Lymphoproliferative processes of the skin. Part 2 – Cutaneous T-cell and NK-cell lymphomas

Processos linfoproliferativos da pele. Parte 2 – Linfomas cutâneos de células T e de células NK

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Abstract: The cutaneous NKT/cell lymphomas are a group of extranodal lymphoproliferative disorders currently classified and subdivided based on their clinical behavior, according to a consensus reached between the World Health Organization and the European Organization for Research and Treatment of Cancer. The cutaneous NKT/cell lymphomas of indolent clinical behavior comprise the classical mycosis fungoides, folliculotropic mycosis fungoides, pagetoid reticulosis, granulomatous slack skin, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, subcutaneous panniculitis-like T-cell lymphoma and primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma. The aggressive clinical behavior cutaneous NKT/cell lymphomas include Sézary syndrome, extranodal NK/T-cell lymphoma, nasal type, primary cutaneous aggressive epidermotropic $CD8^+$T-cell lymphoma, cutaneous gamma-delta T-cell lymphoma and primary cutaneous peripheral T-cell lymphoma, unspecified. The adult T-cell leukemia lymphoma and $CD4^+$ $CD56^+$ hematodermic neoplasm are considered systemic lymphomas but are addressed in this article for their initial cutaneous manifestations in a significant number of patients. The diagnosis of these processes is based on histological examination complemented by phenotypic analysis of neoplastic cells, which is essential for classification. The recommended staging is based on type and extension of cutaneous involvement, clinical conditions and histological examination of lymph nodes and organs. Hematological assessment is fundamental to characterize Sézary syndrome. The recommended therapies include exclusively cutaneous treatment, biological response modifiers and systemic chemotherapy.

Keywords: Cutaneous neoplasm; Lymphoproliferative disorders; NK lymphocytes; NK-cell lymphoma; Non-Hodgkin lymphoma; T lymphocytes; T-cell lymphoma

Resumo: *Os linfomas cutâneos de células T/NK constituem um grupo de doenças linfoproliferativas extranodais atualmente classificadas e subdivididas de acordo com o comportamento clínico segundo consenso da Organização Mundial de Saúde e da Organização Européia para Pesquisa e Tratamento do Câncer. Os linfomas cutâneos de células T/NK de comportamento clínico indolente compreendem a micose fungóide clássica, a micose fungóide foliculotrópica, a reticulose pagetóide, a cútis laxa granulomatosa, o linfoma cutâneo primário de grande célula anaplásica, a papulose linfomatóide, o linfoma subcutâneo de célula T paniculite-símile e o linfoma cutâneo primário de pequena e média célula T $CD4^+$ pleomórfica. Os linfomas cutâneos de células T/NK de comportamento agressivo incluem a síndrome de Sézary, o linfoma extranodal de célula T/NK, tipo nasal, o linfoma cutâneo primário agressivo de célula T $CD8^+$ epidermotrópica, o linfoma cutâneo de célula T $\gamma\delta$ e o linfoma cutâneo primário de célula T periférica, não especificado. O linfoma-leucemia de células T do adulto e a neoplasia hematodémica $CD4^+CD56^+$, embora considerados linfomas sistêmicos, são aqui abordados por apresentarem-se inicialmente na pele em significativo número de pacientes. O diagnóstico desses processos é realizado pelo exame histopatológico complementado pela análise do fenótipo das células neoplásicas, imprescindível no processo classificatório. O estadiamento para a avaliação da extensão anatômica da doença considera além do envolvimento cutâneo, o estado clínico e histológico dos linfonodos e das vísceras. Avaliação hematológica é fundamental na caracterização da síndrome de Sézary. Os tratamentos preconizados incluem terapêuticas dirigidas exclusivamente à pele, modificadores da resposta biológica e quimioterapia sistêmica.*

Palavras-chave: Linfócitos T; Linfócitos NK; Linfoma de células T; Linfoma de células NK; Linfoma não Hodgkin; Neoplasias cutâneas; Transtornos linfoproliferativos

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INTRODUCTION

Primary cutaneous T-cell and natural killer (NK) cell lymphomas comprise a group of malignancies derived from the lymphoreticular system and classified as non-Hodgkin lymphomas. About 30% of non-Hodgkin lymphomas involve extranodal tissues, and the skin is one of the most affected organs, surpassed only by the gastrointestinal track, and represents approximately 18% of these lymphomas.[1] It is estimated that the annual incidence of cutaneous lymphomas in North America and Western Europe is between 0.3 and 1.0 for every 100,000 inhabitants.[2] Lymphomas with primarily cutaneous presentations, with no evidence of extracutaneous disease at the time of diagnosis, frequently have clinical behaviors and prognoses different from those of systemic lymphomas with a similar histological subtype. In recent consensus conferences between two significant cancer research organizations, the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC), a classification was proposed that allows greater uniformity in diagnosis, management, and treatment of cutaneous lymphoproliferative processes (Charts 1 and 2).[3,4] Between 75 and 80% of primary cutaneous lymphomas are cutaneous T-cell lymphomas (CTCL), with an absolute predominance of mycosis fungoides (MF) and its variants.

T-cells derive from bone marrow stem cells, but, unlike B-lymphocytes, do not differentiate in the bone marrow. At a very early stage, they migrate to the thymus, which provides a specialized microenvironment for the differentiation and maturation of these cells. Once in the thymus, certain lymphocytes are already designated to T-lineage differentiation since, at this stage, they express the CD7 antigen on the membrane and the CD3 antigen in the cytoplasm. These progenitor cells in the thymus can transform themselves into intrathymic dendritic cells and γδ and αβ thymocytes. Interactions with the thymic stroma lead to the expression of markers specific for the T-lineage. These mature T-lymphocytes will be $TCR\alpha\beta^+CD3^+CD5^+CD2^+CD7^+CD4^+CD8^-$, $TCR\alpha\beta^+CD3^+CD5^+CD2^+CD7^+CD4^-CD8^+$ or $TCR\gamma\delta^+CD3^+CD7^+CD2^+CD4^-CD8^-$. Approximately 10% of the circulating mononuclear cells have $TCD3^+CD7^-$ cell phenotypes. Most are $TCR\alpha\beta^+CD3^+CD4^+CD7^-CD45RO^+$ $CD45RA^-$ helper memory cells.[5] During this phase they leave the thymus, enter the circulation and migrate to peripheral lymphoid organs (lymph nodes and skin, among others).[6] Some studies have shown that certain memory T-cells, probably those presented to antigens introduced into the body through the skin, return to this organ and become constitutional residents.[7] The advent of monoclonal antibodies has made it possible not only to evaluate distinctive molecules of T-cell differentiation (TCR, CD3, CD2, CD5, CD7, CD4 and CD8), but also to characterize the molecules responsible for cellular interaction, such as the cutaneous lymphocyte antigen (CLA) that contributes to lymphocyte skin-homing properties.

CHART 1: WHO-EORTC classification for cutaneous NK/T cells lymphomas with primary cutaneous manifestations

CUTANEOUS T-CELL AND NK-CELL LYMPHOMAS
Mycosis fungoides
Mycosis fungoides – variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia lymphoma
Primary cutaneous $CD30^+$ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
Cutaneous ãä T-cell lymphoma (provisional)
Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)
PRECURSOR HEMATOLOGICAL NEOPLASM
$CD4^+CD56^+$ hematodermic neoplasm (blastic NK-cell lymphoma)

Source: Willenze R, et al.[3]

CHART 2: WHO-EORTC classification for cutaneous NK/T-cell lymphomas, considering clinical behavior

INDOLENT CLINICAL BEHAVIOUR
Mycosis fungoides
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma
AGRESSIVE CLINICAL BEHAVIOR
Sézary syndrome
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous aggressive epidermotropic $CD8^+$T-cell lymphoma
Cutaneous γδ T-cell lymphoma
Primary cutaneous peripheral T-cell lymphoma, unspecified

Source: Willenze R, et al.[3]

NK cells constitute a subpopulation of lymphocytes present in the blood and mainly in the spleen. These large lymphocytes, with numerous cytoplasmatic granules, are called large granular lymphocytes. They also derive from bone marrow but do not have markers for the B-lineage or the T-cell receptor specific for antigen recognition. These are $TCR\alpha\beta^-TCR\gamma\delta^-CD3^-CD16^+CD56^+$, cells involved with the innate response (non-adaptive). They are capable of destroying certain tumoral cells and normal cells infected by viruses.[8]

There is evidence that MF/SS neoplastic cells derive from memory $TCR\alpha\beta^+CD4^+$ lymphocytes ($CD45RO^+$) of the skin's immune surveillance arsenal (CLA^+), which exhibit the Th2 phenotype exacerbated by the progression of the disease.[10] In the Sézary syndrome, circulating neoplastic lymphocytes do not habitually express certain surface markers such as CD7 and CD26.[11,12] In rare situations, cutaneous lymphomas arise from $TCR\alpha\beta^+CD8^+$, $TCR\gamma\delta^+$ or NK cells.[9-12]

The gold standard for the diagnosis of cutaneous T-cell lymphomas is the histopathological examination. Phenotype analysis of neoplastic cells is important in the classification process, but rarely contributes towards the diagnostic conclusion. The study of genetic modifications of these malignancies is still at an investigative stage, and there is no distinctive diagnostic alteration. Investigation of gene rearrangements for TCR, demonstrating clonal lymphocyte proliferation in the skin, lymph nodes, and/or peripheral blood, aids the diagnosis in certain cases.

Clinical staging for cutaneous lymphomas focuses primarily on cutaneous epidermotropic lymphomas, mycosis fungoides, and Sézary syndrome (Chart 3).[13,14] The proposed evaluation of the type and extent of cutaneous involvement (T) is primarily adaptable to mycosis fungoides in its most classic, erythrodermic and SS forms. According to the authors, however, it is not adequate for application even in some variants of mycosis fungoides, much less in non-epidermotropic lymphomas. In the case of mycosis fungoides, for a given T stage, there may be patients with very diverse clinical presentations from the biological standpoint who will have different clinical courses both in therapeutic response and disease-free intervals, and in survival time.

The initial assessment for clinical staging of these lymphoproliferative processes includes an adequate medical history and physical examination with careful palpation of lymph node chains, mapping of cutaneous lesions (type and extent of involvement), complete blood cell count with percentages of anomalous convoluted cells (Sézary cells [SC] per 100 lymphocytes in blood smear or in leukocyte concentrate [buffy coat]) and absolute quantification (Sézary cells per mm^3); chemistry profile (including liver function, lactate dehydrogenase, protein electrophoresis, IgE levels), lymph node biopsy (this procedure is questionable in the absence of lymphadenomegaly), chest X-ray, and total abdomen ultrasound. It is questionable if sophisticated imaging tests such as tomography, magnetic nuclear resonance, Gallium scan or PET-CT help in evaluating systemic involvement. The authors recommend these tests at the initial assessment in patients with histological diagnoses of "non-mycosis fungoides" cutaneous T-cell lymphomas in order to ascertain that the cutaneous involvement is not from a systemic lymphoma. A bone marrow biopsy may be indicated under the same circum-

CHART 3: Staging of cutaneous T-cell lymphomas, according to Sausville et al., 1988 (National Cancer Institute)

EC	Skin (T)	Lymph node Clinical aspect (Nc)	Lymph node Pathology (Np)	Organ Pathology (M)	Blood (B)
IA	1	0	1. 2	0	0
IB	2	0	1. 2	0	0
IIA	1. 2	1	1. 2	0	0
IIB	3	0,. 1	1. 2	0	0
IIIA	4	0. 1	1, 2	0	0
IIIB	4	0. 1	1. 2	0	1
IVA	1-4	0. 1	3. 4	0	0. 1
IVB	1-4	0. 1	1-4	1	0. 1

T1: Limited eczematous lesions (patches), papules or patches affecting < 10% of skin surface; T2: Limited eczematous lesions (patches), papules or patches affecting ≥ 10% of skin surface; T3: Presence of tumors (≥ 1); T4: Generalized erithroderma; Nc0: absence of lymphadenomegaly; Nc1: lymphadenomegaly (≥ 1); Np1: reactional lymph node; Np2: dermatophatic lymphadenitis with small clusters of atypical lymphocytes; Np3: dermatophatic lymphadenitis with large clusters of atypical lymphocytes; Np4: change in lymph node architecture due to lymphomatous involvement; M0: no visceral involvement; M1: visceral involvement proven by histopathological examination; B0: absence or < 5% circulating Sézary cells; B1: presence of ≥ 5% circulating Sézary cells.

Source: Sausville EA, et al.[14]

stances and in cases where the peripheral blood Sézary cell count is over 20% or 1000 CS/mm^3, as well as in patients with aggressive CTCL who express a cytotoxic phenotype (CD8, TIA, granzyme) and NK.[15,16] Flow cytometry lymphocyte immunophenotyping in peripheral blood is recommended for erythrodermic patients with skin biopsies non-diagnostic for lymphoma, as well as in cases of absolute lymphocytosis in peripheral blood, increased CD4:CD8 ratio, and/or presence of circulating small and/or medium anomalous cells.[17]

MYCOSIS FUNGOIDES

Mycosis fungoides (MF) is a CTCL of small- and medium-sized lymphocytes, with convoluted nuclei, that characteristically present epidermotropism. Although the recent WHO-EORTC classification recognizes only its classic Alibert-Bazin form and three variants – folliculotropic, pagetoid reticulosis, and granulomatous cutis laxa –, this lymphoma presents with many clinicopathological variations, and the epidemiologic, therapeutic, and evolution implications must be taken into consideration (Chart 4). Sézary Syndrome (SS) is a leukemic variant of the disease with erythroderma from the onset and frequently courses with diffuse alopecia, palmoplantar hyperkeratosis, and diffusely enlarged lymph nodes.

Mycosis fungoides typically affects adults aged 55 to 60 years at diagnosis, with a slight predominance for the male gender (1.6 - 2:1). Although rarely described in children and young adults, it is possible that many cases begin during the first two decades of life but are not recognized as mycosis fungoides.[18,19]

CLASSIC MYCOSIS FUNGOIDES

General and clinical aspects

In its classic form described by Alibert, mycosis fungoides is a progressive disease with an indolent course that evolves from non-infiltrated lesions to forming plaques and tumors. In the early phases, lesions may have a non-specific aspect similar to inflammatory skin disorders like chronic eczemas, tinea corporis, undetermined leprosy, or pityriasis alba. Lesions may also have better-delineated borders and be erythematous or hypochromic, or be poikilodermic with slightly atrophic surfaces (parapsoriasis in plaques). They initially appear on the skin of the pelvic area, buttocks, lower trunk, inguinal region, axillae, and breasts, varying in number and gradually disseminating. Over time, the lesions infiltrate and become elevated erythematous or reddish-brown plaques, having well-defined borders and frequently bizarre contours with a foveolar, semi-annular, and serpiginous aspect. Tumors may arise from pre-existing patches or it is common to observe a combination of non-infiltrated lesions, plaques, and tumors. Highly infiltrated plaques and tumors frequently ulcerate, and erythroderma may arise in this process. Even though the disease has a prolonged course, there are cases with a much more rapid progression along the three phases described, and others with infiltrated plaques from the onset. Many patients remain in the initial stage with non-infiltrated lesions for many years, and most of them do not progress to plaque and tumor formation. In the natural history of the disease, regional lymph nodes may increase in size and be histologically

CHART 4: Clinical and pathological spectrum of mycosis fungoides

Classic
Folliculotropic with follicular mucinosis
Folliculotropic without follicular mucinosis
Syringotropic
Pagetoid reticulosis
Granulomatous slack skin
Granulomatous
Vesicobullous
Pustulous
Localized poikilodermic
Lichenoid/ generalized poikilodermic
Hyperpigmented
Hypopigmented
Unilesional
Palmoplantar
Hyperkeratotic/verrucous
Papillomatous/vegetating
Ichthyosiform
Erythroderma
Sézary syndrome

affected by the lymphoma; furthermore, in clinically advanced phases, multiple organs may be compromised.[20,21]

Histopathological, immunophenotypical and genetic aspects

The cytological aspects and architectural pattern of the cellular infiltrate in mycosis fungoides correlate with the clinical stage of the disease. Widely accepted histological diagnostic criteria include the presence of lymphocytes with hyperchromatic and convoluted nuclei encircled by a clear halo in the basal layer of the epidermis, approximately the size as keratinocytes, isolated or aligned in a linear configuration. There may also be intense lymphocyte exocytosis and Pautrier microabscesses (Figure 2).[22,23] 23 In the very early stages of the illness (premycotic phase), the histological aspect is non-specific. Typically, there is a discrete perivascular inflammatory infiltrate in the upper dermis with no evident lymphocyte atypias and no epidermotropism. As the lesions become more distinctive, the cellular infiltrate involves the upper dermis with a perivascular band-like or lichenoid pattern, mostly with lymphocytes and histiocytes, and epidermotropism may occur in isolated cells. The epidermis may be acanthotic, hyperkeratotic, or psoriasiform (particularly in cases of erythroderma). Papillary fibrosis of the dermis and vascular hyperplasia may be present.[22] The infiltrate in the plaques is dense and shows a band-like distribution pattern; epidermotropism is present. Pautrier microabscesses occur in about 25% of cases.[23] The neoplastic cells are small- to medium-sized, pleomorphic, amid a cellular infiltrate containing eosinophils and plasmocytes. In tumors, infiltrate is diffuse and/or nodular, occupying all of the dermis and, frequently, the subcutaneous layers. The infiltrate consists of atypical medium-sized pleomorphic lymphocytes. During this phase, epidermotropism may no longer be evident. In about 50% of these cases, large atypical pleomorphic, anaplastic, and blastic cells are observed, with prominent nuclei. If the number of large cells exceeds 25% of the infiltrate, the possibility of progression/ transformation into diffuse large cell lymphoma should be considered.[24]

The neoplastic cells in mycosis fungoides have a $CD3^+CD4^+CD45RO^+CD8^-$ memory phenotype, negative for the expression of the CD7 antigen in approximately 70% of cases. Infrequently, they may be $CD3^+CD4^-CD8^+$, presenting the same clinical behavior and prognosis, and should not be considered separately.[3] The immunohistochemical test is not a routine diagnostic aide since phenotypes aberrant because of the loss of mature T-cell antigens, such as CD2, CD3 and CD5, are only demonstrated in more advanced cases of the disease.[25] In tumors with blastic transformation, the cells may be $CD30^+$, but are more commonly $CD30^-$. In around 10% of mycosis fungoides cases with plaques undergoing blastic transformation, the $CD4^+$ neoplastic cells express cytotoxic proteins (T-1 cell (TIA-1) intracellular antigen).[26] Clonal rearrangements for the T-cell receptor (TCR) gene are detected in the majority of cases. Non-specific structural and numeric chromosomal abnormalities have been described mainly in advanced cases.[23]

Disease evolution

Mycosis fungoides is a habitually indolent lymphoma characterized by a prolonged natural history. Patients with limited disease and a good response to topical treatments have survival expectancy similar to that of the normal population. A recent study demonstrated that only 2% of those with localized lesions died after 32 years of evolution, and only 9% show a progression of mycosis fungoides.[27] Cases with a progressive form of the illness are at risk for extracutaneous lymph node and visceral involvement. Systemic involvement, as well as T-lymphocyte breakdown and failure of the organ itself, the skin, lead to patient death. Sepsis, especially by *Staphylococcus aureus*, represents one of the most frequent causes of death in advanced cases.[19,28] Ten-year survival rate is 97% for patients with non-infiltrated lesions or localized plaques (≤ 10% of skin surface), 83% for patients with generalized lesions (>10% of skin surface), 42% for patients with

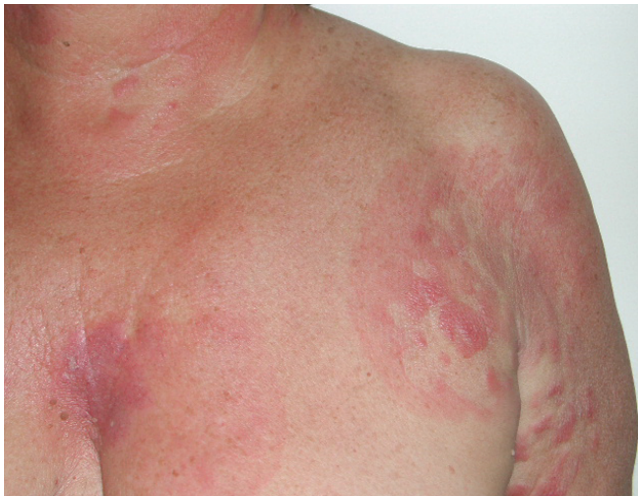

Figure 1: Classic mycosis fungoides. Plaques in the trunk

tumors, and approximately 20% for those with lymph node disease.[20,27,29,30]

Treatment

Treatment of the early disease with lesions confined to the skin includes topical corticosteroids, topical bexarotene, topical chemotherapy with nitrogen mustards (mechlorethamine or carmustine), phototherapy with UVB, narrow-band UVB, PUVA, or localized or total skin radiation with electrons. In cases of infiltrated plaques and tumors, preferred treatment is total skin electron beam irradiation. Biological response modifiers, such as interferon-alpha, bexarotene, interleukin 2 fused to diphtheria toxin (denileukin diftitox), have been used progressively more often, whether alone or in combination with topical treatments, in advanced skin condition, in systemic disease, and in refractory cases, with partial remission rates. Multiagent chemotherapy regimens similar to those used for nodal non-Hodgkin lymphomas (COP, CHOP, PROMACE-CYTABON) are indicated in cases of significant lymph node and/or visceral involvement and in advanced cutaneous disease unmanageable by skin-targeted treatment schemes.[31,32]

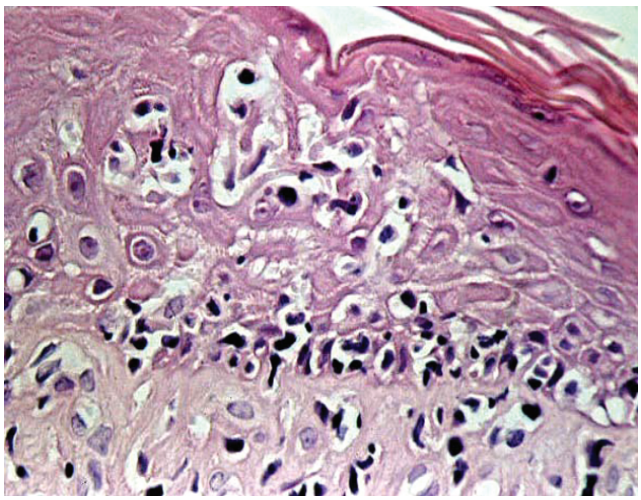

Figure 2: Mycosis fungoides. Epidermotropism of convoluted lymphocytes and Pautrier microabscesses (HE 400X)

VARIANTS OF MYCOSIS FUNGOIDES

Folliculotropic mycosis fungoides

The follicular, folliculotropic, folliculocentric, or pilotropic form of mycosis fungoides, with or without association with follicular mucinosis, is currently considered a variant of CTCL belonging to the spectrum of mycosis fungoides, with a preference for hair follicles.[21] More common in adults, it is clinically manifested as acneiform lesions with corneal plug formation similar to comedones, follicular papules, epidermic cysts, erythematous plaques, and alopecia in the affected areas. The follicular ostia frequently exude a mucinous substance. The most commonly affected areas are the cephalic segment and trunk (Figure 3). Alopecia of the eyebrows is characteristic. As the disease progresses, voluminous tumoral masses are formed and the face commonly acquires a leonine aspect. Pruritus is a constant symptom. Histologically, there is a dense lymphocytic infiltrate surrounding and penetrating the hair follicles, which usually spares interfollicular regions. Keratinocytes are dissociated, and follicles have cystic dilations, corneal plugs, and in some cases, mucin deposits. Infiltration of eccrine sudoriparous glands may also occur.[33] The immunopheno-

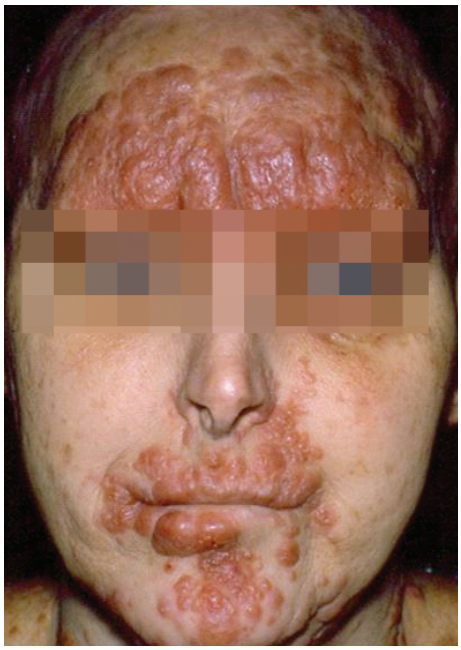

Figure 3: Pilotropic mycosis fungoides. Papules, nodules and plaques on the face

type is similar to that of classic mycosis fungoides. Large blastic CD30$^+$ cells may be observed permeating the infiltrate. There are no descriptions of clinical and evolution differences between the forms with and without mucinous degeneration.[34] The prognosis for this form of mycosis fungoides seems to be more guarded, with a 70 to 80% five-year survival rate comparable to that of the classic tumoral form of mycosis fungoides. Since the infiltrate is more deeply situated, it is less responsive to skin-directed treatments. Total skin electron beam irradiation may be effective, although long-lasting complete remissions are rare. The use of PUVA in association with retinoids or with IFN should be considered. Persistent tumoral masses should be treated with localized radiotherapy.[34]

Pagetoid reticulosis

This is characterized by atypical lymphoid infiltrate with small- and medium-sized cells located exclusively in the epidermis. Currently, pagetoid reticulosis is just considered the localized form named Woringer-Kolopp disease. Clinically it is manifested by erythemo-squamous or hyperkeratotic verrucous lesions, generally well delineated, with slow growth, and is commonly located in the inferior portion of the legs. Neoplastic cells may present a CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ phenotype, with frequent expression of the CD30 antigen. No deaths caused by the disease are known, and its treatment consists in surgical excision of single lesions or localized radiotherapy with low energy photons or electrons. Presently, the Ketron-Goodman generalized form is classified as an aggressive epidermotropic CD8$^+$ cytotoxic T-cell lymphoma or γδ T-cell lymphoma.[3,35,36]

Granulomatous slack skin

Recently accepted as a form of mycosis fungoides in which reddish-copper-toned sarcoid papules and plaques develop predominantly in skin folds, which progress to slack pendulous masses with atrophic surfaces. The small and medium neoplastic CD4$^+$ lymphocytes diffusely involve all the dermal and subcutaneous layers amid CD68$^+$ macrophages and a variable number of giant cells, exhibiting elastophagocytosis and sparse granulomas. Approximately 30% of the cases reported show an association with Hodgkin's disease, and a connection with classic mycosis fungoides has been described as well. Although the clinical course is indolent, treatment is difficult. Surgical excisions are followed by relapses, and radiotherapy may control localized disease.[37,38]

Mycosis fungoides – other variants

The hypochromic, localized poikilodermic, generalized poikilodermic, and vesicobullous forms of mycosis fungoides, among others, are considered similar to classic mycosis fungoides by the WHO-EORTC.[3] The authors of this article do not fully agree with this assertion. New studies that include larger numbers of cases of each one of these forms should confirm peculiarities of their clinical behaviors.[21]

SÉZARY SYNDROME

General and clinical aspects

Patients with Sézary syndrome (SS) characteristically present with exfoliative, edematous, and pruriginous erythroderma, with or without lichenification, generalized lymphadenopathy, and circulating neoplastic T-cells in peripheral blood (Figure 4). Palmoplantar hyperkeratosis, ungual dystrophies, and alopecia, are common findings and patients complain of intense pruritus. It occurs exclusively in adults.[39] Recently the International Society for Cutaneous Lymphomes (ISCL) proposed stricter diagnostic criteria, in addition to clinical characteristics, for Sézary Syndrome classification in order to adequately categorize cases for studies related to prognosis and therapeutic response. Although they are not yet definite, ISCL proposes that one or more of the following criteria be present for a Sézary syndrome diagnosis: absolute Sézary cell count ≥ 1000 cells/mm^3; evidence of immuno phenotypical abnormalities in circulating lymphocytes (an expanded CD4$^+$ T-cell population result-

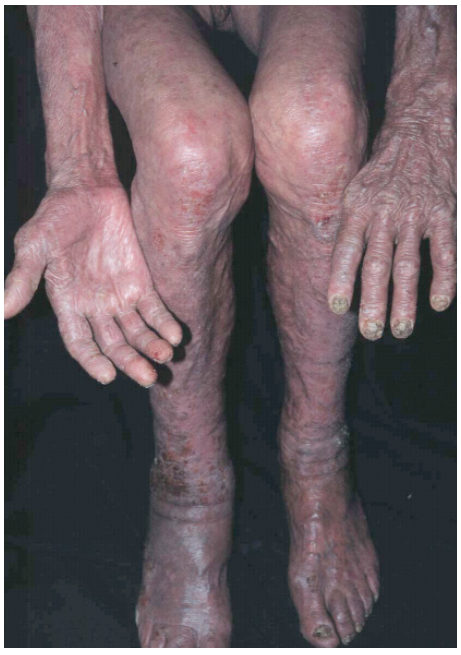

FIGURE 4: Sézary syndrome. Erythroderma, palmoplantar keratoderma and ungual dystrophies

ing in a CD4:CD8 ratio more than 10; loss of at least one T-cell antigen CD2, CD3, CD4 and CD5, or both), or evidence of a T-cell clone in peripheral blood by molecular or cytogenetic analysis. Until these criteria are completely validated, the demonstration of a circulating T-cell clone (preferably identical to the clone present in the skin) in association with one of the cytomorphological or immunophenotypical abnormalities mentioned above is considered the only proof capable of excluding inflammatory conditions that simulate the Sézary syndrome. An expansion greater than 40% of $CD4^+CD7^-$ lymphocytes and $CD4^+CD26^-$ cells, observed by flow cytometry in peripheral blood, and an elevation of serum lactate dehydrogenase are auxiliary diagnostic criteria.[40,41]

Histopathological, immunophenotypical and genetic aspects

The lymphomatous infiltrate superimposes that of mycosis fungoides; however, in about 30% of patients with Sézary syndrome, the histopathological examination is non-specific. Frequently, the cellular infiltrate is monotonous with discrete epidermotropism. Pautrier microabscesses are rarely observed. Phenotypical and genetic findings have characteristics in common with those of mycosis fungoides.[42-44]

Disease evolution

Sézary syndrome is an aggressive disease with a poor prognosis; the 5-year survival rate ranges from 10 to 20%. Progression to large cell lymphomas is frequently observed, many times associated with the terminal event.[41]

Treatment

Extracorporeal photopheresis, when available, is the treatment of choice and yields complete remission rates between 14 and 25%. Treatment with PUVA in association with IFN-alpha and the combined use of chlorambucil (2-4 mg/day) and prednisone (20-30 mg/day) have been used, resulting in low complete remission rates.[39]

PRIMARY CUTANEOUS $CD30^+$ LYMPHOPROLIFERATIVE DISORDERS

This group corresponds to the spectrum of cutaneous lymphoproliferative processes classified among lymphomatoid papulosis, borderline cases and primary cutaneous anaplastic large cell lymphoma. It is not usually possible to differentiate these conditions only by the pathological examination. In most cases the diagnosis of lymphomatoid papulosis or primary cutaneous anaplastic large cell lymphoma is based on dermatological and clinical assessment. They correspond to approximately 30% of CTCL and are the second most frequent group, after classic MF and its variants.[3,4]

PRIMARY CUTANEOUS ANAPLASTIC LARGE-CELL LYMPHOMA

General and clinical aspects

It is preferentially observed in young adults and it is two to three times more frequent in males. In most patients there are papules or single nodules that may ulcerate. Rarely there are multiple localized lesions in a certain anatomic region, and could be multifocal (20% of cases). Partial or complete spontaneous regression may occur.[45-47]

Histopathological, immunophenotypical and genetic aspects

There is a diffuse and dense infiltrate, without epidermotropism, composed of very large $CD30^+$ cells, with a characteristic morphology of anaplastic cells with rounded, oval or irregular nuclei, with prominent nucleoli eosinophilic and abundant cytoplasm (Figure 6). Infrequently they could have a non-anaplastic appearance (pleomorphic or immunoblastic). Reactive lymphocytes in the periphery of lesions are often observed. In ulcerated lesions this lymphoid infiltrate could be plentiful with histiocytes, neutrophils, eosinophils and few $CD30^+$ cells. The neoplastic cells have activated $CD4^+$ T cell phenotype ($CD45RO^+$), with variable loss of CD2, CD5 and CD3 and frequent expression of cytotoxic proteins (granzyme B, TIA-1, perforin). The CD30 expression must be present in most neoplastic cells (> 75%). Different from systemic anaplastic large-cell lymphoma, cutaneous lymphoma expresses the cutaneous lymphocyte antigen (CLA), but not the epithelial membrane antigen (EMA) and the anaplastic lymphoma kinase (ALK), thus indicating 2;5 chromosome translocation. Contrary to Hodgkin's lymphoma, neoplastic cells do not express CD15. Most cases demonstrate clonal rearrangement for TCR genes. The (2;5)(p23;q35) chromosome translocation is a characteristic finding of systemic anaplastic lymphoma, which is not observed in cutaneous anaplastic lymphoma (or is rarely found).[48-51]

Disease evolution

It is an indolent neoplasm with good prognosis and 10-year survival rate is greater than 90%. Cutaneous recurrences are frequent and extracutaneous dissemination occurs in roughly 10% of cases, mainly to regional lymph nodes. Multifocal cutaneous disease or regional lymph node involvement apparently do not change prognosis of patients with localized skin lesion.[46,48]

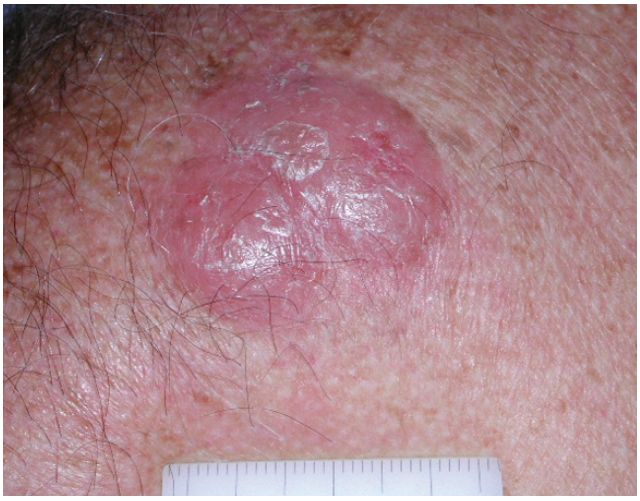

Figure 5: Primary cutaneous anaplastic large cell lymphoma. Single nodule on right shoulder

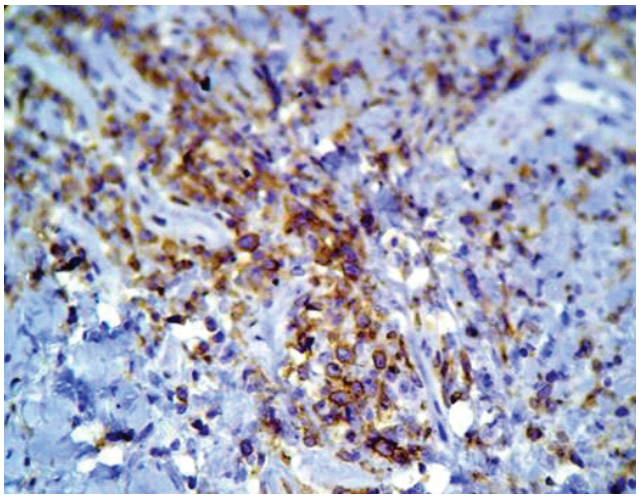

Figure 6: Primary cutaneous anaplastic large cell lymphoma. Anaplastic large lymphocytes expressing CD30 (IHQ 200X)

Treatment

Radiotherapy and lesion exeresis are the treatments of choice for patients with localized lesions. Low dose methotrexate could be an alternative for patients with multiple lesions, but it is not a curative option. Rapidly progressing or extracutaneous disease should be treated with systemic multiagent chemotherapy with doxorubicin.[46-52]

LYMPHOMATOID PAPULOSIS

General and clinical aspects

It manifests as a papulonodular or papulonecrotic, spontaneously regressive eruption, which progresses in recurrent episodes (Figure 7). It occurs in young adults, with a median age of 45 years, and is rarely observed in children. The literature reports slight predominance of males.[46,47]

Histopathological, immunophenotypical and genetic aspects

Three histological subtypes have been described for lymphomatoid papulosis (LP), which probably represent the spectrum of the disease. It is possible to observe more than one finding in one lesion or in different lesions of one single patient. In type A (histiocytic type), there are large $CD30^+$ cells, which are sometimes multinucleated, similar to Reed-Sternberg cells, in small groups or scattered among histiocytes, neutrophils, eosinophils and lymphocytes. Type B (mycosis fungoides type) accounts for less than 10% of cases and is characterized by an infiltrate of atypical lymphocytes with convoluted nuclei with epidermotropism, which superimposes the histological aspects found in MF. Type C (anaplastic large cell lymphoma type) presents a monotonous infiltrate of large $CD30^+$ cells with mild inflammatory infiltrate. The large cells in type A and C lymphomatoid papulosis express T cell markers - $CD2^+$, $CD3^+$, $CD5^+$, $CD45RO^+$, $CD4^+$, $CD8^-$, $CD15^-$ and are $CD30^+$. Atypical cells in type B lymphomatoid papulosis present the same phenotype but are $CD30^-$. Some studies demonstrated a clonal rearrangement for TCR-genes in approximately 60-70% of lymphomatoid papulosis lesions.[53-55]

Disease evolution

Although not curable, lymphomatoid papulosis has an excellent prognosis. Previous studies reported up to 20% association with past history of lymphoma, concurrent lymphoma or progression to lymphoma (mycosis fungoides, anaplastic large cell lymphooma, Hodgkin disease); however, a recent study demonstrated that only 4% of patients with LP developed systemic lymphoma and 2% died of the systemic disease in an approximately six-year follow-up.[46]

Treatment

There is no curative treatment. The use of topical steroids, systemic steroids, PUVA, topical chemotherapy or methotrexate may induce temporary remissions. The risk/benefit ratio of these therapies should be carefully assessed. Periodical clinical follow-up is recomended.[46,52]

SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

General and clinical aspects

The current WHO-EORTC classification considers subcutaneous panniculitis-like T-cell lymphoma only the lymphoproliferative processes of cytotoxic $TCR\alpha\beta$ $CD8^+$ T-cells that exclusively

involve the subcutaneous tissue, sparing the dermis and epidermis, and usually presenting a more indolent course.[56,57] The cases with TCRγδ $CD4^-$ $CD8^-$ $CD4^-$ $CD8^-$ phenotype that often co-express CD56, are not confined to subcutaneous tissue and have poorer prognosis are today classified as cutaneous gamma-delta T-cell lymphoma.[58] 58 It affects adults and children and both sexes. It manifests as single or multiple patches and nodules that are usually not ulcerated. Systemic symptoms, such as fever, fatigue and weight loss may be observed. Hemophagocytic syndrome might occur, but it is more common in cutaneous gamma-delta T-cell lymphoma with panniculitis-like lesions. Extracutaneous dissemination is very rare. This lymphoma may be clinically and histologically similar to benign panniculitis for many years.[59]

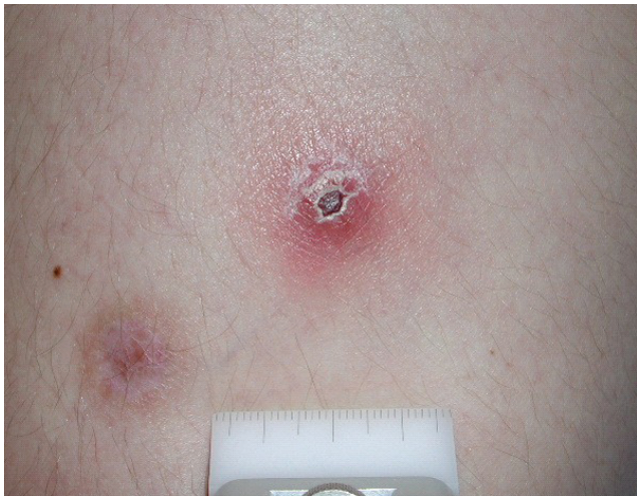

Figure 7: Lymphomatoid papulosis. Papular necrotic lesion and residual atrophic scar

Histopathological, immunophenotypical and genetic aspects

It presents a dense, nodular or diffuse infiltrate of small, medium and large pleomorphic lymphocytes, with hyperchromatic nuclei and the frequent presence of many macrophages in subcutaneous tissue. Although not specific, the presence of aligned cells around individual fat cells is useful for diagnosis. In the initial phases it might be difficult to differentiate from inflammatory processes. Necrosis, karyorrhexis and cytophagocytosis are frequently observed. The neoplastic cells are TCRαβ$^+$ $CD3^+$ $CD4^-$ $CD8^+$, with expression of the cytotoxic proteins granzyme, perforin and TIA-1. Expression of CD56 and CD30 are very rare. The macrophages with hemophagocytosis are $CD68^+$. Neoplastic cells show clonality. Specific genetic modifications have not been detected.[60,61]

Disease evolution

The course is usually prolonged with recurrent subcutaneous lesions, and with a five-year survival in more than 80% of cases.[58-60]

Treatment

Multiagent chemotherapy with doxorubicin is indicated but many patients could be controlled with prolonged systemic steroids.[58,60]

EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

General and clinical aspects

The extranodal NK/T-cell lymphoma affects more often the nasal cavity and rhinopharynx; however, the skin, soft tissues and intestine may be primarily involved. Nodal dissemination is rare. The lesions in the nose and central face were called lethal midline granuloma. Clinically, it presents erythematous, purpuric papular and nodular lesions that ulcerate rapidly, leading to extensive necrotic areas (Figure 8).[57,62,63] There are reports of a variant type similar to hydroa-vacciniforme, which involves mainly the face and exposed areas in children, as observed in cases in Latin America and Asia, with a poor prognosis.[64-66]

Histopathological, immunophenotypical and genetic aspects

The lymphomatous infiltrate of small, medium or large cells is diffuse, angiocentric and angiodestructive, involving the dermis and often the subcutaneous tissue. It is followed by an intense inflammatory infiltrate composed of histiocytes, plasmocytes and granulocytes, primarily eosinophils.[62,67] The neoplastic cells comprise $CD2^+$, $CD56^+$, $CD3c^+$, $CD3s^-$, $CD43^+$ and $CD45RO^+$ (Figure 9). They are usually $CD4^-$, $CD5^-$, $CD8^-$, $CD16^-$, $CD57^-$. The cytotoxic proteins TIA-1, granzyme B and perforin are frequently present. The Epstein-Barr virus (EBV) is detected in most cases, suggesting the virus possibly plays a role in the pathogenesis of the process.[68,69]

Disease evolution

The course is generally aggressive, with high mortality rate despite treatment. The median survival rates reported from 5 to 27 months, and the best rates concern patients with exclusively cutaneous lesions.[70]

Treatment

The treatment indicated is systemic chemotherapy.[71,72]

PRIMARY CUTANEOUS AGRESSIVE EPIDERMOTROPIC CD8$^+$ CYTOTOXIC T-CELL LYMPHOMA, (PROVISIONAL ENTITY)

General and clinical aspects

A rare form of cutaneous lymphoma characterized by sudden appearance of nodules with central necrosis, which are localized or generalized, or by superficial disseminated hyperkeratotic plaques (they superimpose the cases previously described as pagetoid reticulosis type Ketron-Goodman). The lesions have an aggressive behavior. The differentiation with other CD8$^+$ CTCL (such as pagetoid reticulosis and rare cases of MF CD8$^+$) is based on clinical manifestations and prognosis.[35,72]

Histopathological, immunophenotypical and genetic aspects

The neoplastic infiltrate is composed of variable cells, small, medium or large pleomorphic or blastic cells. It manifests as acanthotic or atrophic epidermis, necrotic keratinocytes and moderate or severe spongiosis, with blisters. There is marked epidermotropism in well-established lesions, with linear configuration in the basal layer or with pagetoid aspect. Adnexal and vascular invasion is frequently observed with destruction of these structures. The neoplastic cells express betaF1$^+$, CD3$^+$, CD8$^+$, CD45RA$^+$, CD45RO$^-$, CD2$^-$ and CD5$^-$. phenotype. They also show cytotoxicity granules TIA-1, granzyme and perforin. They are EBV$^-$. The neoplastic cells present rearrangement for TCR gene, but no specific genetic modifications have been described.[35,57,72]

Disease evolution

The disease usually has an acute progression with rapid systemic dissemination. The median survival rate reported is 32 months.[73]

Treatment

Systemic chemotherapy with schemes including doxorubicin is indicated.

CUTANEOUS GAMMA/DELTA T-CELL LYMPHOMA (PROVISIONAL ENTITY)

General and clinical aspects

It is a lymphoma of mature and activated gamma-delta T-cells, with cytotoxic phenotype. This group includes cases already described as subcutaneous T-cell lymphoma with gamma-delta phenotype. It is characterized by necrotic plaques and/or nodules that are more often observed on the extremities. It could disseminate to mucosae and extranodal sites, but rarely involves lymph nodes, spleen and bone marrow.[74-76]

Histopathological, immunophenotypical and genetic aspects

The neoplastic infiltrate comprises pleomorphic medium to large cells, with gross chromatin and few blastic cells with vesiculous nuclei and prominent nucleoli. Three patterns were described: epidermotropic, dermal and subcutaneous.[74,77] The subcutaneous involvement may be similar to panniculitis or could be denser. The epidermal infiltration may be mild or even pagetoid. These patters often coexist. Apoptotic and necrotic

Figure 8: Extranodal NK/T-cell lymphoma, nasal type. Erythematous infiltrated plaques lesion, with necrotic areas involving the nose and right hemiface

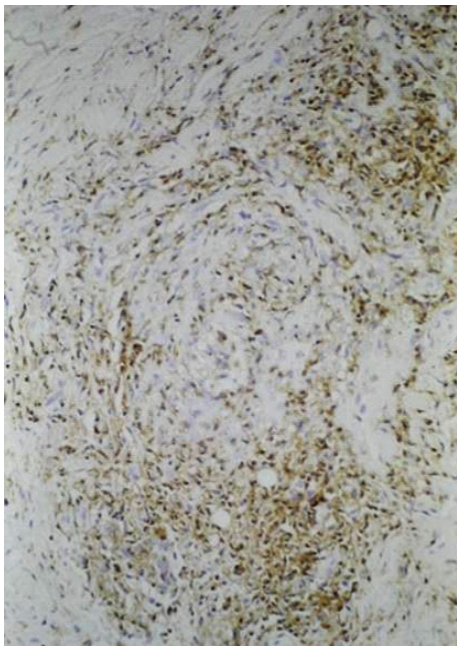

Figure 9: Extranodal NK/T-cell lymphoma, nasal type. Atypical lymphocytes, with angiocentric distribution, expressing CD56 (IHQ 200X)

keratinocytes and vascular invasion are common events. The neoplastic cells present betaF1$^-$, CD3$^+$, CD2$^+$, CD56$^+$, granzyme B$^+$, TIA-1$^+$, perforin$^+$, CD5$^-$, CD4$^-$, (rarely CD8$^+$) and CD7$^{-/+}$ phenotype. In frozen samples of the tumor, cell positivity for TCR$\gamma\delta$ may be demonstrated. The cells show clonal rearrangement for TCR$\alpha\beta$ whereas TCR$\alpha\beta$ may be rearranged or deleted, but not expressed. EBV test is negative.[75-77]

Disease evolution

Most patients suffer an aggressive course, with a median survival rate of 15 months. Patients with subcutaneous involvement seem to have shorter survival.[77]

Treatment

The treatment indicated is systemic chemotherapy, although the results are quite poor.

PRIMARY CUTANEOUS CD4$^+$ SMALL/MEDIUM-SIZED PLEOMORPHIC T-CELL LYMPHOMA (PROVISIONAL ENTITY)

General and clinical aspects

It is defined as CD4$^+$ pleomorphic small/medium-sized T-cell lymphoma with no history of typical MF patches or plaques. It presents as a single plaque or tumor, generally located in the face, neck or upper trunk.[73,78-81]

Histopathological, immunophenotypical and genetic aspects

There is a dense, diffuse or nodular infiltrate likely to involve the subcutaneous tissue. Epidermotropism, if present, is mild and focal. A significant infiltrate of small reactive lymphocytes and histiocytes may be observed. The neoplastic cells express CD3$^+$, CD4$^+$, CD8$^-$ and CD30$^-$ phenotype. Loss of one or more pan-T-cell markers (CD3, CD2, CD5) may occur. The TCR genes are clonally rearranged.[73,78]

Disease evolution

This lymphoma has a very favorable prognosis, particularly in cases with single or multiple localized lesions. The estimated five-year survival rate is approximately 60-80%.[73,79-81]

Treatment

Surgical excision or radiotherapy is indicated for localized lesions. There is no consensus about management of more generalized lesions.

PRIMARY CUTANEOUS PERIPHERAL T-CELL LYMPHOMA, UNSPECIFIED

General and clinical aspects

This term comprises a heterogeneous group of cutaneous lymphomas that do not meet the criteria for the lymphoproliferative processes defined by the WHO and EORTC and so far described. They predominantly affect adults, with localized, single or generalized nodules, with no preferential sites.[3]

Histopathological, immunophenotypical and genetic aspects

The lesions show an infiltrate of medium to large, pleomorphic or imunoblastic-like cells, with absent or mild epidermotropism. The phenotype is usually CD4$^+$, with variable loss of pan-T-cell antigens (CD2, CD3, CD5). They are negative for CD30 expression. The co-expression of CD56 and the presence of cytotoxic proteins are not common.[73,78]

Disease evolution

Prognosis is generally poor, with five-year survival rates of less than 20%, and they are apparently similar for the cases with localized or generalized cutaneous lesions.[73,78,82]

Treatment

Treatment is performed with multiagent chemotherapy.

ADULT T-CELL LEUKEMIA LYMPHOMA

General and clinical aspects

It is a lymphproliferative disease associated to infection by the retrovirus HTLV-1. It may be manifested in the leukemic form. Cutaneous lesions are observed in about 50% of patients, and most cases have the disseminated disease. There are four clinical variants: acute, lymphomatous, chronic and smoldering (indolent). The indolent and slowly progressive form has been described presenting only cutaneous lesions.[83] It is an endemic disease in areas with a high prevalence of HTLV-1 infection, such as Southeastern Japan, the Caribbean, South America, including the Northeastern and Southeastern regions of Brazil, North Iran and some Central Africa regions. The lymphoma develops in approximately one to five percent of soropositive individuals, often after over two decades of viral persistence. The virus could be transmitted by breast milk and exposure to blood and blood products. It affects adults (median age of 55 years), with a slight predominance in males. The specific cutaneous lesions may be papules, patches, tumors and erythroderma, and sometimes they may be similar to those of MF. Xerosis and acquired ichthyosis are frequently present and could be unspecific or specific manifestations of lymphoma.[84]

Histopathological, immunophenotypical and genetic aspects

It usually presents a diffuse infiltrate with significant epidermotropism of small to medium or medium to large lymphocytes with pleomorphic or polylobated nuclei. The histological aspect may be difficult to distinguish from that of MF. The cutaneous lesions in the smoldering type could present only a mild lymphocitary infiltrate with few atypical cells. The neoplastic cells express $CD3^+$, $CD4^+$ and $CD8^-$ phenotype. There is an intense expression of IL-2 ($CD25^+$) receptor in the lymphomatous cells, as well as a clonal rearrangement of TCR genes. The determination of the clonal integration of HTLV-1 genes is found in all cases and it is useful to differentiate adult T-cell leukemia lymphoma –chronic and smoldering variants – from MF/SS.[83-85]

Disease evolution

The prognosis depends on the clinical subtype. Survival in acute and lymphomatous forms varies from two months to over one year. The chronic and smoldering variants have a prolonged course and longer survival; however, they could become acute and have an aggressive progression.[83,84]

Treatment

Systemic chemotherapy is indicated in most forms. In more indolent prolonged variants, the cutaneous lesions may be treated with skin-directed therapies that are usually prescribed for MF. The association of IFN alpha 2a mainly with PUVA and the use of antiretroviral agents, such as zidovudine, seem to be of benefit to patients.[86,87]

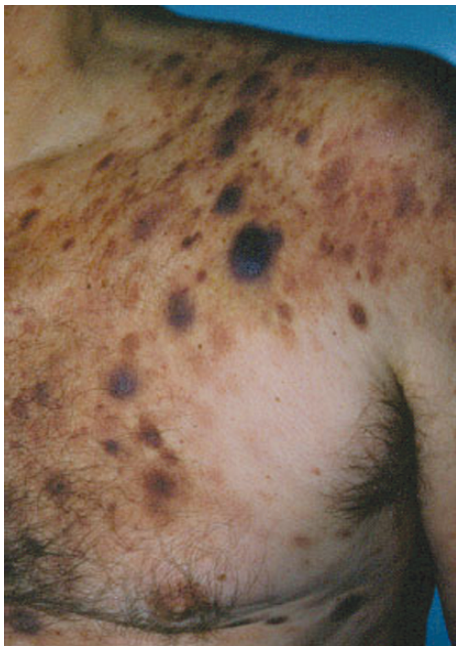

FIGURE 10: $CD4^+CD56^+$ hematodermic neoplasm. Papules and nodules on the trunk

$CD4^+CD56^+$ HEMATODERMIC NEOPLASM (BLASTIC NK-CELL LYMPHOMA)

General and clinical aspects

It is a rare and aggressive systemic lymphoma, with common involvement of the skin and risk of leukemic dissemination. It affects middle-aged and elderly individuals. The lesions are erythematous, purplish, multiple and disseminated plaques and nodules, which are sometimes ulcerated and often involve the mouth and nose (Figure 10). The blastic cytological aspect and CD56 expression suggest deriving from NK precursor cells.[88]

Histopathological, immunophenotypical and genetic aspects

The cell infiltrate is dense in the dermis and subcutaneous tissue, with frequent periadnexal and perivascular distribution. The neoplastic cells vary in size and shape, from medium pleomorphic T cells to large elements similar to lymphoid or myeloid blasts. Mitoses are frequent. The cells present $CD4^+$, $CD56^+$, $CD8^-$, $CD7^{+/-}$, $CD2^{+/-}$ and $CD45RA^+$ phenotype. They do not express the CD3 molecule in the surface and cytoplasm ($CD3s^-$, $CD3c^-$), neither cytotoxic proteins. The cells may be TdT^+ and $CD68^+$. The granulocytic lineage markers should be negative ($CD33^-$, MPX^-). The tumor cells are negative for EBV. There is no reordering of TCR genes, which are in the germline configuration.[3,88]

Disease evolution

It is an aggressive neoplasm and the median survival is 14 months.[70,88]

Treatment

Treatment comprises systemic chemotherapy leading to short-duration remission, and recurrences do not respond to re-treatment. There is evidence that the disease might be better managed with chemotherapeutic schemes for acute leukemias.[3,70]❑

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Questions and answers to questions

1. Most primary cutaneous lymphomas are composed of:
   a) B-cells
   b) T-cells
   c) NK-cells
   e) macrophages

2. The T-cell differentiation takes place in the:
   a) bone marrow
   b) spleen
   c) thymus
   d) liver

3. According to the WHO-EORTC classification cuta neous T /NK-cell lymphomas, the following are considered lymphomas of aggressive clinical behavior:
   a) mycosis fungoides, primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma, cutaneous γδ T-cell lymphoma
   b) pagetoid reticulosis, primary cutaneous peripheral T-cell lymphoma, unspecified, lymphomatoid papulosis
   c) subcutaneous panniculitis-like T-cell lymphoma, granulomatous slack skin, extranodal NK/T-cell lymphoma, nasal type
   d) Sézary´s syndrome, extranodal NK/T-cell lymphoma, nasal type, primary cutaneous aggressive epidermotropic $CD8^+$T-cell lymphoma

4. The gold standard to diagnose cutaneous T-cell lymphomas is:
   a) histopathological examination
   b) immunophenotyping
   c) genetic rearrangement
   d) imaging studies

5. The histological picture that enables diagnosing mycosis fungoides is:
   a) hydropic degeneration of the basal layer, presence of band-like lymphocytes in superficial dermis
   b) hyperkeratosis, acanthosis, preserved basal layer, lymphocytic infiltrate in reticular dermis
   c) epidermal atrophy, hydropic degeneration of the basal layer, perivascular and periadnexal mononuclear infiltrate
   d) lymphocyte exocytosis to epidermis and formation of Pautrier microabscesses

6. Tick the INCORRECT option regarding classic mycosis fungoides:
   a) it shows a Th2 cytokine profile
   b) it derives from $TCR\alpha\beta^+CD4^+$ memory lymphocytes ($CD45RO^+$)
   c) the diagnosis is confirmed by immunohisto chemical examination
   d) the usual course is indolent and chronic

7. In the advanced phases of mycosis fungoides, a frequent cause of death is:
   a) sepsis, mainly by *Staphylococcus aureus*
   b) organ failure, such as liver and kidney
   c) failure of hematopoietic system
   d) multiple thrombotic phenomena

8. When mycosis fungoides is diagnosed in an initial phase, the best treatment is:
   a) conventional radiotherapy
   b) phototherapy
   c) interferon
   d) chemotherapy

9. Folliculotropic mycosis fungoides affects more often the:
   a) lower limbs
   b) upper limbs
   c) head and trunk
   d) abdominal region

10. Tick the INCORRECT option regarding pagetoid reticulosis:
   a) it is characterized by an atypical intraepidermal lymphoid infiltrate of large blastic cells
   b) it presents erythemo-squamous or hyperkeratotic verrucous lesions
   c) it could present $CD4^+CD8^-$ or $CD4^-CD8^+$ phenotype with frequent expression of CD30 antigen
   d) it has a benign course and usually does not cause death

11. Hodgkin's disease is associated with:
   a) classic mycosis fungoides
   b) granulomatous slack skin
   c) primary cutaneous anaplastic large cell lymphoma
   d) subcutaneous panniculitis-like T-cell lymphoma

12. The diagnostic criteria for Sézary´s syndrome include:
   a) >10% of Sézary cells in peripheral blood, histology similar to that of MF, poikiloderma
   b) lymphadenomegaly, absolute SC count <1000 cells/mm^3, without phenotypical abnormalities
   c) expansion of CD4+CD7- lymphocytes >40%, as well as of CD4-CD26- cells observed in flow cytometry, in peripheral blood
   d) absolute SC count ≥1000 cells/mm^3, showing phenotypical abnormalities in circulating blood

13. Extracorporeal photopheresis is indicated for:
   a) hypochromic MF
   b) Sézary´s syndrome
   c) granulomatous slack skin
   d) folliculotropic MF

14. The histological features of type A lymphomatoid papulosis comprises:
    a) large cells, which are sometimes multinucleated, similar to Reed- Sternberg cells, CD30$^+$, in small clusters or scattered among histiocytes, neutrophils, eosinophils and lymphocytes
    b) an atypical infiltrate of lymphocytes with convoluted nuclei with epidermotropism, superimposed to the histological aspect of MF
    c) monotonous infiltrate of large CD30$^+$ cells with discreet inflammatory infiltrate
    d) diffuse and dense infiltrate, without epidermotropism, composed of very large CD30$^+$ cells, with a characteristic morphology of anaplastic cells

15. As to extranodal NK/T-cell lymphoma, one could state that:
    a) it has frequent nodal dissemination
    b) the lymphomatous infiltrate is rich in neutrophilic cells and absence of angiocentrism
    c) in most cases it is associated with HTLV
    d) it is frequently located in the nasal cavity and rhinopharynx

16. The adult T-cell leukemia lymphoma is associated with:
    a) EBV
    b) HIV
    c) HTLV-I
    d) HSV-8

17. The adult T-cell leukemia lymphoma is associated with:
    a) palmoplantar hyperkeratosis
    b) xerosis and ichthyosis
    c) follicular keratosis
    d) poikiloderma

18. Concerning blastic NK-cell lymphoma, one could state that:
    a) on histological examination there is a band-like cell infiltrate with frequent distribution in fat tissue
    b) the disease responds to treatment with IFN-alpha associated with PUVA therapy
    c) it is an aggressive lymphoma with common cutaneous involvement and risk of leukemic dissemination
    d) it often expresses CD3 molecule in the cell surface and cytoplasm

19. A patient presents reddish-copper-toned sarcoid patches predominantly in skin folds. On histological examination, there are small and medium atypical CD4$^+$ lymphocytes with a diffuse distribution in the whole dermis and subcutaneous tissue amid CD68+ macrophages, with a variable number of giant cells, showing elastophagocytosis and sparse granulomas. Which type of MF does the picture suggest?
    a) classic
    b) syringotropic
    c) folliculotropic
    d) granulomatous slack skin

20. The primary cutaneous CD30$^+$ lymphoproliferative diseases include:
    a) lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma
    b) subcutaneous panniculitic-like T-cell lymphoma and cutaneous gamma-delta T-cell lymphoma
    c) primary cutaneous aggressive epidermotropic CD8$^+$T-cell lymphoma and primary cutaneous CD4$^+$ small/medium-sized pleomorphic T-cell lymphoma
    d) primary cutaneous peripheral T-cell lymphoma, unspecified, and adult T-cell leukemia lymphoma

ANWSERS

Accidents caused by lepidopterans (moth larvae and adult): study on the epidemiological, clinical and therapeutic aspects
2005;80(6):461-71.

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