Mycosis fungoides and Sézary syndrome: clinical, histopathological and immunohistochemical review and update *

Micose fungóide e síndrome de Sézary: revisão e atualização clínica, histopatológica e imuno-histoquímica

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Abstract: This paper reviews the diagnostic and classificatory concepts of mycosis fungoides and Sézary syndrome in light of the latest normative publications. It describes the great variability of the clinical expression of mycosis fungoides in its early stages as well as the histopathological and immunohistochemical aspects that help with diagnosis. The diagnostic criteria required for characterizing Sézary syndrome and the staging system used for both mycosis fungoides and Sézary syndrome are described.
Keywords: Lymphoma, T-Cell, cutaneous; Mycosis fungoides; Sézary syndrome

Resumo: O artigo revisa os conceitos diagnósticos e de classificação da micose fungóide e da síndrome de Sézary a luz das publicações normativas mais recentes. Descreve a grande variabilidade de expressão clinica da micose fungóide em seus estágios iniciais assim como os aspectos histopatológicos e imuno-histoquímicos auxiliares ao diagnóstico. São descritos os critérios de diagnósticos exigidos para que se caracterize a síndrome de Sézary e o sistema de estadiamento, utilizado para ambas, micose fungóide e síndrome de Sézary.
Palavras-chave: Linfoma cutâneo de células T; Micose fungóide; Síndrome de Sézary

INTRODUCTION

Concept: primary cutaneous lymphomas

Primary cutaneous lymphomas (PCL) are defined as non-Hodgkin lymphomas. They are found in the skin without an extra primary cutaneous location at the moment of diagnosis.[1] The current PCL classification is a result of the cooperation between the World Health Organization (WHO) and the European Organization of Research and Treatment of Cancer (EORTC), published in 2005 under the title "WHO-EORTC Classification for Cutaneous Lymphomas", and largely referenced and disseminated in 2008 in the publication by the WHO titled "WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues".[2]

The WHO-EORTC classification distinguishes between two large PCL groups: lymphomas from T

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lymphocytes with residence in the skin, referred to as "cutaneous T-cell lymphomas" (CTCL), and those from B-lymphocytes, referred to as "cutaneous B-cell lymphomas" (CBCL). In addition, there are cutaneous lymphomas from Natural Killer cells (NK) and groups of temporarily unclassifiable lymphomas with undefined phenotypic characteristics.[1,2]

CTCLs comprise a group of heterogeneous lymphomas with a clinical behavior that is distinct from that of systemic lymphomas, including those with a similar histological subtype. Even among themselves, CTCLs vary widely, from patches to tumors, from indolent to aggressive. They also vary in their biological behavior, in their histological and immunophenotypic aspects and, consequently, in prognosis and survival. [1-5]

Indolent CTCL subtypes include mycosis fungoides (MF) and its variants, anaplastic large T-cell PCL, lymphomatoid papulosis, subcutaneous panniculitis-like T-cell lymphomas with alpha/beta T-cell phenotype, and cutaneous lymphomas of T CD4+ cells of small and medium-sized pleomorphic cells. Aggressive subtypes include Sézary Syndrome (SS), PCL such as nasal-type T/NK-cell, T CD4- and CD8+ cells, unspecific T-cell and the T cell lymphoma/leukemia of adults. Among PCL, more than 65% are of the T-cell type, 25% are formed by B cells and 10% are unspecific. [1-5]

Concept: mycosis fungoides

The predominant CTCL subtype is mycosis fungoides. It corresponds to the cutaneous lymphoma originated in the peripheral epidermotropic T-lymphocyte, which expresses the T-cell receptor (TCR) with $\alpha\beta^+$subunits and $CD4^+$ immunophenotype, known as memory T-lymphocyte ($CD45RO^+$), and constitutes the skin immunosurveillance. [2,5] The designation MF can only be used for classic cases characterized by the development of patches, plaques and tumors and for variants with a similar clinical course. [2] MF represents less than 1% of the total number of non-Hodgkin lymphomas; however, it is the most common cutaneous lymphoma. It usually has an indolent course and good prognosis when identified in its early stages. [1-5]

The classic form of MF, which is also referred to as Alibert-Bazin, and three variants, namely, the "folliculotropic", "pagetoid reticuloid" and "granulomatous cutis laxa" variants, are acknowledged in the WHO-EORTC classification and in the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues.[1,2] Other subtypes have been reported in the literature due to their peculiar clinical, demographic or histological characteristics: "hypopigmented/hyperpigmented", "erythrodermic", "poikilodermic", "pigmented purpura-like", "bullous/ dyshidrotic", "papular" and even the "invisible" subtype. [5] The leukemic MF subtype is referred to as SS, with distinct clinical and evolutive expressions.[1-7]

Historical aspects

In 1806, MF was first described in France by Alibert, who named it in 1814 "Pian fungoides". The term "mycosis fungoides " was only adopted by Alibert in 1832.[5] In 1870, Bazin described its evolution according to the natural history of the disease and defined its stages. Such description is classic and has been used to this date: patch, plaque, tumoral and systemically disseminated.

In 1885, Vidal and Brocq introduced the term "mycosis fungoides d'*emblée*" for cases of cutaneous lymphomatous tumorations virtually from the beginning, without precursor lesions. [1] Currently, this old MF clinical subtype corresponds to the "unspecific peripheral cutaneous T-cell lymphoma" and is no longer considered an MF variant. [1,2,6]

In 1892, the erythrodermic form of MF was described. It is characterized by erythema, scaling and generalized infiltration of the skin. In 1938, the description of Sézary syndrome was made. [1] "Pagetoid reticulosis" was described in 1931 as "Ketron-Goodman's disease", which would correspond to the generalized form of pagetoid reticulosis, and, in 1939, solitary hyperkeratosis was described by Woringer-Kolopp. The Ketron-Goodman subtype is no longer considered pagetoid reticulosis and probably corresponds to the aggressive epidermotropic CD8+ cutaneous T-cell lymphoma.[8]

In 1968, "lymphomatoid papulosis" was described by Macaulay as a benign clinical form of CTCL that develops in outbreaks, despite its malignant morphological aspect on histopathological examination. [9] The immunophenotype of lymphomatoid papulosis corresponds to $CD3^+$, $CD45RO^+$ and $CD30^+$. [10]

The denomination "cutaneous T-cell lymphoma" (CTCL) was used for the first time in 1975 to include MF and its variants, and it later included other PCL types and the spectrum of $CD30^+$ PCL, primary subcutaneous panniculitis-like T-cell lymphomas, nasal-type NK/T-cell PCL, and non-classifiable T-cell PCL.[5-7]

In 2007, the International Society for Cutaneous Lymphoma (ISCL) and the EORTC published a review of the staging and specific classification of MF and SS. The review modified the staging system and provided an accurate definition of SS, in particular. [6]

Epidemiological aspects

Primary cutaneous lymphomas are the second most frequent extranodal non-Hodgkin lymphomas; they are preceded by gastrointestinal lymphomas. PCL

show an estimated annual incidence in Europe of 1/100,000 inhabitants. [1,2]

In contrast to nodal non-Hodgkin lymphomas, which are mostly of the B type, T-type lymphomas predominate in the skin. They correspond to 65%-80% of the total PCL diagnosed in Europe. [11] MF and its variants correspond to more than 50% of the cases of PCL and to approximately 90% of the total number of T-cell lymphomas.[1,2,11] In the United States, from 1973 to 1992, the incidence of MF was 0.36 cases/100,000 inhabitants.[11] Incidence of the disease was higher in the black population compared to Caucasians, at a proportion of 1.7/1. The proportion between Asians and whites was 0.6/1.[12] In the period studied, the mortality rate decreased for MF cases specifically, and this was considered a result of early diagnosis.[11]

In a study conducted in Switzerland from 1990 to 2009, 263 PCL cases were identified. The mean age of the patients was 59 years, and the male/female ratio was 1/1.4.[12] CTCLs added up to 190 cases (72.2%), and MF corresponded to 60% (114/190) of these cases. In the period studied, the incidence of MF was stable, and SS decreased from 17% to 7% of cases. The incidence of CD30+ lymphomas increased from 7% to 18% of the total number of cases.[12]

In Brazil, data from the National Institute of Cancer (Instituto Nacional do Câncer- INCA) indicate an estimated incidence of 9,640 new cases in 2012 (5,190 in males and 4,450 in females) for the group of extranodal non-Hodgkin lymphomas, which is equivalent to approximately 5.0/100,000 inhabitants. This estimate includes PCL; however, the INCA publication does not distinguish between the different subtypes of PCL.[13]

MF particularly affects male and female adults, with an M/F ratio between 1.6 and 2/1. These individuals are usually older than 50 years, but incidence has increased in children and adolescents. [1,2,5]

The survival percentage in the fifth year of follow-up ranges from 16% to 100%, depending on clinical CTCL subtype, and from 80% to 100% when MF and its variants are considered, except for SS, which shows a reserved prognosis. [2,5-7]

MYCOSIS FUNGOIDES AND SÉZARY SYNDROME. CLINICAL ASPECTS

Mycosis fungoides

It is a neoplasia of lymphocytes, generally of the $CD4^+$ phenotype, and a cytokine production pattern with Th2 profile. Other phenotypes associated with typical MF are $CD8^+$, $CD56^+$ and the double negative, $CD4^-$ and $CD8^-$. Classic MF follows some clinical stages that are used to identify the disease and its staging. In the early phases, diagnosis is difficult, and the disease mimics different clinical conditions, such as chronic eczema, psoriasis, parapsoriasis, sclero-atrophic lichen, chronic lichenoid pityriasis, pityriasis alba, atopic dermatitis, leprosy, chloracne (MF follicular subtype) and, by analogy, those of other cutaneous lymphomas.[5,7] In this phase, clinical and histological aspects may be unspecific and the disease evolves for years without a diagnosis.

The early lesions, when fully established, correspond to patches (Figures 1 and 2), which are referred to as "*plaques*" in the French literature and described as erythematous-scaling plaques in the textbook entitled *Dermatologia* by Sampaio & Rivitti.[14] They resemble psoriasis or parapsoriasis, which has led to semantic confusions and difficulty with the definition and characterization of the early stage of MF. [14,15]

The early clinical aspect of the disease is that of a patch-like lesion with a slight erythematous, pinkish or brownish coloration, or hypochromic, with thin scaling and, at times, with slight atrophy (Figures 1 and 2). Single or multiple lesions of different diameters and locations develop, often in covered areas and particularly in the gluteal region and on the root of the thighs. In certain cases, the lesion is poikilodermic, with mottled patches with hyper and hypopigmentation, lichenification and telangiectasias. Pruritus generally varies from mild to moderate. These lesions may remain stable for years, go into remission or indolently progress to plaque stage.

The main differential diagnosis in this phase is parapsoriasis, which presents clinical and histological superposition with MF. In this context, two types of parapsoriasis must be distinguished: small and large plaques that were generically defined by Brocq in 1902 [1] as chronic, recurrent, erythematous scaling lesions comparable to "eczematoid, psoriasiform and lichenoid lesions".

Although they are referred to as plaque parapsoriasis, the lesions are, in fact, of the patch-type. The

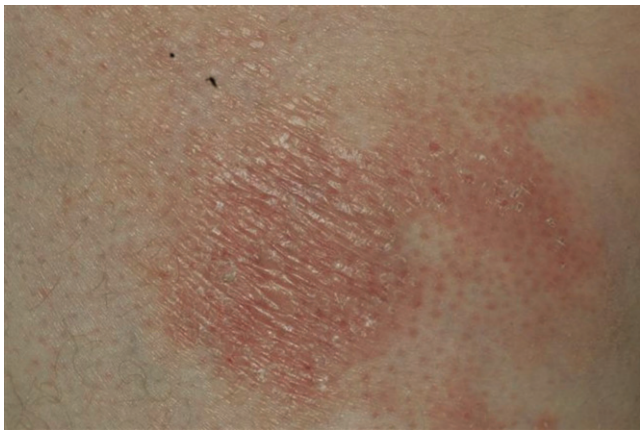

Figure 1: Mycosis fungoides - patch: erythematous, atrophic and slightly hyperkeratotic lesion on the gluteal region

distinction between "small-plaque" parapsoriasis and "large-plaque" parapsoriasis is based on clinical and histopatological correlation. Small plaques have a smaller diameter with a digitiform aspect. They are usually located on the trunk and do not present atrophy or telangiectasia. [16] Lesions are 2 to 6 cm in diameter, but they can reach 10 to 20 cm in length, and this is why they are referred to as "digitiform" [16] Histologically, "small-plaque" parapsoriasis is characterized by unspecific alterations, such as spongiosis, psoriasiform or lichenoid pattern with exocytosis of small lymphocytes. Currently, it is consensual that "small-plaque" parapsoriasis shows minimum or even no potential to become MF.[16]

"Large-plaque" parapsoriasis presents with lesions that are larger than 6 cm in diameter, and they frequently show signs of atrophy and poikilodermia. They are located on the gluteal region, trunk, root of the thighs, internal part of the arms and mammary region. Histologically, the pattern resembles that of "small-plaque" parapsoriasis; however, the infiltrate contains lymphocytes with cerebriform nuclei, similarly to what is observed in MF. [16-20]

"Large-plaque" parapsoriasis progresses to frank MF in around 7.5% to 14% of cases.[16,17] Sanchez and Ackerman (1979) suggested that "large-plaque" parapsoriasis must be understood as a synonym for MF in its early stage. [18] King-Ismael and Ackerman (1992) reported that even "small-plaque" parapsoriasis is the early manifestation of MF, which is not accepted by other authors. [19,20]

Other dermatoses are possible differential diagnoses of MF, particularly chronic eczema of undefined etiology, which is little responsive to appropriate therapy. These cases frequently remain under clinical suspicion of MF for a long time until accurate diagnostic definitions are made.

In the plaque stage, lesions individually show clear infiltration and increased diameter, and new lesions appear (Figure 3). There is a tendency for lesions to take an annular, polycyclic or horseshoe-shaped aspect; they seem to be infiltrated at palpation and to have well-demarcated edges and asymmetrical distribution. They may also affect the face and the scalp. Occasionally, plaque lesions may ulcerate prior to becoming tumor-like lesions. [21,22]

They change from an erythematous pinkish to erythematous purplish or brownish color, with scaling of variable intensity. Pruritus tends to be more intense than in the patch stage. Patients may remain in this stage indefinitely, go into remission for an indefinite period or progress to tumor stage. [21,22]

Clinical differential diagnosis in this phase is made with diseases showing cutaneous infiltration; other cutaneous lymphomas, whether primary cutaneous lymphomas or not, are noteworthy, namely, cutaneous sarcomas and infectious dermatoses with emphasis on leprosy, which can simulate infiltrated MF lesions, infectious dermatoses caused by fungi and even tumic lupus erythematosus. The histological diagnosis is more sensitive and more specific in this phase than in the patch phase, with frank epidermotropism and the presence of Pautrier's abscesses.

In the tumor stage, lesions have a papular or nodular aspect, with erythematous-purplish coloration and possible progression to large-diameter lesions (Figure 4). In this phase, it is not uncommon to find the coexistence of patches and plaque-type lesions. Lesions tend to be multiple and accompanied by cutaneous infiltration which, when located on the face, render a lion-like facial aspect. [22] In addition to the face, preferential sites are the axillary, inguinocrural, inframammary and antecubital regions. However, uncommon sites may be affected, such as the oral and genital mucosae. [5]

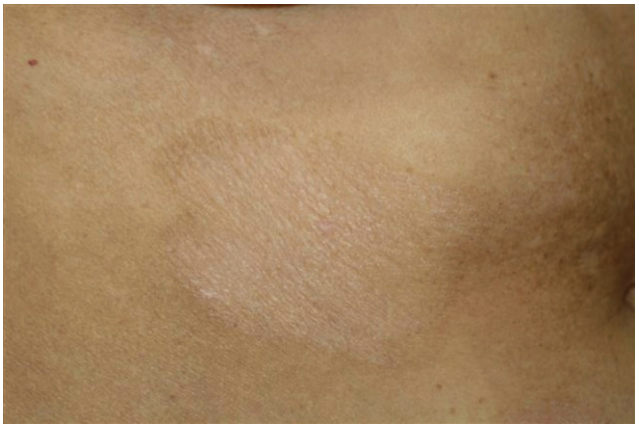

Figure 2: Mycosis fungoides - patch: hypochromic and atrophic lesion on the thorax

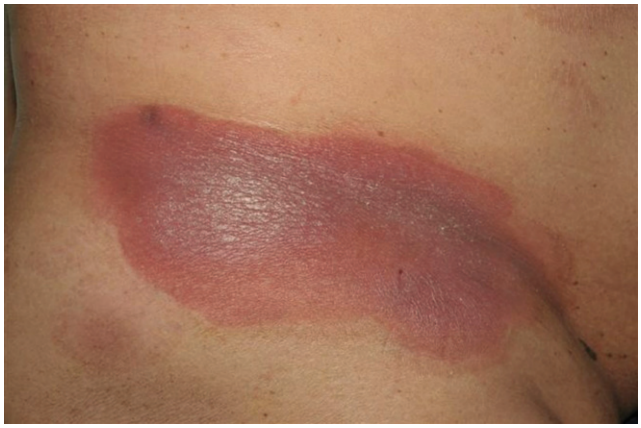

Figure 3: Mycosis fungoides - plaque: erythemato-violaceous lesion with mild hyperkeratosis localized on the inguino-crural region

It is noteworthy that patients in the tumor stage and with clinical remission following treatment may relapse under the form of patches and plaques or even tumors. The development of patches is usually the first sign of disease recurrence. In these circumstances, the natural history of the disease shows a faster course and new tumors will be soon present.[5]

Lymphonodal or visceral dissemination does not occur in the patch stage; it is rare in the plaque stage, but becomes relatively frequent in the tumor stage. [2,21] Regional lymph nodes are the first areas to be affected, and visceral compromising may occur in various organs, such as spleen, liver and lungs, although the bone marrow is rarely affected. [2,5,7]

MF transformation into the anaplastic variant of large CTCL CD30+ cells has been reported among 8% to 55% of tumor-phase MF cases. [5-7] $CD30^+$ lymphomas secondary to MF show a reserved prognosis with mean survival of 11 to 36 months. [2,5-7]

Sézary syndrome

Sézary Syndrome corresponds to 3% of all cutaneous lymphomas, and it is characterized by a triad of manifestations: erythrodermia with pruritus, limphonodomegalia and atypical circulating lymphocytes (referred to as Sézary or Lutzner cells). [5,22,23] Associated clinical manifestations include lagophthalmos, alopecia, palmoplantar hyperkeratosis and onycodystrophy. Erythrodermia may be the progression of previous patches and plaques, developing from idiopathic erythrodermia or emerging *de novo*. [5, 22,23]

Patients are usually elderly. The clinical aspects of erythrodermia in SS are not very distinguishable from those of erythrodermia associated with other diseases, except in certain cases, as it is less desquamative and shows more infiltration than the others. [24] However, in its early stages, SS is indistinguishable solely on clinical bases and must be differentiated from erythrodermia of eczematous origin, psoriasis and pharmacodermia. [23,24]

It is interesting to note that SS must be differentiated from erythrodermia in MF progression. In the WHO-EORTC classification, MF and SS are listed as independent diseases, and patients with a previous history of MF who develop erythrodermia are diagnosed as having an erythrodermic form of MF instead of SS. [1,2,5-7,24] Nevertheless, some authors suggest that these cases must be classified as "MF-preceded SS". [24]

Although the syndrome is understood as a leukemic phase of T-cell cutaneous lymphomas, bone marrow compromising is rare, and it is only found in advanced forms of the disease. [25]

The diagnostic criteria for the syndrome, as recommended by ISCL-EORTC and countersigned in the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues, are that the circulating monoclonal lymphocyte population should be identified by molecular or cytogenetic methods and there should be an identity between the circulating T-lymphocyte clone and the clone presented in the skin, in addition to one of the following: at least 1,000 Sézary cells per mm^3 of peripheral blood, an increased population of $CD4^+/CD7^-$ in peripheral blood with remarkable predominance of $CD4^+$ cells in relation to $CD8^+$ (CD4/CD8 ratio > 10), Sézary cells with a diameter > 14 μm representing > 20% of the circulating lymphocytes and, some markers like CD2, CD3, CD4 and CD5 must be absent. [1,2,5,22,23]

The staging system used for MF is also used for SS, and by definition the syndrome is classified in stage III from the beginning. SS prognosis is poor, with a mean survival of 2 to 4 years. [6] Both MF and SS patients have an increased chance of developing a second malignant neoplasia and even a second lymphoma. The opposite also seems to be true, that is, patients with a type-B lymphoma may develop type-T MF or SS more frequently than the general population.[5,6,22]

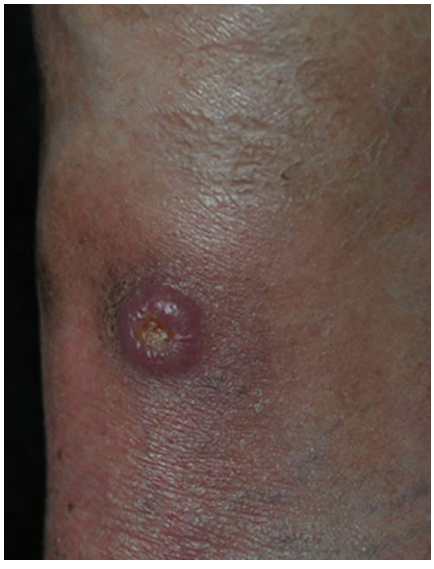

Figure 4: Mycosis fungoides: tumoral lesion appearing over a previous patch-type lesion on the leg

MYCOSIS FUNGOIDES. Clinical variants described in the "WHO-EORTC Classification for Cutaneous Lymphomas" and "WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues"

Follicular/folliculotropic mycosis fungoides

Folliculotropic mycosis fungoides has been classified as an entity that is separated from the classic form because of its clinical and histological characteristics and refractoriness to treatment. [2,5,22] It is described in the literature under different designations: folliculotropic, follicular, pylotropic, folliculocentric and

follicular mucinosis.[2,5,22,26-33] Some authors understand that the latter must be distinguished from follicutropic MF; however, most authors agree that both belong to the spectrum of clinical and histopathological manifestations of follicular MF. [26-30]

Some publications refer that folliculotropic mycosis fungoides occurs mainly in females. [27,36] Lesions initially show an acneiform or comedo-like aspect, or one with milia *en plaque*, follicular papules, follicular keratosis, erythematous plaques, papular or alopecic plaques (alopecia mucinosa), including mucin secretion (mucinorrhea).[5, 26-33]

The preferential locations for clinical lesion onset are the face, neck and upper trunk, and pruritus is moderate to intense. One third of the cases affect the eyebrow with follicular prominence and the possibility of alopecia. Severe compromising of the pilous follicle with follicular hyperplasia may result in the formation of lesions with a tumor aspect, even in the absence of an actual tumor, thus corresponding to pseudotumoral MF. [30]

The differential diagnoses of folliculotropic MF must be diseases that progress with cyst formation, pseudocomedos and plaques, such as chloracne, nevus comedonicus, granulomatous rosacea and facial granuloma. [26-33]

Microscopically, folliculotropic MF expresses a dense lymphocytic infiltrate, which surrounds and infiltrates the pilous follicle and usually spares the epidermis in interfollicular space. In approximately 10% of cases, there is epidermotropism and folliculotropism. [5,26-30] The infiltrate consists of small and medium-sized lymphocytes with irregular nuclei and formation of Pautrier's microabscesses inside the follicular epithelium. [33,34] The follicles classically show a corneous plug and, at times, epithelial mucin degradation with variable intensity.[30-33]

Evidence indicates that the prognosis of folliculotropic MF is worse than that of the classic form. The survival rate is 26% in 10 years of follow-up, and with regard to staging, a diagnosis of folliculotropic MF would implicate considering that the patient belongs to stage III, regardless of the clinical appearance of the lesion at diagnosis. [6,30,33]

Pagetoid reticulosis (Woringer-Kolopp type)

Pagetoid reticulosis is considered an MF variant due to its clinical, evolutive and anatomopathological characteristics. The term pagetoid reticulosis must be reserved for localized lesions known as Woringer-Kolopp disease, which was described in 1939. [8] Ketron-Goodman disease, described in 1931, was previously considered a generalized form of pagetoid reticulosis for showing a histological pattern of intense epidermotropism, in contrast with dermal infiltrate, which is not pronounced. [7] However, it is no longer accepted as an example of pagetoid reticulosis and seemingly represents generalized forms of classic MF or cytotoxic, epidermotropic $CD8^+$ CTCL of severe evolution.[8,22,34]

Clinically, pagetoid reticulosis usually presents as an acral isolated erythematous infiltrated lesion, plaque-type, with a remarkable hyperkeratotic or psoriatic aspect. Histologically, it shows pronounced epidermal hyperplasia with intense epidermotropism of small or medium-sized lymphocytes with cerebriform nuclei.

There are immunophenotypic differences between pagetoid reticulosis and classic MF since the former may express $CD4^+$ and $CD8^+$ or be negative for both, as well as express $CD30^+$. [5, 22,31,34] The cellular proliferation rate estimated by Ki-67 immunostaining is higher than 30% in pagetoid reticulosis and lower than 10% in MF, but it still has a good prognosis. [5, 22,31,34]

Granulomatous slack skin

Granulomatous slack skin shows a clinical pattern of erythematous or dark-erythematous, atrophic, flaccid, pendular and redundant cutaneous lesions, cutis-laxa-type (slack skin) in folding areas.

The granulomatous infiltrate may have a sarcoidic pattern, be of annular-granuloma-type or have a multinucleated-giant-cell pattern. The granulomatous infiltrate is sometimes so expressive that diagnosis of MF is not established and the disease is interpreted as "granulomatous dermatosis". [5,35]

In granulomatous cutis laxa, dense epidermotropism is added to the granulomatous histological pattern, and cells engulfing lymphocytes and elastic fibers are observed. This phenomenon is referred to as emperipolesis, in which elastic fibers may be totally absent and mucin is detected in the lesion. [2,5, 22,36]

MYCOSIS FUNGOIDES: CLINICAL/HISTOLOGICAL VARIANTS DESCRIBED IN THE LITERATURE

Hypopigmented mycosis fungoides

It is characterized by the presence of isolated hypochromic lesions or by the coexistence of multiple erythematous and hypochromic lesions of small or large diameters, sometimes alopecic. It can be expressed as a single MF manifestation or coexist with plaque lesion or even tumors.

Hypopigmented MF is the clinical subtype most often observed in children and adolescents and in patients with skin phototype IV-VI. However, it is also observed in fair-skinned patients. [5,22,37] Lesions may be asymptomatic or discreetly pruriginous.

Indeterminate leprosy, pityriasis alba, atopic dermatitis, chronic eczema of indefinite etiology, inflammatory vitiligo, extensive pityriasis versicolor

and post-inflammatory hypopigmentation are differential diagnoses. In confirmed cases, histology is indistinguishable from classic MF. However, the immunophenotype can reveal an increased frequency of $CD8^+$ lymphocyte as observed on a report of 15 patients with hypopigmented MF. [37] Ardigó et al. (2003) suggested that $CD8^+$ immunomarking would be more common in high-phototype patients with hypopigmented MF and in children, as opposed to $CD4^+$, which is more frequent in hypopigmented MF observed in Caucasian adults. [38] Based on a review of 106 literature reports, Werner et al. (2005) indicated the possibility of diagnostic error due to the clinical and histological similarity of the disease to various others, particularly pityriasis alba. [39]

The clinical course of the disease is the same as that of classic MF, with a good therapeutic response to phototherapy and post-treatment repigmentation. [40]

Erythrodermic mycosis fungoides

Patients with classic MF may develop erythrodermic conditions in the advanced stage of the disease, but this is rare. These conditions are almost clinically indistinguishable from those of SS; however, its distinct history and the non-fulfillment of the syndrome's diagnostic criteria consolidate the difference. [22,24] Its histological and immunophenotypic aspects are identical to those of MF. After treatment, the patient may relapse and exhibit conventional plaques and tumors or relapse with the previous erythrodermic pattern. [22,24]

Poikilodermatous mycosis fungoides (*poikiloderma atrophicans vasculare*)

In this clinical subtype, lesions are characterized by erythematous brownish patches, alternating hypo and hyperpigmentation with an atrophic pattern and with xerosis and telangiectasias on the surface. In a series of 49 cases, this condition was more common in young patients and more associated with lymphomatoid papulosis.

The main sites of involvement are breasts, trunk, gluteal region and flexures. The disease may also be generalized. Histological findings are peculiar, as they show atrophic epidermis losing interpapillary crests, lichenoid infiltrate and fibrosis of the papillary dermis. Pautrier's microabscesses are usually absent. [5, 22, 41,42] Dilated vessels and macrophages containing melanin are observed in the superficial dermis. The immunohistochemical pattern is predominantly $CD8^+$ and $CD4^-$. When other manifestations of classic MF are inexistent, diagnosis is certainly difficult and it is based on clinical evolution, histopathological and immunophenotype correlation. [5, 22, 41,42]

Purpuric mycosis fungoides

This is a rare form of MF in which patch lesions are persistent and pigmented. Histologically, they also show extravasated red cells in the dermis, melanophages and histiocytes. However, there is histological evidence of classic MF, such as band-like infiltrate in the superficial dermis, epidermotropism of atypical lymphocytes and lymphocyte alignment in the basal layer, which help with differential diagnosis from lichen aureus, nummular eczema or pharmacodermias that show purpuric conditions. [43]

Most cells are $CD4^+$, but there may be expression of $CD8^+$ cells. Monoclonal molecular rearrangement of T cell receptor (TCR) has been shown in the infiltrate of purpuric MF, but also in cases of purpuric pharmacodermias referred to as "atypical pigmented purpuric". Therefore, it is not always easy to clearly define the diagnosis of purpuric MF. [31,43,44]

Syringotropic mycosis fungoides

This is a rare form of MF in which accentuated infiltration of eccrine sweat glands and ducts by lymphomatous cells occur. [5,45] Clinically, lesions tend to be single, isolated in erythematous brownish plaques and slightly desquamative, or in groups of erythematous papules.[5,45]

Alopecia is frequently associated with the lesion. Apparently, there is no preferential location, and the infiltrate is dense around and in the gland. The follicles and the epidermis may be infiltrated. Epidermotropism is not common, and visualization of Pautrier's microabscesses is rare. [45,46] Detection of monoclonal $CD4^+$ lymphocytes and TCR gene rearrangement indicates that these conditions belong to the MF spectrum, although the term "syringotropic T-cell cutaneous lymphoma" is used for such conditions. [5, 22,31,45,46]

Vesiculobullous mycosis fungoides

Vesicular, bullous and dyshidrosiform lesions associated with MF are extremely rare. [5] They present as isolated or multiple, flaccid or tense lesions. They appear on normal skin or on an erythematous base or in association with plaques and tumors. Patients are generally older than those diagnosed with classic MF, and the reported cases involve Caucasian individuals.[47,48] The trunk and limbs are the preferential locations.

Histologically, there is epidermotropism of cerebriform lymphocytes and even Pautrier's microabscesses.[47,48] A blister or a vesicle may form in subcorneal, intraepidermal and subepidermal locations; therefore, bullous eruptions could be flaccid or tense. [5] It is suggested that the bullous originates from the confluence of Pautrier's microabscesses and the accumu-

lation of lymphocytes in the basal layer, thus missing the dermal-epidermal cohesion. [5,49-51]

The presence of blisters or vesicles accompanying MF may indicate a bad prognosis as approximately 50% of the patients have one year of life after these lesions appear. [5, 22,47,48] A dyshidrosiform variant with lesions located on the palms and plants has also been described. [49]

Other subtypes

In addition to the clinical subtypes described above, MF may manifest as or be accompanied by uncommon and atypical morphological expressions, such as papular, anetodermic, hyperkeratotic, vegetative, pustular, ichthyosiform or even "invisible" MF. [49-55] The latter is related to skin with a normal appearance which shows, on histopathology, immunophenotype and electron microscopy, evidence of infiltration by monoclonal and atypical lymphocytes. In general, these patients show classic or suggestive lesions of MF that are referred to as "invisible" MF lesions due to their normal appearance on clinical examination, and sometimes as "invisible" MF for corresponding to the hypochromiant MF present in patients with very fair skin and, therefore, "identical" to normal skin.[54,55]

Mycosis fungoides in childhood and adolescence

It is estimated that only 5% of all MF cases occur in childhood and adolescence; however, MF is the most common cause of cutaneous lymphoma at this age range. [56] The incidence of MF in individuals younger than 20 years is low, but it appears to be increasing, particularly the hypochromiant subtype, in patients with a high skin phototype. In addition to hypochromiant MF, another subtype reported in childhood and adolescence is Woringer-Kolopp pagetoid reticulosis. Cases that are clinically similar to lichenoid and acute varicelliform pityriasis also occur in childhood, and they are particularly difficult to be diagnosed as MF. [57,58]

The progressive course of MF in childhood and adolescence is controversial. Some authors suggest that progression is faster and more aggressive with frequent extracutaneous involvement; however, others report that progression follows the MF standard observed among adults. [5,22]

Staging and classification

Olsen et al. (2007) published the staging norms of MF and SS as a result of the ISCL – EORTC discussions taking into account the advancement of cellular and molecular biology and the advancement in diagnostic methods shown in charts 1 and 2. [6]

Histopathology of mycosis fungoides

Histopathology of MF depends on the stage in which a biopsy is performed. In the classic early patch-stage MF, microscopic findings are often unspecific and they overlap with those of other inflammatory or non-neoplastic diseases. Empirical clinical treatment with the use of topical corticosteroids can alter the histological aspect, making it even more unspecific; therefore, treatment should be discontinued for approximately 2 to 4 weeks before performing a biopsy. The same applies for the use of the PUVA method. [15]

In the patch stage with well-established lesions, lymphocyte infiltrate on the edges of the basal layer and epidermotropism of isolated cells are histologically observed. Most of these cells are small and differentiated lymphocytes with slightly rounded or cerebriform nuclei. The epidermis may show acanthosis, hyperkeratosis or signs of damage in the basal layer (pigmentary incontinence) and edema. There may be prominence of postcapillary venules and infiltrate containing eosinophils, plamocytes, macrophages and dermal dendritic cells. Papillary dermal fibrosis may also be present. Density of the infiltrate is variable and it increases as the lesion develops and clinically resembles plaque lesions. [15, 31,59-62]

In well-constituted plaques, the microscopic finding is an epidermis with a certain degree of acanthosis, psoriasiform pattern and rare or absent spongiosis. There is a dense subepidermal and band-like lymphocyte infiltrate with cerebriform nuclei (Figure 5). Epidermotropism is most prominent (Figure 6). Pautrier's abscesses are found in one-third of the cases, and lymphocyte alignment in the basal layer as well as dermal infiltrate with atypical cells with irregular and ceribriform nuclei are frequently found (Figures 7 and 8). [15,31, 59]

The tumor stage is characterized by diffuse and dense dermal infiltrate of medium-sized and large cerebriform lymphocytes and epidermotropism loss. There is a concomitant decrease in the number of T-reactive lymphocytes and dendritic cells. In this phase, transformation into large T cell lymphoma $CD30^+$ or $CD30^-$ may occur. [15, 31, 59-62]

The histopathological aspects of Sézary syndrome are indistinguishable from those of MF. Epidermotropism is less intense, but Pautrier's microabscesses may be present. The lymphocytic infiltrate is small to medium-sized and the cerebriform nuclei aspect is similar to that observed in MF. Presence of granulomatous reaction, mucin deposit on pilous follicles and transformation into large cell lymphoma in advanced stages are histopathological variants These aspects may also be present in MF. Lymphonodal compromising shows the same infiltrate pattern as that of MF. [5,22]

CHART 1: classification for mycosis fungoides and Sézary syndrome

	SKIN
T1	Patches, papules and/or plaques limited to 10% of the body surface. It may be stratified into T1A (patches) or T1b (patches and plaques).
T2	Patches, papules or plaques covering more than 10% of the body surface. It may be stratified into T2a (only patches) or T2b (patches and plaques).
T3	One or more tumors (≥ 1 cm in diameter).
T4	Confluence of erythema covering ≥ 80% of the body surface.
	LYMPH NODE
N0	Absence of abnormal peripheral lymph nodes.
N1	Presence of abnormal peripheral lymph nodes. Histopathology Dutch grade 1.
N1a	Negative clone. N1b - positive clone.
N2	Presence of abnormal peripheral lymph nodes. Histopathology Dutch grade 2.
N2a	Negative clone and N2b - positive clone.
N3	Presence of abnormal peripheral lymph nodes. Histopathology Dutch grade 3 or 4 with a positive or negative clone
Nx	Presence of abnormal peripheral lymph nodes without histological confirmation
	VISCERAL
M0	Absence of visceral compromising.
M1	Presence of visceral compromising (histopathological confirmation is necessary, and the involved organ must be specified)
	Peripheral blood
B0	Absence of major blood compromising (≤ 5% of the lymphocytes in peripheral blood are atypical - Sézary cells)
B0a	Negative clone and B0b - positive clone
B1	Presence of > 5% of atypical lymphocytes in peripheral blood, but it does not meet the criterion for B2. B1a - negative clone and B1b – positive clone
B2	Presence of ≥ 1,000 Sézary cells per mm3 of peripheral blood, with a positive clone
	Histological grading of lymph nodes according to the Dutch classification system recognized by ISCL/ EORTC
	STAGING
N1	Grade 1 - dermatopathic lymphadenopathy
N2	Grade 2 - MF compromising (presence of cerebriform lymphocytes > 7.5μm)
N3	Grade 3 - partial replacement of the lymph node architecture (presence of several atypical cerebriform cells). Grade 4- complete replacement of the lymph node architecture.

Source: ISLC/EORTC (2007)[6]

Immunohistochemical and molecular aspects

MF tumor cells are characterized by epidermotropic peripheral T lymphocytes whose phenotype is $CD2^+$, $CD3^+$, $CD4^+$, $CD5^+$, $CD8^-$, $CD45RO^+$, $CD20^-$ and $CD30^-$. (Figures 9, 10). $CD4^-$ or $CD8^+$, double positive or double negative cases are rarely seen. [15,63,64]

The loss of CD7 expression can be observed even in the early phases of the disease. However, isolated negativity for CD7 is not a sufficient criterion for diagnosis, as it can be shown in inflammatory dermatoses. With rare exceptions, both Ki-67 and CD 30 tend to negativity in early MF phases. [63]

The specific antigen for the cutaneous tropism of lymphocytes (cutaneous leucocyte-associated antigen receptor – CLA), recognized by antibody HECA-452, is expressed in the form of lymphomas and T-cell dyscrasias in most MF cases. [63] Markers such as T-cell intracellular antigen (TIA-1), granzyme B and perforin are negative in MF. [5,22]

Complete evaluation of T-antigen expression or immunomarking loss, of CD2 and CD5, for instance,

CHART 2: Staging for mycosis fungoides and Sézary syndrome

Stage	T	N	M	B
IA	1	0	0	0 or 1
IB	2	0	0	0 or 1
II	1 or 2	1 or 2	0	0 or 1
IIB	3	0 to 2	0	0 or 1
III	4	0 to 2	0	0 or 1
IIIA	4	0 to 2	0	0
IIIB	4	0 to 2	0	1
IVA1	1 to 4	0 to 2	0	2
IVA2	1 to 4	3	0	0-2
IVB	1 to 4	0 to 3	1	0-2

Source: ISLC/EORTC (2007)[6]

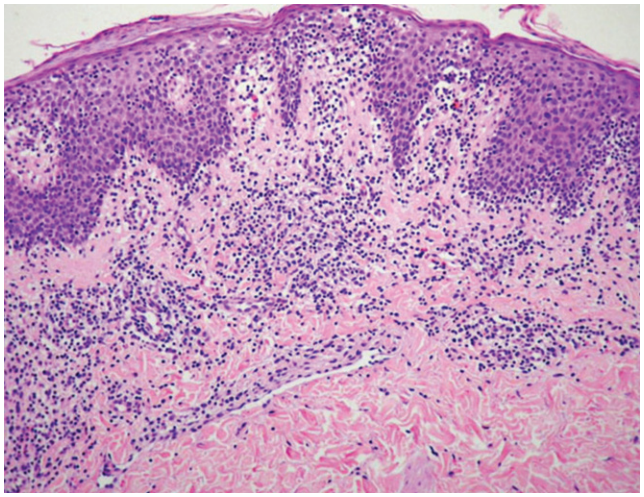

Figure 5: Mycosis fungoides: psoriasiform pattern with hyperplasia of the epidermis, band-like inflammatory infiltration and epidermotropism of lymphocytes. HE, (100X)

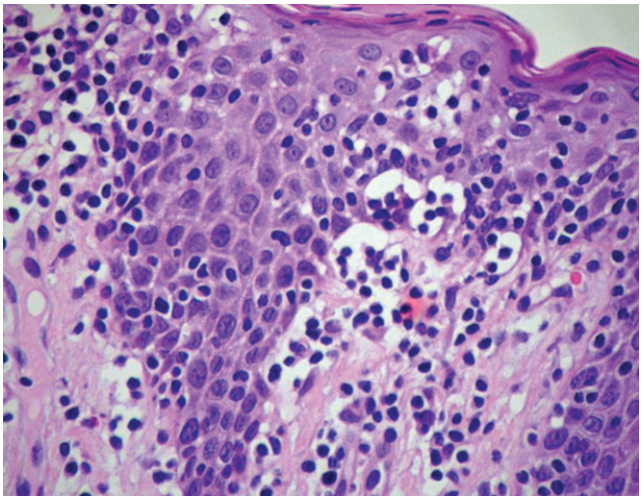

Figure 7: Mycosis fungoides: epidermotropism of lymphocytes and Pautrier's micro-abscess. (HE X 400)

can provide information that corroborates diagnosis, but even so, sensitivity remains low. [15,63] On the other hand, the study on clonality, associated with immunohistochemistry, provides high diagnostic specificity, particularly when there is isolated loss of CD7 expression. [15,63] It has been recently suggested that regulatory T cells correlate with stage of disease and prognosis in mycosis fungoides, particularly FOXP3$^+$ Tregs, which could be expressed in the epidermotropic infiltrate in different stages of MF.[65]

The diagnostic method most often used in molecular biology for detecting monoclonal T-lymphocytes is TCR gene rearrangement analysis, which can be performed by polymerase chain reaction (PCR) methods or Southern blot. However, some studies have shown that only 53% of early-stage MF cases showed a population of monoclonal T-lymphocytes. An additional inconvenience is that various skin diseases may also have monoclonal T-cell expansion. [21,66-68]

The observations above have led specialists to discuss the diagnostic difficulties of early MF lesions, and histopathology, immunohistochemistry and molecular biology techniques have been proposed to improve diagnostic accuracy and establish early diagnosis. [16,18,21,23,31,64-70]

The immunohistochemical pattern of Sézary syndrome is CD3$^+$, CD4$^+$, CD7$^-$ and CD8$^-$ cells, which does not distinguish it from MF. Immunostaining for MUM-1 (multiple myeloma oncogene) might be positive in the syndrome and negative in MF. This could help with differential diagnosis. [71]

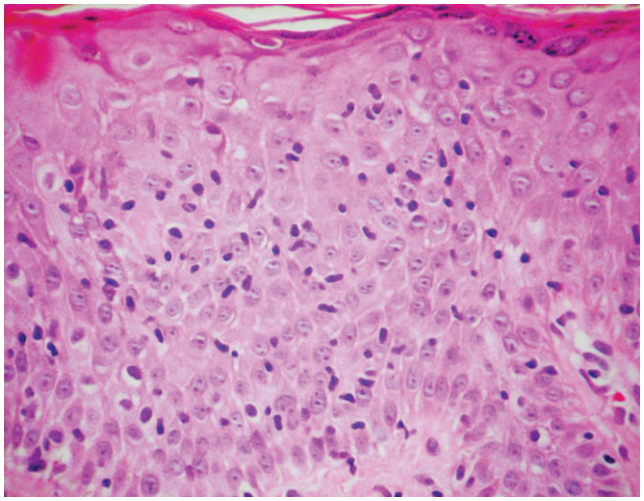

Figure 6: Mycosis fungoides: intense epidermotropism of lymphocytes on the epidermis and mild spongiosis. HE, (400X)

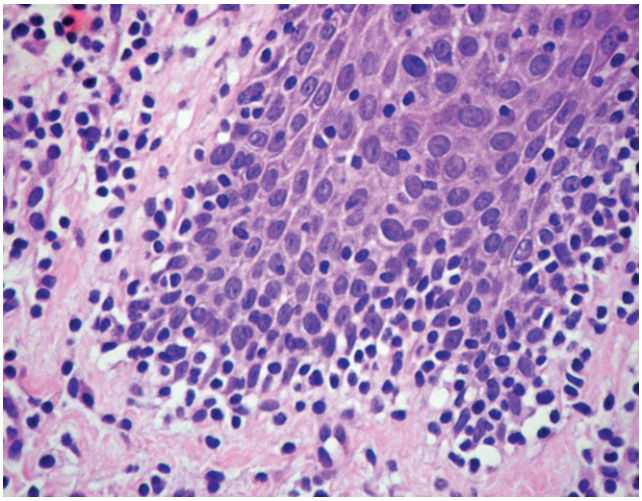

Figure 8: Mycosis fungoides: epidermotropism and lymphocyte alignment in the basal layer are shown. HE, (400X)

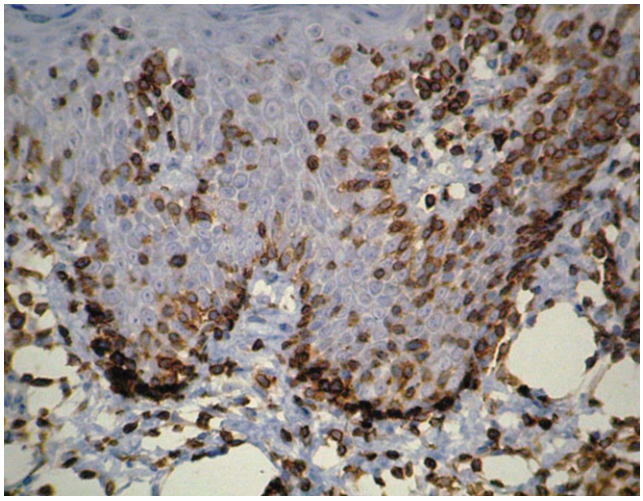

Figure 9: Mycosis fungoides: phenotypic studies showing CD3-positive T-cell on the epidermis and dermis. (CD3 immunostain 400X)

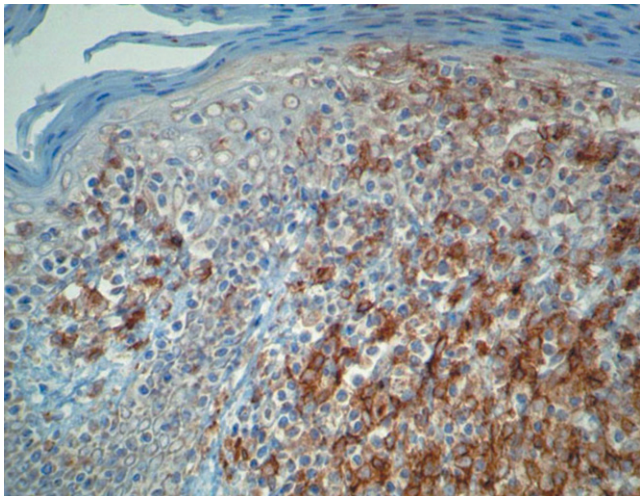

Figure 10: Mycosis fungoides: phenotypic studies showing CD4-positive T-cell on the epidermis and dermis. (CD4 immunostain 400X)

CONCLUSION

Primary cutaneous lymphomas are rare, not always clearly classifiable, but of essential knowledge to dermatologists. Mycosis fungoides is the most frequent primary cutaneous lymphoma, and various differential diagnoses can be made in the early phases of the disease. It is typically a disease with difficult clinical, histopathological and immunohistochemical findings. The authors presented classic manifestations of MF and its clinical and histopathological variants. Sézary syndrome is very rare, but must be considered a routine differential diagnosis when investigating erythrodermias whose etiology must be clarified. And, as a sign of its identity in the mycosis-fungoides "spectrum", Sézary syndrome exhibits histological and immunohistochemical aspects that are indistinguishable from those observed in MF. ❑

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QUESTIONS

1. Which is an example of T-cell primary cutaneous lymphoma:
a) Mycosis fungoides
b) Lymphomatoid papulosis
c) Sézary syndrome
d) All of the above

2. Which is an example of aggressive T-cell primary cutaneous lymphoma:
a) Subcutaneous panniculitis-like T-cell lymphoma with alpha-beta phenotype
b) Sézary syndrome
c) Hypopigmented mycosis fungoides
d) Lymphomatoid papulosis

3. Which is a recognized variant of mycosis fungoides (WHO-EORTC classification):
a) Granulomatous slack skin
b) Pagetoid reticulosis
c) Folliculotropic mycosis fungoides
d) All of the above

4. Which of the following is historically connected to mycosis fungoides but is no longer accepted as a subtype of MF:
a) Pagetoid reticulosis
b) Tumor d'emblée
c) Woringer-Kollop subtype
d) Granulomatous slack skin

5. Choose the correct alternative:
a) T-cell primary cutaneous lymphomas are the most common extra-nodal lymphomas
b) Mycosis fungoides corresponds to 50% or more of T-cell primary cutaneous lymphomas
c) In the United States of America, mycosis fungoides is almost always associated with white people
d) T-cell primary cutaneous lymphomas basically affect individuals who are between 40-50 years old

6. The immunophenotype of mycosis fungoides can express:
a) CD3+
b) CD4+ and CD8+
c) CD4+ and CD20-
d) All of the above

7. Which of the following can be considered a differential diagnosis of mycosis fungoides:
a) Chronic eczema and pityriasis alba
b) Parapsoriasis and atopic dermatitis
c) Leprosy and cloracne
d) All of the above

8. The concept of "parapsoriasis" is nothing else than mycosis fungoides" is related to what kind of parapsoriasis?
a) Small-plaque type
b) Digitiform
c) Large-plaque type
d) Localized on thorax

9. Mycosis fungoides is preferentially located on:
a) Photoexposed areas
b) Photoprotected areas
c) Scalp
d) Breast

10.Post-treatment relapse of tumor-stage mycosis fungoides is presented as:
a) Always tumor-stage
b) Patch or plaque
c) Always Plaque
d) Ulcers

11.Mycosis fungoides transformation into large cell T-cell lymphoma CD30+ is:
a) Impossible
b) Disputable
c) Possible in the tumor stage
d) Possible, but with no impact on prognosis

12. It is possible to state the following about Sézary syndrome:
a) It is the same as erythrodermic-mycosis fungoides
b) It is a rare subtype of T-cell lymphoma - no more than 30% of all cutaneous T-cell lymphomas
c) Itching is a rare symptom
d) It is common in young individuals

13. The following is considered a criterion to confirm the diagnosis of Sézary syndrome:
a) Detection of ≥ 1000 Sézary cells/mm3 of peripheral blood
b) CD4+/CD8+ > 10 on peripheral blood
c) Sézary cells are more than 20% of all circulating lymphocytes
d) Alternative?

14. It is possible to state the following about follicular-mycosis fungoides:
a) It is located preferentially on the trunk and limbs
b) The follicle and the epidermis are the target of lymphocyte epidermotropism
c) The eyebrow area is often compromised
d) The prognosis is the same as that of classic mycosis fungoides

15. It is possible to state the following about pagetoid reticulosis:

a) Woringer-Kollop and Ketron-Goodman T-cell lymphoma subtypes are examples of the same lymphoma phenotype
b) It is characterized by intense lymphocyte epidermotropism
c) There are usually multiple lesions
d) Ulceration is a common complication

16. It is possible to state the following about hypopigmented-mycosis fungoides:

a) It is more common in individuals with skin phototype IV and above
b) It is reported more commonly in young individuals
c) CD8+ immunophenotype is not rare
d) All of the above

17. It is possible to state the following about poikilodermatous mycosis fungoides:

a) It is histologically characterized by atrophy of the epidermis, interface dermatitis and widely dilated capillaries in the dermis
b) It is more common in photoexposed areas
c) CD4- /CD8+ is a common imunophenothype
d) It is not common to find melanin in the dermis

18. It is possible to state the following about tumor-stage mycosis fungoides:

a) Tumor lesions do not erupt from patch or plaque lesions
b) There is a dense lymphocyte infiltrate in the dermis, but epidermotropism is discrete
c) In this subtype there is no risk of large T-cell transformation
d) Ulceration is a rare event

19. It is possible to state the following about plaque-mycosis fungoides:

a) Its phenotype is typically CD3+ CD4+ CD8- CD20- CD45RO+
b) The CD7- phenotype is irrelevant for diagnosis
c) The CD30+ phenotype is irrelevant for prognosis
d) CD8+ is a phenotype that rules out the diagnosis of mycosis fungoides

20. It is possible to state the following about T2 mycosis fungoides staging:

a) There is predominance of plaques of 10 cm or more of diameter
b) There are plaques and tumors but, not necessarily, predominance of tumors
c) The existing plaques must be ulcerated
d) There are patches, plaques and even papules covering > 10% of the body surface

Answer key

Tumor necrosis factor-alpha and the cytokine network in psoriasis. 2012;87(5):673-83.

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

Papers

Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.