

dermis, called the "bottom-heavy pattern". Lesions at early stages of cutaneous B-cell lymphomas tend to present irregular or nodular perivascular and periadnexal infiltrates in the superficial reticular dermis (Figure 5), whereas old lesions tend to present a more diffuse cell infiltrate, from the dermis to the subcutaneous tissue, with or without the presence of reactive lymphoid follicles. Reactive T-lymphocytes are observed in the periphery or among the neoplastic B-cells, mainly in initial lesions. Mitosis figures can also be found in great amounts. Chart 2 presents the main histological characteristics of primary cutaneous B-cell lymphomas.[31,42-45]

Immunohistochemical aspects

The immunohistochemical study is designed to identify the cell line and the differentiation stage of the lymphocyte population, as well as other cells present in the cell infiltrate under study. The main B-lymphocyte markers used in paraffin-embedded tissues are: anti-immunoglobulin κ and λ light-chain antibodies, CD20, CD79a, CD10 and CD5 (marking a subpopulation of B-lymphocytes from the mantle zone) (Figures 6 and 7). In the study of cutaneous B-cell lymphomas, it is also necessary to investigate the presence of T-cells. The main T-lymphocyte markers used in paraffin-embedded tissues are: CD3 and CD45RO. The anti (bcl-2, bcl-6, CD21, CD23 and Ki-67) antibodies are also helpful in diagnosing B-cell lymphoproliferative processes.[30,46]

Lymphoid cells with B immunophenotype express immunoglobulin light chains on their surface. The investigation of the immunoglobulin light chains κ and λ is used to study clonality in lymphocyte populations as an aid to the diagnostic investigation of lymphoproliferative processes and a contribution mainly to differing between lymphomas and pseudolymphomas. However, there are technical difficulties during the histological processing, when the immunohistochemical test for these chains is performed. The integrity of the cell surface immunoglobulins is often compromised, which may allow their release into the interstitium, leading to a high background an unspecific background reaction and making it difficult to interpret the reactivity for the light chains kappa and lambda chains.[30] The in situ hybridization technique is described as an aid to minimize false-positive or false-negative results, using labeled probes to detect the messenger RNA of the immunoglobulin light chains.[47,48] As a rule, lymphoid infiltrates are monoclonal in malignant lymphoproliferative processes and polyclonal in benign reaction conditions. In polyclonality, the κ/λ rate is usually 3:1 or 2:1. In monoclonality, this rate indicates kappa restriction when it is higher than 5-10:1, or lambda restriction when it is lower than 0.5-1:1.[32, 49, 50]

The cell markers (CD) are antigens expressed by the cell, both on its surface and inside. Identification of each CD is carried out by using specific antibodies, as already described. The antibody panel is designed with the purpose of identifying B and T/NK lymphocytes, as well as the stages of cell maturation, differentiation and activation, besides providing an adequate evaluation of the infiltrate architectural arrangement.[3,11,51] For large-cell lymphoid infiltrates, frankly neoplastic on HE, the most important antibodies are those used to distinguish T from B cells. In small- and medium-cell lymphoid

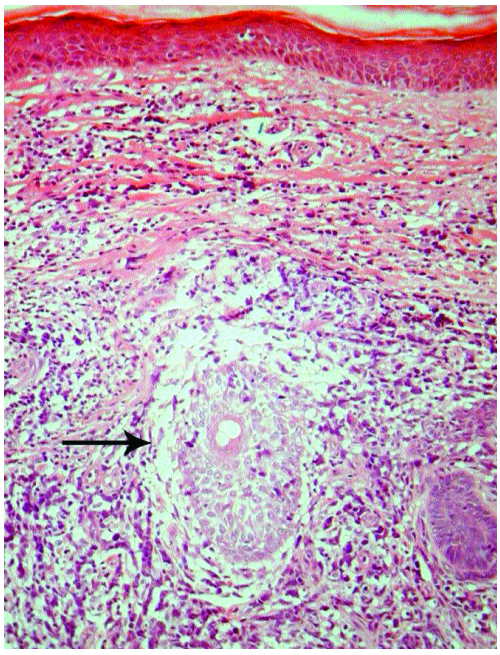

FIGURE 5: Primary cutaneous diffuse large B-cell lymphoma, adnexal invasion (arrow) HE (100X)

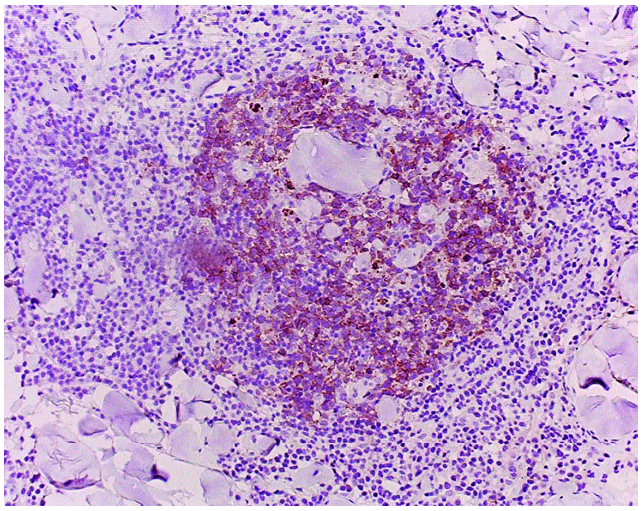

FIGURE 7: Primary cutaneous follicular center lymphoma. CD 10+ in the neoplastic cells outlining a follicle (arrow) (200X)

infiltrates, the use of the complete panel is important, both for the differentiation between T and B cells and for the differentiation between lymphomas and pseudolymphomas. Markers such as bcl-2, bcl-6 and Ki-67 are important to complement diagnosis and classify these processes. In chart 2, the main immunophenotypic characteristics of primary cutaneous B-cell lymphomas are listed.[52-56]

Molecular biology aspects

The search for a rearrangement of the immunoglobulin heavy chain gene by means of molecular biology techniques has been used as a complementary method in the diagnosis of B-cell lymphoproliferative processes. In lymphoma, clonal proliferation occurs, that is, cells originated from a single cell clone, expressing identical surface molecules and presenting the same gene rearrangement for these molecules. Thus, the detection of the gene rearrangement for immunoglobulin heavy chains demonstrating clonal proliferation in the B-cell lymphoproliferative processes strongly suggests a malignant aspect of the lymphocyte population studied.[3,31]

The investigation of the gene rearrangement is performed using the Southern Blot or PCR (polymerase chain reaction) method. The PCR method, in which DNA is amplified by the polymerase chain reaction, is more sensitive than the Southern Blot. Therefore, PCR requires a smaller amount of DNA and can be performed in paraffin-embedded material.[50,57-59] Chromosome translocation $t^{14,18}$ is present in secondary involvement of the skin by nodal follicular lymphoma and absent in primary cutaneous lymphomas.[60-63] The genetic alterations demonstrated in primary cutaneous B-cell lymphomas are not specific, and therefore not valued in diagnostic verification, classification, prognosis and therapeutic design of such processes. Concepts, classifications and diagnostic techniques regarding cutaneous lymphomas are in constant evolution. The best definition of these processes will be reached by gaining knowledge about their molecular abnormalities, etiologies and pathogeneses. This fact stimulates new research to find diagnostic methods and adequate treatments for the cutaneous lymphoproliferative processes.[17,64,65]

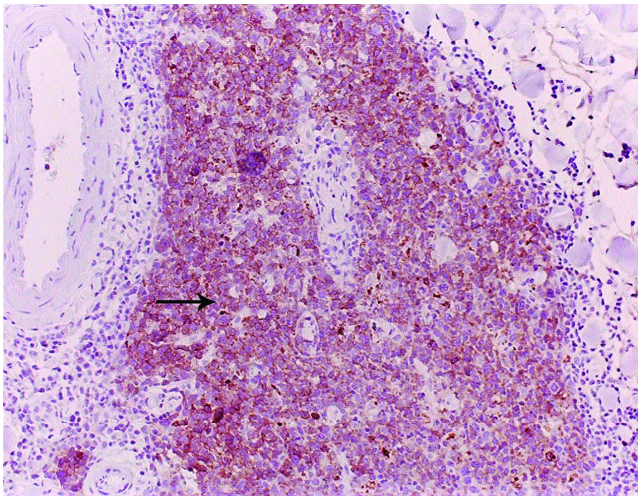

FIGURE 6: Primary cutaneous follicular centrer B-cell lymphoma. CD 20+ in the neoplastic cells (arrow) (200X)

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Questions and answers to questions

The cell population involved in the skin immune response is primarily composed of:

a) keratinocytes, Langerhans cells, NK lymphocytes and T lymphocytes
b) keratinocytes, Langerhans cells, T lymphocytes and B lymphocytes
c) keratinocytes, Langerhans cells, dermal den drocytes and T lymphocytes
d) keratinocytes, mast cells, fibroblasts and Langerhans cells

2. Primary cutaneous lymphomas belong to the group of:

a) Hodgkin`s lymphomas
c) nodal non-Hodgkin`s lymphomas
d) extranodal non-Hodgkin`s lymphomas
d) they do not apply to this classification

3. The concept of primary and secondary cutaneous lymphomas:

a) appeared with the advent of immunohistochemistry
b) appeared with the concept of monoclonality
c) appeared with discovery of the protein bcl-2
d) is a relatively new concept

4. The most often used classifications for cutaneous lymphomas are proposed by:

a) WHO/EORTC
b) W-F/EORTC
c) REAL/WHO
d) REAL/EORTC

5. The most recent classification proposed for primary cutaneous B-cell lymphomas comprises the following types:

a) primary cutaneous marginal-zone B-cell lymphoma; primary cutaneous follicle-center lymphoma; anaplastic variant of cutaneous B-cell lymphoma; primary cutaneous intravascular large B-cell lymphoma
b) primary cutaneous diffuse large B-cell lymphoma, leg-type; primary cutaneous diffuse large B-cell lymphoma, other; primary cutaneous mantle zone B-cell lymphoma; anaplastic variant of B-cell lymphoma
c) cutaneous follicular center B-cell lymphoma; primary cutaneous marginal-zone B-cell lymphoma; primary cutaneous mantle zone B-cell lymphoma; primary cutaneous intravascular large B-cell lymphoma
d) primary cutaneous marginal-zone lymphoma; primary cutaneous follicle-center lymphoma; primary cutaneous diffuse large B-cell lymphoma, leg-type; intravascular primary cutaneous large B-cell lymphoma

6. Regarding the primary cutaneous B-cell lymphomas, it is correct to state that:

a) to characterize a lymphoma as primary cutaneous, only the skin could be affected, with no evidence of systemic involvement during one-year follow-up after the initial evaluation
b) primary cutaneous B-cell lymphomas represent approximately 25% of all primary cutaneous lymphomas
c) although their etiology is still unknown, they are often associated with B. burgdorferi infection, particularly in the United States.
d) In the United States, the incidence is approximately 150 cases per 100,000 inhabitants

7. The lymphoma described in the past as Crosti lymphoma or reticulohistiocytoma of the back corresponds in current classifications to:

a) primary cutaneous follicle-center lymphoma
b) primary cutaneous marginal-zone B-cell lymphoma
c) primary cutaneous diffuse large B-cell lymphoma, leg-type
d) primary cutaneous diffuse large B-cell lymphoma, other

8. By and large, the clinical presentation of primary cutaneous B-cell lymphomas is:

a) patches and plaques that are never ulcerated
b)ulcerated plaques or nodules
c) papules, plaques or nodules
d) large edematous areas circumscribed by papules

9. The diagnostic routine of cutaneous lymphomas consists of the following tests:

a) immunohistochemistry and gene rearrangement analysis
b) H&E and gene rearrangement analysis
c) H&E and chromosome analysis
d) H&E and immunohistochemistry

10. Using hematoxylin-eosin (HE) in histological examination, it is possible to identify the following in cutaneous B-cell lymphomas:

a) lymphoplasmocytic infiltrate, which is usually superficial, asymmetric, nodular or diffuse
b) lymphocytic infiltrate, bottom-heavy pattern, with well-formed marginal zones
c) lymphocytic infiltrate more intense in the deep dermis, called bottom-heavy pattern
d) lymphoplasmocytic infiltrate in the epidermis and looks like follicles

11. The so-called Grenz zone corresponds to:

a) the normal collagen band in the superficial dermis, separating the epidermis from the dermal

lymphocytic infiltrate
b) band-like and diffuse infiltrate in the superficial dermis, usually found in cutaneous B-cell lymphomas
c) the follicular aspect of secondary germinal centers, often observed in cutaneous B-cell lymphomas
d) T-cell infiltrate permeating the normal collagen in superficial dermis in B-cell lymphomas

12. The diffuse primary cutaneous large B-cell lymphoma (leg-type) may present:
a) histologically, a dense infiltrate of large cells in the dermis and subcutaneous tissue
b) intense epidermotropism with typical micro abscesses mimicking T-cell lymphoma
c) infrequent mitosis figures
d) specific and diagnostic immunohistochemical profile

13. Regarding clonality analysis in immunohistochemical study of cutaneous B-cell lymphomas, we could say that:
a) a k/l rate of 3:1 is suggestive of kappa restriction; therefore, it indicates monoclonality
b) kappa and lambda chains are heavy and light chains, respectively, of immunoglobulins
c) the investigation of heavy chain is more precise for monoclonality analysis since it causes less background reaction
d) the integrity of cell surface immunoglobulins is frequently compromised during specimen processing, making it difficult to interpret the exam

14.The main markers of B-lymphocytes used to classify cutaneous lymphomas are:
a) CD20, CD79a, CD56
b) CD20, CD79a, CD10
c) CD19, CD10, CD3
d) CD3, CD45RO, CD5

15. Important immunohistochemical characteristics for diagnosis of follicular lymphoma (WHO) are:
a) negative CD20 and negative CD 10
b) negative CD20 and positive CD10
c) positive CD 20 and positive CD10
d) positive CD 20 and negative CD10

16. The five-year survival in primary cutaneous B-cell lymphomas with indolent behavior is:
a) approximately 45%
b) > 90%
c) < 70%
d) < 95%

17. As to concept of clonality in cutaneous lymphomas, it is not correct to state that:
a) monoclonality indicates rare cell origin
b) usually monoclonality indicates malignant processes
c) polyclonality corresponds to benign reactive processes
d) polyclonality indicates cell origin from several cell clones

18. Due to its higher sensitivity, the method most often used to study gene rearrangement for immunoglobulin heavy chain is:
a) Southern Blot
b) PCR (polymerase chain reaction)
c) FISH
d) RAPDT

19. Choose the correct sentence:
a) mycosis fungoides was the last type of lymphoma to be classified as primary cutaneous lymphoma
b) cutaneous lymphomas are considered extranodal Hodgkin lymphomas
c) the incidence of cutaneous lymphomas has decreased in the past decades
d) in the past, cutaneous lymphomas with skin manifestations were usually considered as secondary skin involvement

20. Primary cutaneous diffuse large B-cell lymphoma, leg-type:
a) its clinical presentation is similar to that of cutaneous T/NK-cell lymphomas
b) it may have a clinical picture suggestive of panniculitis
c) its clinical presentation is very diverse
d) its treatment should be targeted at skin lesions

ANSWERS

Update on the pathophysiology with special emphasis on CD8 effector T cells and CD4 regulatory T cells 2005;80(4):335-47.

1. d	**11. d**
2. d	**12. b**
3. a	**13. c**
4. c	**14. d**
5. c	**15. a**
6. d	**16. b**
7. d	**17. d**
8. a	**18. d**
9. d	**19. c**
10. d	**20. d**