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REVIEW ARTICLE

The clinicopathological manifestations and differential diagnoses of mycosis fungoides variants (the great mimickers): a comprehensive review

As manifestações clinicopatológicas e diagnósticos diferenciais de variantes de micose fungoides (os grandes imitadores): uma revisão abrangente

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Abstract

Mycosis fungoides (MF) is the most prevalent type of primary cutaneous T-cell lymphoma (CTCL), which is considered a great imitator due to the wide spectrum of its clinical manifestations that can mimic numerous skin disorders. MF can also resemble a wide range of dermatoses on histopathological and clinicopathological bases. The various clinical and histopathological manifestations of MF often lead to missing or delaying the diagnosis, which leads to a poorer prognosis as a consequence. In this article, we presented a comprehensive review of the clinical presentations and differential diagnoses of the clinical, histopathological, and clinicopathological variants of MF with a focus on the histopathologic manifestations of each variant.

Keywords: Cutaneous lymphoma. Cutaneous T-cell lymphoma. Mycosis fungoides. Mycosis fungoides variants. Skin cancer.

Resumo

A micose fungóide (MF) é o tipo mais prevalente de linfoma cutâneo primário de células T, que é considerado um grande imitador devido ao vasto espectro das suas manifestações clínicas e ainda porque a MF pode assemelhar-se a uma vasta gama de dermatoses com idênticas bases histopatológicas e clinicopatológicas. As várias manifestações clínicas e histopatológicas de MF conduzem frequentemente a uma falta ou atraso no diagnóstico, o que leva a um prognóstico mais pobre. Neste artigo, apresentámos uma revisão abrangente das apresentações clínicas e diagnósticos diferenciais das variantes clínicas, histopatológicas e clinicopatológicas de MF com enfoque nas manifestações histopatológicas de cada variante.

Palavras-chave: Linfoma cutâneo. Linfoma cutâneo de células T. Micose fungoide. Variantes de micose fungoide. Cancro da pele.

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Introduction

Mycosis fungoides (MF) is the most common type of CTCL, which represents about 50% of all primary cutaneous lymphomas[1,2]. It was first described by Jean Alibert in 1806[2].

MF affects mainly adults, mostly males[2]. Black populations have a higher rate of MF and worse prognosis[3].

Atypical cerebriform lymphocytes in the epidermis and superficial dermis are the main histopathologic feature of MF[4,5], but, as some skin disorders have similar histopathological features, this may lead to misdiagnosis[6]. Therefore, the diagnosis of MF is a real challenge to physicians and needs an association between clinical and histopathological examinations, as many skin disorders may mimic the various variants of MF[1,6,7].

This article provides a comprehensive review of MF variants with a focus on their differential diagnoses and distinct characteristics to approach the most likely diagnosis of each variant.

Classification and variants

Aside from classic MF, many clinical, histopathologic, and clinicopathologic variants of MF have been reported (Table 1)[4,8]. Since the majority of variants exhibit a clinical behavior comparable to that of classic MF, they are not classified separately in recent classifications[1]. Only folliculotropic MF (FMF), pagetoid reticulosis (PR), and granulomatous slack skin (GSS) are recognized as distinct variants of MF in the World health organization: European Organization of Research and Treatment of Cancer (WHO-EORTC) classification due to their distinct clinicopathologic features, clinical behavior, and/or prognosis[1].

Classic MF

Classic MF, also known as Alibert–Bazin type of MF, is the most reported type of this CTCL[1,2,6]. It represents about 90% of all MF cases and accounts for approximately 4% of all non-Hodgkin lymphomas[2,6].

Males are more frequently affected[9], typically adults in their 5th-6th decade[9].

It is classified into three stages that include patch, plaque, and tumor stages[6]. Asymmetric telangiectasias and erythematous macules are the clinical manifestations of patch-stage MF[6], which typically involves sun-protected areas like the breast (in female patients), buttocks, and trunk and extremities[6]. The plaque stage is usually characterized by erythematous, reddish-brown, or scaling lesions[6]. The last stage is characterized by nodules ≥ 1 cm[6].

The stage of classic MF determines its prognosis[9]. Early-stage patients have an excellent prognosis and a survival rate comparable to that of age, sex, and race-matched individuals[9], whereas advanced-stage patients over 60 years old are considered with a poor prognosis[9]. Anyway, most MF patients have a slow clinical progression over years or decades[9].

The histopathological hallmark in the patch stage is the proliferation of large pleomorphic lymphocytes at the dermal-epidermal junction, focal parakeratosis, and papillary dermis fibrosis[6]. The plaque stage highly resembles the patch stage and reveals intersurface vascular changes like infiltration of the upper dermis by lymphocytes, which characteristically have hyperchromatic nuclei and nuclear membranes which are convoluted, in addition to Pautrier's microabscesses[6]. Neoplastic lymphocytes are widely distributed throughout the dermis in dense sheets at the tumor stage[6].

Many disorders can be considered differential diagnoses of classic MF, such as perioral dermatitis, seborrheic eczema, palmoplantar eczema, dyshidrotic eczema, atopic eczema, contact dermatitis, tinea corporis, tinea pedis, psoriasis, and parapsoriasis[10].

Clinical variants

Hypopigmented MF

Hypopigmented MF is an uncommon clinical variant characterized by hypopigmented-to-achromic papules and macules without atrophy, sometimes with vitiligo-like lesions, in addition to patches ranging from small-size to large-size lesions[8,11].

Hypopigmented MF can be the only MF manifestation or coexist with classic MF lesions or other variants[4]. Lesions are mainly distributed on the trunk, extremities, and buttocks and may be associated with pruritus[11].

Hypopigmented MF is considered one of the commonly reported variants in children, although cases have been reported in adults too[8]. Dark-skinned individuals and Asians are commonly affected by hypopigmented MF[4,8]. Despite it is believed to have no gender predilection, some studies observed remarkable female predominance[11].

The prognosis is typically excellent, at least compared to classic MF[11].

Table 1. The clinical, histological, and clinicopathologic variants of MF

Clinical variants
Hypopigmented MF
Erythrodermic MF
Papular MF and pityriasis lichenoides-like MF
Unilesional (solitary) MF
MF palmaris et plantaris
Ichthyosiform MF
Vegetating/papillomatous MF (acanthosis nigricans-like MF)
Erythema annulare centrifugum and erythema gyratum repens-like MF
Invisible MF
Clinicopathologic variants
Folliculotropic MF
Bullous and vesicular MF
Poikilodermatous MF
Pagetoid reticulosis (Woringer-Kolopp disease)
MF with eruptive infundibular (epidermoid) cysts
Syringotropic MF
Granulomatous slack skin
Hyperpigmented MF
Anetodermic MF
Verrucous MF
Psoriasiform MF
Dyshidrosis-like vesicular eruption
Pigmented purpuric dermatosis-like MF
Pustular MF
Histopathologic variants
Granulomatous MF
Interstitial MF
MF with large-cell transformation

Hypopigmented MF lesions are indistinguishable histopathologically from classic MF[4]. Some of the most common features include focal parakeratosis, lymphocytic infiltration in the upper dermis, slight or no spongiosis, and a variable number of lymphocytes at all levels of the viable epidermis disposed of as single units and episodically in small collections[11]. Pautrier microabscesses are rarely observed[11]. Other features involve slight psoriasiform epidermal hyperplasia, vacuolar alteration of the dermal-epidermal junction mimicking an interface dermatitis, scattered dyskeratotic keratinocytes, folliculotropism, and melanin incontinence associated with melanophages in the papillary dermis[11].

The differential diagnoses may include sarcoidosis, atopic dermatitis, leprosy, pityriasis alba, pityriasis versicolor, pityriasis lichenoides (PL) chronica, vitiligo, syphilis and other treponematoses, lichen sclerosus, postinflammatory hypopigmentation, idiophatic guttate hypomelanosis, onchocerciasis, hypomelanosis of Ito, and halo nevus[11].

Erythrodermic MF (EMF)

In erythrodermic MF (EMF), patients with the classic histopathologic findings of MF develop generalized erythroderma but with no diagnostic criteria of Sézary syndrome (SS), namely with the absence of blood involvement typical of SS[2,8,12]. Additionally, they have a lower occurrence of lymphadenopathy[12]. Anyway, SS is the main differential diagnosis of EMF[8].

Generalized erythroderma is considered a progression of typical patch or plaque lesions of classic MF, but in some cases, erythroderma arises de novo[2,12]. Pruritus is often present, and in rare cases, it may occur before the onset of the skin eruption[12].

Patients with EMF and Sézary syndrome had a poor overall prognosis[12], very particularly patients with erythroderma who have skin tumors[12].

Histopathological findings of EMF reveal classic features of MF with absent or a low amount of circulating neoplastic lymphocytes[2]. However, epidermotropism is not present in some EMF cases[12].

Papular MF and pityriasis lichenoides-like MF

Pityriasis lichenoides-like MF (PL-like MF) is rare and occurs as a distinct variant of MF with a good prognosis presenting as localized or widespread erythematous scaly papules but without spontaneous regression of the lesions compared to PL[4,13,14]. PL-like MF is commonly reported in young patients and less in adults and children[4,13].

Papular MF was primarily characterized in 2005 based on criteria including papules with histopathologic features of MF, spontaneous regression of lesions, and no additional evidence of lymphomatoid drug reaction or MF[4]. The prognosis is good in case there was no previous history of patches or any other clinical characteristics of MF; otherwise, the prognosis is bad if there is a previous history of patches or clinical features of MF[13].

Papular MF lesions are presented as chronic and papular eruptions mainly located on the trunk and limbs with symmetric distribution[13].

The histopathological findings of PL-like MF resemble both findings of MF (haloed lymphocytes, lymphocytes aligned along basal cells, Pautrier's microabscess, stuffed lymphocytes in the dermal papilla, coarse collagen bundles in the papillary dermis, and intraepidermal lymphocytes larger than dermal lymphocytes) and of PL (erythrocyte extravasation, spongiosis, necrotic keratinocytes, and exocytosis of lymphocytes and neutrophils)[13]. However, MF is distinguished from PL by the presence of epidermotropism and numerous atypical lymphocytes[14].

The histopathological findings of papular MF do not comprise PL findings (such as necrotic keratinocytes or erythrocyte extravasation)[13].

The differential diagnoses of PL-like MF include papular MF, PL, and lymphomatoid papulosis[13], and the differential diagnoses of papular MF include, PL, lymphomatoid drug eruption, lymphomatoid papulosis type B, and persistent arthropod bite reactions[4].

Unilesional MF

Unilesional MF, also known as solitary MF, presents as an isolated erythematous scaly patch or plaque generally located in sun-protected areas[15,16]. Lesions grow slowly and may be present for several years without confirming the diagnosis[4,16]. An excellent prognosis has been reported in previous studies[7].

Unilesional MF is indiscernible histopathologically from the classic MF (patch and plaque-stage)[7], but generally, atypia is more notable in the epidermotropic lymphocytes compared to those in the dermis[7].

Unilesional follicular MF is a possibly curable form distinguished by neoplastic lymphocyte infiltration into the follicle[17].

The main differential diagnosis of unilesional MF includes Bowen's disease, papulosquamous or eczematous lesions, and dermatophyte infection[4].

Mycosis fungoides palmaris et plantaris (MFPP)

Mycosis fungoides palmaris et plantaris (MFPP) is a rare disorder expressed by erythematous hyperkeratotic patches or plaques with fissures and scales limited to palms or/and soles, often affected bilaterally, with or without itch, and without extracutaneous involvement[4,18]. This variant can occur in classical MF patients (about 10% of the cases)[4].

MFPP commonly presents in middle-aged individuals (16–68 years; mean age 55 years)[18], occasionally with pustular, vesicular, annular, verrucous, dyshidrotic, psoriasiform, hyperpigmented or ulcerative lesions, and nail dystrophy[4].

Histopathological features are typical of MF, but spongiosis may be more distinct in MFPP, which makes it challenging to differentiate MFPP from spongiotic dermatitis[4].

Differential diagnoses of MFPP may include palmoplantar psoriasis, hand eczema, contact dermatitis, hyperkeratotic lichen planus, secondary syphilis, dermatophytosis, and verrucae[18].

Ichthyosiform MF

Ichthyosiform MF is uncommon and generally presents as dry, diffuse, and scaling skin with well-circumscribed scaly patches or flat plaques, with a pattern resembling ichthyosis vulgaris's cobblestones[4,8]. Lesions are typically located on the trunk and extremities and can be associated with other variants of MF, particularly FMF, or present only as ichthyosiform lesions[4,19]. It has an indolent course and a favorable prognosis, with a mean age of onset is around 32 years[19].

Ichthyosiform MF reveals compact orthokeratosis, hypogranulosis, and a band-like epidermotropic infiltrate comprised of small cerebriform lymphocytes[9].

Many differential diagnoses can be taken into account, including ichthyosis vulgaris, drug eruption, sarcoidosis, underlying malignancy (such as paraneoplastic eruption), and endocrinologic and autoimmune disorders[4].

Vegetating/papillomatous MF

Vegetating/papillomatous MF, also known as acanthosis nigricans-like MF, is a rare variant of MF that presents as brownish or velvety hyperpigmented, polygonal plaques with varying patches of erythema between the lesions located on the neck, axillae, groin, popliteal fossae, intergluteal, nipple, areolae, and periumbilical areas[4,9,20]. Some lesions may become more prominent and even nodular[20]. Lesions may be itchy[4,9,20].

Histopathologic features of acanthosis nigricans-like MF include the typical features of MF in addition to acanthosis and papillomatosis together with a band-like infiltrate of atypical lymphocytes that may be epidermotropic or not[4,20]. Interconnected rete pegs and horny pseudocysts with seborrheic keratosis-like

features may be present[4], which can mimic acanthosis nigricans or seborrheic keratosis based on their presentation, size, and color[9].

Erythema annulare centrifugum (EAC) and erythema gyratum repens (EGR)-like MF

Many cases of MF with annular or polycyclic erythematous patches and/or plaques have been reported in the literature[21]. EAC-like MF is characterized by trailing scales and erythematous concentric rings, which expand outward without central clearing[21], whereas EGR-like MF lesions are also characterized by symmetrically distributed red patches with erythematous concentric rings and trailing scales[4,21], but no evident central clearing, as the whole patch is comprised of band-like rings[4].

Histopathologically, EAC-like MF has typical features of MF[4] without the perivascular lymphocytic "coat-sleeve-like" infiltration typical of EAC[4].

EAC-like MF may simulate Lyme disease, superficial fungal infection, and tinea imbricata[4,21].

Invisible MF

Invisible MF is an extremely rare variant that presents with persistent and occasionally generalized pruritus as the only clinical manifestation[22-25] but has the histopathologic findings of classic MF[22-25], including occasional Pautrier microabscesses[23,25].

Systemic amyloidosis, pseudoxanthoma elasticum, and pretibial myxedema has been reported in normal-looking skin, and they are considered differential diagnoses of invisible MF[22].

Clinicopathologic variants

Folliculotropic MF (FMF)

Folliculotropic MF (FMF) is the most common atypical clinicopathologic variant[1,4]. It is classified as a clinicopathological variant by WHO-EORTC classification that clarifies the existence of follicle-based lesions and folliculotropism as the predominant histopathological characteristics, with or without follicular mucinosis[4].

FMF diagnosis comprises idiopathic follicular mucinosis, even though it is discussed whether this represents universal FMF or a distinct entity, and another entity that is amalgamated with CTCLs such as SS, MF, adult T-cell leukemia, and lymphomatoid papulosis[26].

The clinical presentation of FMF includes various morphologies such as erythematous plaques, follicular papules, acneiform lesions, prurigo-like lesions, cysts, and patches of alopecia that can associate with eyebrow involvement and maybe with scarring[6,27,28], in addition to other unusual presentations that include pseudotumors, rosacea-like lesions, lupus tumidus-like, and lichen spinulosus-like lesions in association with alopecia and hypopigmentation[28]. Alopecia is a common and typical featured finding of FMF which is observed in up to 81% of patients[28]. Lesions are located mainly on the upper trunk and extremities (in up to 73% of patients), neck, and face[27], very often reported as predilection locations[26]. Leonine appearance is a rare expression of MF, which is associated with stage-IV CTCL and with blood and folliculotropism involvement during the disease progression[26,27].

Difficult-to-manage pruritus is a common symptom in adult patients, but in contrast, children with FMF complain of mild pruritus[26]. FMF mainly affects adults but has also been reported in adolescents and children with a male predominance[4,26].

Erythroderma also may manifest in up to 6% of FMF cases[26]. 92% of patients have skin-restricted involvement, while 8% of them have visceral or nodal involvement at their first presentation[28]. Secondary bacterial infections are commonly noticed in FMF patients[1].

FMF is characterized histopathologically by infiltration of atypical lymphocytes surrounding the hair follicles and generally spares the interfollicular epidermis and is occasionally accompanied by the follicle's disruption[4,27]. A mild perivascular inflammatory infiltrate occurs in the upper dermis without evident lymphocyte atypia in the early stage[27,28], and apart from follicles, infiltration can also affect eccrine sweat glands (syringotropism): adnexotropic MF[1]. In addition, mucin degeneration of the follicular epithelium was typically reported in many cases[1,27].

The most paramount histopathological differential diagnoses of FMF include pseudolymphomatous folliculitis, follicular lymphomatoid papulosis, and follicular eczema[26].

FMF diagnosis may be delayed, 18–48 months on average, after the lesion onset due to its distinct clinical presentation of classic MF[26,28].

Recent studies classified an early-stage FMF with a good prognosis and a more aggressive advanced-stage FMF subgroup[26], which has a poor prognosis with a 5-year surviving rate of 70–80%[27]. The survival range of tumor FMF is similar to classical tumor-stage MF[4]. Reduced survival has been linked to large cell transformation, advanced age, and broad secondary bacterial infection[1].

Differential diagnoses depend upon the various clinical presentations of FMF[4]. Erythematous lesions on the scalp can be misdiagnosed as psoriasis capitis, atopic dermatitis, and seborrheic dermatitis[4]. Alopecia on the scalp can mimic trichotillomania, cicatricial alopecia, and alopecia areata[4]. Rosacea, adult-onset acne, follicular-comedogenic graft-versus-host disease, chloracne, and Favre-Racouchot syndrome have to differentiate from acneiform lesions[4]. Pityriasis rubra pilaris, lichen spinulosus, lichen planopilaris, and keratosis pilaris should be taken into account as differential diagnoses in follicular spiky papules[4]. In addition, alopecia mucinosa should be considered as a differential diagnosis in hairless patches and/or plaques[4].

Bullous and vesicular MF

Bullous and vesicular MF, also known as vesiculobullous MF lesions, are rare and aggressive variants of MF that can occur on normal-appearing skin and/or on the affected skin with classic MF/SS[4,29]. Vesiculobullous MF lesions usually manifest as multiple flaccid or tense bullae on the trunk and proximal limbs with a predisposition to form ulcers[4,6,29,30]. The lesions have a poor prognosis and mostly affect older people without gender predominance[29].

Has been reported; an association between bullous MF, bullous pemphigoid, former treatment with psoralen plus ultraviolet A, topical mechlorethamine, or/and systemic interferon[4,29]. In addition, it is very probable that vesicular MF can onset on the affected skin with atopic diathesis[5].

The histopathological mechanism underlying blister formation has not been demonstrated[29]. The confluence of malignant lymphocytes within the epidermis causes the secession of the epidermis from the dermis[5].

Vesiculobullous MF lesions are expressed by intraepidermal or subepidermal blisters combined with classic findings of MF like atypical lymphocytes, epidermotropism, and the aggregation of Pautrier's microabscesses[5,8,29].

Bullous MF can mimic many disorders, including autoimmune bullous disorders (bullous pemphigoid, bullous lichen planus, bullous lupus erythematosus, and pemphigus vulgaris), porphyria, drug eruptions, and viral infections[4,6,29]. Besides, vesicular MF should be differentiated from autoimmune bullous disorders, eczematous dermatitis, bacterial or viral infections, and drug eruption[4]. However, vesiculobullous MF lesions are distinguished from blistering autoimmune diseases by their negative direct and indirect immunofluorescence results[8].

Poikilodermatous MF

Poikilodermal MF, also known as poikiloderma vasculare atrophicans, is a variant of MF, that is characterized by cutaneous atrophy, macular pigmentary changes, mild scaling, and telangiectasia[4,8,31]. It is usually considered a clinicopathologic variant of patch-stage classic MF[4].

Poikilodermal MF manifests as small plaques or papules, usually asymptomatic or mildly pruritic, ordered in a net-like pattern at the onset of the lesions, then the lesions usually develop into large plaques or affect the skin generally[31]. However, the lesions are typically either stable or slowly expanding[31].

The most common locations of poikilodermatous MF are the breast (in women) and buttocks (in both women and men)[8]. The skin of the patient may resemble "cigarette paper" as a result of atrophy and thinning[31].

Poikilodermatous MF has been reported in children with a higher percentage compared to adults[15]. Also, there have been reports of progression from poikilodermal MF in childhood to EMF in adulthood[15]. Anyhow, the prognosis of poikilodermal MF is favorable, and it responds to phototherapy[8].

Histopathologically, poikilodermal MF shows an atypical T-cell infiltrate in the papillary dermis, often with obvious epidermotropism[31]. In addition, melanophages and melanin incontinence are present, associated with ectasia of the superficial dermal vessels and epidermal atrophy[31]. Pautrier microabscesses are not typically present[8].

Morphea, lichen sclerosus, ashy dermatosis, and radiation dermatitis are considered differential diagnoses of poikilodermal MF[4].

Pagetoid reticulosis (PR)

Pagetoid reticulosis (PR), also known as Woringer-Kolopp disease, is a rare variant of MF occurring both in children and adults[4,6]. It typically manifests as a slowly progressive, solitary, hyperkeratotic or psoriasiform patch or plaque with a well-defined elevated border and a central clearing that usually affects the limbs, especially the feet and hands[1,6]. In some cases, ulceration and pain were also reported[6].

PR has an excellent prognosis with no disease-related deaths or extracutaneous involvement[1].

However, PR may progress to a disseminated PR or Ketron-Goodman disease, which currently corresponds to a more aggressive form of cutaneous lymphoma (epidermotropic cytotoxic T-cell lymphoma in almost all reported cases)[8].

Typical histopathologic findings of PR include epidermal hyperplasia and marked infiltration by small to

medium-sized atypical pagetoid cells, ordered separately or in nests or clusters[1]. Atypical cells consist of medium to large-sized cerebriform nuclei with abundant, vacuolated cytoplasm[1]. Neoplastic T-cells are rarely observed in the superficial dermis, but an infiltration mostly of small lymphocytes can occur[1].

The differential diagnoses of PR may involve psoriasis, chronic dermatitis, verrucous squamous cell carcinoma, tuberculosis verrucosa cutis, and blastomycosis[4].

Mycosis fungoides (MF) with eruptive infundibular (epidermoid) cysts

Some MF patients have reported having a localized or generalized follicular eruption with comedones and infundibular cysts, which appears to be a rare variant of MF[8]. This form combines MF with multiple, tiny, and eruptive epidermoid cysts and comedones[32]. Keratinous cysts can occur on uninvolved skin or on MF patches and plaques[32]. Some lesions have an acne-like or comedo-like manifestation[32]. Lesions may occasionally resemble tumor-stage lesions due to their size and inflammatory appearance[8].

MF with eruptive infundibular cysts needs to be differentiated from FMF, although some authors consider these two variants are part of the same spectrum with follicular involvement in MF[8]. Also, Favre-Racouchot disease should be considered as a differential diagnosis if MF with eruptive infundibular cysts lesions are located on the face[32].

Histopathology shows the characteristic features of an infundibular cyst encompassed by a dense infiltrate formed mainly by atypical lymphocytes in the cyst wall[8]. Infundibular cysts may be associated with the infiltration of follicular openings by neoplastic cells, causing expansion of the infundibula and subsequent blockage[8].

Syringotropic MF (STMF)

Syringotropic MF (STMF) is a rare variant of MF characterized by eccrine sweat gland infiltration[1,4]. It is also called syringotropic CTCL, syringolymphoid hyperplasia with alopecia, or adnexotropic T-cell lymphoma[4]. STMF features imbricate with FMF and, therefore, it was classified as a subtype of FMF within the WHO-EORTC classification[4], but differences in survival between STMF and FMF in a recent study suggested they should be categorized separately[33]. STMF is much less aggressive than FMF[34].

STMF is usually located in sun-protected areas with a tendency to affect males twice as often as females, with a mean age of 55[4,34]. It presents as a solitary lesion or numerous erythematous patches, papules, or plaques with dotted follicular accentuation, in addition to overlying alopecia, which is reported commonly in STMF[4,34]. Also, hypohidrosis is periodically observed in STMF[34].

STMF demonstrates histopathological features, including hyperplasia of eccrine glands and ducts encompassed and penetrated by dense infiltration of atypical lymphocytes in the dermis[34].

The differential diagnoses of STMF involve perniosis, neutrophilic eccrine hidradenitis, classic MF, and syringometaplasia without a significant lymphocytic infiltrate, as in post-chemotherapy, ischemia, and radiation dermatitis[35].

Granulomatous slack skin (GSS)

Granulomatous slack skin (GSS) is a very rare clinicopathologic variant of MF that shares histopathological characteristics with granulomatous MF (GMF), which makes it difficult to differentiate it from this variant[1,6]. It is more common in younger people[6].

Initial cutaneous lesions in GSS have a similar presentation to classic MF, including patches and plaques[1]. Then GSS lesions develop into large and pendulous folds of atrophic skin, due to the loss of elastic fibers, in locations such as groins and axilla (flexural areas) resembling cutis laxa[1,2]. Extracutaneous involvement of GSS is uncommon[6]. Hodgkin lymphoma or nodal non-Hodgkin lymphoma has been reported as an associated disease in 30–50% of GSS cases[2].

GSS is manifested by a slow and indolent advanced clinical course[1]. However, the complete recovery of GSS has never been reported[1].

Histopathology of GSS includes multinucleated giant cells (comprising > 10 nuclei for each cell) in addition to elastophagocytosis, emperipolesis (engulfment of lymphocytes), and loss of elastic tissue[1]. The infiltration by small atypical T-cells with cerebriform nuclei in the epidermis may be observed, as in the classic MF[1].

It is necessary to take into account differential diagnoses such as infectious granulomas, sarcoidosis, granuloma annulare, and anetodermic MF (AMF)[36,37].

Hyperpigmented MF

Hyperpigmented MF is a very rare variant of MF classified as an unusual clinical manifestation of palmaris et plantaris MF and presents clinically as hyperpigmented macules, patches, and/or plaques without

the presence of poikilodermatous changes[4,8,38]. Some cases manifest with indistinct borders and diverse degrees of skin atrophy and scaling[4].

Although some patients may present with associated lesions of classic MF or other MF variants, hyperpigmented MF may be the only manifestation of MF[4].

Hyperpigmented MF typically affects people with dark skin and younger ages (under 35 years old), and it has slowed clinical progression[38]. Anyhow, it has a better prognosis compared to classic MF[38].

Histopathologically, in addition to findings of classic MF, diffuse vacuolar degeneration of basal keratinocytes imitating "interface dermatitis", along with melanophages, have been observed in the most hyperpigmented MF cases[4].

Many disorders should be considered as differential diagnoses of hyperpigmented MF, including pigmented contact dermatitis, cutaneous amyloidosis, fixed drug eruption, post-inflammatory hyperpigmentation, idiopathic eruptive macular hyperpigmentation, atrophoderma of Pasini and Pierini, and erythema dyschromicum perstans[4].

Anetodermic MF (AMF)

Anetodermic MF (AMF) is a cutaneous disorder characterized by progressive loss of dermal elastic tissue, which results in atrophic plaques with a featured parchment-like surface[8]. The most involved locations are limbs, face, buttocks, and trunk[37].

Primary anetoderma occurs when there is no underlying associated disease, and it arises on clinically normal skin, whereas secondary anetoderma appears on the same site as a prior specific skin lesion[37]. However, the appearance of AMF in classic MF lesions is extremely rare[8].

Histopathologically, T-helper lymphocytes are infiltrated into the dermis with a few histiocytes and some multinucleate large cells engulfing deformed elastic fibers[37]. In the dermis, elastic fibers are almost completely absent[37].

GSS is the main differential diagnosis of AMF[37].

Verrucous MF

Verrucous MF is a quite rare variant of MF which presents as warty, hyperkeratotic, pruritic plaques that can be located on the trunk, face, and limbs and can be associated with classic MF lesions[4].

Verrucous MF lesions may manifest as single or many erythematous papules that progressively enlarge and become more raised with a verrucous surface[39]. Apart from pruritus, most verrucous MF lesions are asymptomatic[39].

Location on the extremities was commonly reported in African-Americans with a history of long-standing MF[39]. It has been noticed that African-American women are more likely to develop early-onset MF with a poor prognosis[39].

Histopathologic characteristics of verrucous MF involve classic MF findings along with hyperkeratosis and papillomatosis, inflammatory infiltration into the papillary dermis, and exocytosis and spongiosis in the epidermis[8].

Many disorders can be assumed as differential diagnoses, such as verrucae vulgaris, keratoacanthoma, palmoplantar hyperkeratosis, seborrheic keratosis, porokeratosis of Mibelli, and inflammatory linear verrucous epidermal nevus[4].

Psoriasiform MF

Psoriasiform MF is a rare variant of MF considered an unusual clinical manifestation of palmaris et plantaris[4,40].

The clinical presentation of psoriasiform MF involves scaly, well-defined, thick, erythematous psoriasiform plaques, which can mimic psoriasis[4]. Additional alopecia, induration, erosions, and ulcerative lesions may occur in some patients[4]. However, many cases reported generalized lesions[40,41].

The majority of reported cases were in males, with a mean age of 54 years[41].

Histopathological findings are characterized by epidermotropism of atypical lymphocytes[40]. Scant spongiosis and a lichenoid pattern have also been reported[4]. In addition, histopathologic findings of psoriasis, including elongation of the rete ridges with regular acanthosis, thinning, parakeratosis with hyperkeratosis, or Munro microabscesses and total effacement of the granular layer are present[42].

The clinical differential diagnoses of psoriasiform MF include psoriasis vulgaris, lichen planus, lichen simplex chronicus, leprosy, and ashy dermatosis[40].

Dyshidrosis-like vesicular eruption (DLVE)

Dyshidrosis-like vesicular eruption (DLVE) is an extremely rare variant of MF[30]. It presents as vesicles restricted to palms and soles with a possible expansion to the trunk and extremities, but there have been no

reported cases of extracutaneous involvement[30]. DLVE has been reported in association with adult T-cell lymphoma/leukemia[30].

The microscopic sections show typical features of MF, including cerebriform lymphocytes, epidermotropic lymphocytes, and Pautrier microabscesses[30]. In addition, lymphokines released by neoplastic T-cells might obstruct normal keratinocyte adhesion[30]. Immunofluorescence studies of DLVE are negative, but acantholysis may occur[30].

Contact dermatitis, atopic eczema, and palmoplantar eczema are considered differential diagnoses of DLVE[6].

Pigmented purpuric dermatosis (PPD)-like MF

Pigmented purpuric dermatosis (PPD)-like MF is considered a rare variant of MF[4]. It is usually reported in children and adults with a male predilection[4,43]. PPD-like MF is characterized by golden-brown discoloration and enduring purpuric lesions[4]. It can mimic chronic pigmented purpura clinically[4]. The most common location of PPD-like MF is the lower extremities, with a rare possibility of a generalized involvement[43]. The histopathological examination of PPD-like MF reveals similar characteristics of MF, besides extravasation of erythrocytes in the papillary dermis with the presence of siderophages[4].

Pustular MF

Pustular MF is a very rare variant of MF which is considered an unusual manifestation of palmaris et plantaris MF[4]. It is characterized as a persistent vesicular pustular eruption that gradually transforms into typical MF plaques[8]. Anyway, the pustular MF lesions can be generalized or restricted to the palmoplantar location[8].

Histopathology reveals typical MF findings, such as epidermotropism, band-like infiltration of atypical lymphocytes, and Pautrier microabscesses, in amalgamation with neutrophils, eosinophils, subcorneal pustules containing atypical lymphocytes[8].

Pustular psoriasis, drug reaction, and skin infections are considered differential diagnoses of pustular MF[4].

Histopathologic variants

Granulomatous MF (GMF)

Granulomatous MF (GMF) is a histopathological variant of MF that may be diagnosed at the time of its first onset or years later[4]. It may manifest clinically as papules, plaques, or ulcerated nodules, without the characteristics of a cutis laxa-like that are typical of GSS[4,44]. GMF occurs more frequently in males in their 5th and 6th decades of life[44].

GMF progresses frequently and is associated with a high risk of developing a second lymphoma[8]. In addition, its prognosis is poorer than classic MF[8].

The EORTC's histopathologic criteria for GMF involve a histiocyte-rich infiltrate with histiocytes accounting for > 25% of the whole infiltrate, prominent granuloma formation, or a large number of histiocytic giant cells[4]. GMF has a variety of histopathologic patterns, including epithelioid, sarcoidal, palisaded, periadnexal, tuberculoid, necrobiotic granuloma-like, granuloma annulare-like, and diffuse granulomatous infiltrate[4].

Although GMF is clinically distinct from GSS, histopathologic examination reveals a decreased portion of multinucleated cells[8]. Epidermotropism is typically not a prominent feature[2]. Also, elastophagocytosis is a rare finding, but the loss of elastic fibers is common[4].

The differential diagnoses of GMF include lipoid necrobiosis, annular granuloma, granulomatous panniculitis, and granulomatous rosacea[44].

Interstitial MF

Interstitial MF lesions are a rare histopathologic manifestation of MF, with a persistent cytotoxic phenotype[45]. Patches and plaques are the typical clinical exhibition of interstitial MF, which can arise at any location of the body, in addition to atrophy and lack of scales[4,45,46]. The lesions can also present as erythematous patches surrounding the nasolabial folds and small papules located on the chin, which are called perioral dermatitis-like lesions[47].

Histopathologically, distinguishing features of interstitial MF include lymphocytes infiltrating the dermis and dissecting the collagen bundles[4]. Epidermotropic lymphocytes present focally in many cases[4]. Additionally, mucin deposition may present in the dermis[8]. However, the histopathological features of interstitial MF correspond to the interstitial variant of granuloma annulare[48].

The main differential diagnoses of IMF include interstitial granuloma annulare, interstitial granulomatous dermatitis, and the inflammatory stage of morphea[4,45]. Moreover, the differential diagnoses regarding perioral dermatitis-like lesions include contact dermatitis, seborrheic eczema, and atopic eczema[6].

Table 2. The most involved areas, the typical clinical presentation, and clinical differential diagnoses/mimickers of MF variants

MF variants	The most involved locations	The clinical presentation	Clinical differential diagnoses
Classic MF	Sun-protected areas (breast in females), buttocks, trunk, and extremities.	Patch-stage: asymmetric telangiectasias and erythematous macules. Plaque-stage: erythematous, reddish-brown, scaling lesions. Tumor-stage: nodules ≥ 1 cm.	Perioral dermatitis, seborrhoeic eczema, palmoplantar eczema, dyshidrotic eczema, atopic eczema, contact dermatitis, tinea corporis, tinea pedis, psoriasis, and parapsoriasis.
Hypopigmented MF	Trunk, extremities, and buttocks.	Hypopigmented-to-achromic papules, macules without atrophy, vitiligo-like lesions, small to large-size patches.	Sarcoidosis, atopic dermatitis, leprosy, pityriasis alba, pityriasis versicolor, pityriasis lichenoides chronica, vitiligo, syphilis and other treponematoses, lichen sclerosus, postinflammatory hypopigmentation, idiophatic guttate hypomelanosis, onchocerciasis, hypomelanosis of Ito, and halo nevus.
Erythrodermic MF	Generalized	A progression from a typical patch or plaque lesions of classic MF, but the lesions can also arise de novo.	Sézary syndrome.
Papular MF and pityriasis lichenoides (PL)-like MF	Trunk and extremities.	Papular MF: chronic and symmetrically scattered papular eruptions. PL-like MF: localized or widespread erythematous scaly papules.	Papular MF: PL, lymphomatoid drug eruption, lymphomatoid papulosis type B, and persistent arthropod bite reactions. PL-like MF: papular MF, PL, and lymphomatoid papulosis.
Unilesional (solitary) MF	Sun-protected areas.	Isolated erythematous scaly patch or plaque.	Bowen's disease, papulosquamous or eczematous lesions, and dermatophyte infection.
MF palmaris et plantaris	Palms and soles.	Erythematous hyperkeratotic patches or plaques.	Palmoplantar psoriasis, hand eczema, contact dermatitis, hyperkeratotic lichen planus, secondary syphilis, dermatophytosis, and verrucae.
Ichthyosiform MF	Trunk and extremities.	Dry, diffuse, and scaling skin with well-circumscribed scaly patches or flat plaques.	Ichthyosis vulgaris, drug eruption, sarcoidosis, underlying malignancy (such as paraneoplastic eruption), Infectious diseases, and endocrinologic and autoimmune disorders.
Vegetating/papillomatous MF (acanthosis nigricans-like MF)	Neck, axillae, groin, popliteal fossae, inter-gluteal, nipple, areolae, and peri-umbilical areas.	Brownish or velvety hyperpigmented, polygonal plaques with varying patches of erythema scattered between the lesions.	Acanthosis nigricans and seborrheic keratosis.
Erythema annulare centrifugum (EAC) and erythema gyratum repens (EGR)-like MF	Not enough available data.	EAC-like MF: trailing scales and erythematous concentric rings. EGR-like MF: symmetrically distributed red patches with erythematous concentric rings and trailing scales.	EAC-like MF: lyme disease, superficial fungal infection, and tinea imbricata.
Invisible MF	Some cases reported generalized pruritus as the only manifestation of this variant.	No visible dermatoses.	Systemic amyloidosis, pseudoxanthoma elasticum, and pretibial myxedema.

(Continues)

Table 2. The most involved areas, the typical clinical presentation, and clinical differential diagnoses/mimickers of MF variants *(continued)*

MF variants	The most involved locations	The clinical presentation	Clinical differential diagnoses
Folliculotropic MF	Trunk, extremities, head, neck, and face.	Erythematous plaques, follicular papules, acneiform lesions, prurigo-like lesions, and cysts.	Erythematous lesions on the scalp: psoriasis capitis, atopic dermatitis, and seborrheic dermatitis. Alopecic lesions on the scalp: trichotillomania, cicatricial alopecia, and alopecia areata. Acneiform lesions: rosacea, adult-onset acne, follicular-comedogenic graft-versus-host disease, chloracne, and Favre-Racouchot syndrome. Follicular spiky papules: pityriasis rubra pilaris, lichen spinulosus, lichen planopilaris, and keratosis pilaris. Hairless patches and/or plaques: alopecia mucinosa.
Bullous/vesicular MF	Trunk and proximal extremities.	Flaccid or tense bullae with a predisposition to form ulcers.	Bullous MF: autoimmune bullous disorders (bullous pemphigoid, bullous lichen planus, bullous lupus erythematosus, and pemphigus vulgaris), porphyria, drug eruptions, and viral infections. Vesicular MF: autoimmune bullous disorders, eczematous dermatitis, bacterial or viral infections, and drug eruption.
Poikilodermatous MF	Breast (in women) and buttocks (in both women and men).	Small plaques or papules are ordered in a net-like pattern, cutaneous atrophy, macular pigmentary changes, mild scaling, and telangiectasia.	Morphea, lichen sclerosus, ashy dermatosis, and radiation dermatitis.
Pagetoid reticulosis (Woringer-Kolopp disease)	Extremities (especially the feet and hands).	Solitary, hyperkeratotic or psoriasiform patch or plaque with a well-defined elevated border and a centric clearing.	Psoriasis, chronic dermatitis, verrucous squamous cell carcinoma, tuberculosis verrucosa cutis, and blastomycosis.
MF with eruptive infundibular (epidermoid) cysts	Not enough available data.	Localized or generalized follicular eruption with comedones and infundibular cysts.	Folliculotropic MF and Favre-Racouchot disease.
Syringotropic MF	Sun-protected areas.	Solitary lesions or numerous erythematous patches, papules, or plaques with dotted follicular accentuation.	Perniosis, neutrophilic eccrine hidradenitis, classic MF, and syringometaplasia without a significant lymphocytic infiltrate (as in post-chemotherapy, ischemia, and radiation dermatitis).
Granulomatous slack skin	Flexural areas.	Initial lesions have a similar presentation to classical MF, including patches and plaques.	Infectious granulomas, sarcoidosis, granuloma annulare, and anetodermic MF.
Hyperpigmented MF	Not enough available data.	Hyperpigmented macules, patches, and/or plaques without the presence of poikilodermatous changes.	Pigmented contact dermatitis, cutaneous amyloidosis, fixed drug eruption, post-inflammatory hyperpigmentation, idiopathic eruptive macular hyperpigmentation, atrophoderma of Pasini and Pierini, and erythema dyschromicum perstans.
Anetodermic MF	Extremities, face, buttocks, and trunk.	Atrophic plaques with a featured parchment-like surface.	Granulomatous slack skin.
Verrucous MF	Trunk, face, and extremities.	Single or many erythematous papules with a verrucous surface.	Verrucae Vulgaris, keratoacanthoma, palmoplantar hyperkeratosis, seborrheic keratosis, porokeratosis of Mibelli, and inflammatory linear verrucous epidermal nevus.

(Continues)

Table 2. The most involved areas, the typical clinical presentation, and clinical differential diagnoses/mimickers of MF variants *(continued)*

MF variants	The most involved locations	The clinical presentation	Clinical differential diagnoses
Psoriasiform MF	Many cases reported a generalized presentation of the lesions.	Scaly, well-defined, thick, erythematous psoriasiform plaques.	Psoriasis vulgaris, lichen planus, lichen simplex chronicus, leprosy, and ashy dermatosis.
Dyshidrosis-like vesicular eruption	Palms and soles.	It presents as vesicles.	Contact dermatitis, atopic eczema, and palmoplantar eczema.
Pigmented purpuric dermatosis-like MF	Lower extremities.	Golden-brown discoloration and enduring purpuric lesions.	Chronic pigmented purpura.
Pustular MF	Generalized or restricted to the palmoplantar location.	A persistent vesicular pustular eruption.	Pustular psoriasis, drug reaction, and skin infections.
Granulomatous mycosis fungoides	Not enough available data.	Papules, plaques, or ulcerated nodules.	Lipoid necrobiosis, annular granuloma, granulomatous panniculitis, and granulomatous rosacea.
Interstitial MF	Interstitial MF: any location of the body. Perioral dermatitis-like lesions: surrounding the nasolabial folds and on the chin.	Interstitial MF: patches, plaques, atrophy, and lack of scales. Perioral dermatitis-like lesions: patches and small papules.	Interstitial MF: granuloma annulare, interstitial granulomatous dermatitis, and the inflammatory stage of morphea. Perioral dermatitis-like lesions: contact dermatitis, seborrheic eczema, and atopic eczema.

Mycosis fungoides (MF) with large-cell transformation (LCT)

The development of large T-cell lymphoma from MF is classified as a histopathologic variant of MF which is described as the exhibition of large cells (> 4 times the size of a small lymphocyte) in at least 25% of the dermal infiltrate or forming microscopic nodules in which large cells that are either $CD30^+$ or $CD30^-$[8,49].

Mycosis fungoides (MF) with large-cell transformation (MF-LCT) is commonly present with a poor prognosis and arises in 20-50% of advanced MF[50]. However, it occurs more frequently in tumor-stage MF patients[8].

MF-LCT must be differentiated from other essential cutaneous lymphomas with $CD30^+$ large cells, like lymphomatoid papulosis and anaplastic large-cell lymphoma[8]. Anyway, the prognosis for MF-LCT is poor, while the prognosis for cutaneous anaplastic large-cell lymphoma is excellent[49].

Epidermal hyperplasia and dermal fibrosis at transformation were linked to longer survival[50]. On the other hand, the shorter survival appears to be correlated with a clinically advanced stage at transformation, older age, and serum lactate dehydrogenase of > 220 U/L[50]. A recent study suggests that patients with MF who have $CD30^+$ large-cell tumors have a better prognosis than those with $CD30^-$ large-cell tumors[49].

A summary of the most involved locations, clinical presentations, and differential diagnoses of MF variants are demonstrated in the following (Table 2)[1,2,4-13,15,16,18-47].

Conclusion

The variants of MF exhibit a wide range of clinical and histopathologic manifestations, which can mimic a broad spectrum of benign inflammatory skin diseases either clinically, histopathologically, or clinicopathologically. Therefore, the diagnosis of MF variants may be challenging. High awareness of MF clinical manifestations, in addition to histopathologic correlation along with the immunophenotypical studies, are required to obtain the correct diagnosis of MF.

Authors' contributions

Jacob Al-Dabbagh: wrote and edited the manuscript, performed the literature review, and revised the final manuscript. Nemat Ismail, Moath Alsoleman, and Eman Mohammad Deeb: performed the literature review, and participated in revising the manuscript. Lina Al-Soufi: the mentor, and reviewed the article. Zuheir Al-Shehabi: the guarantor, and revised the manuscript.

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Conflicts of interest

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