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Review Article

Is it mycosis fungoides? A comprehensive guide to reaching the diagnosis and avoiding common pitfalls

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ABSTRACT

Mycosis Fungoides (MF) is known as 'the great mimicker' due to its capacity to emulate several dermatoses, both in the clinic and on histology. This often leads to the diagnosis being missed or delayed, which consequently leads to poorer prognosis. For a timely diagnosis, it is crucial that the physician is aware of the various clinical and histological presentations of MF, as well as the proper diagnostic protocols. In the current review, we concisely encapsulate all the variants of MF as well has the conditions it mimics clinically and histologically. Through this, we aim to provide clinicians with a holistic picture of MF and help them determine when to suspect this disease and steps to take in order to nail the diagnosis.

1. Introduction

Mycosis fungoides (MF) is the most prevalent type of primary cutaneous T-cell lymphoma (PCTCL) [1]. As per the current World Health Organization and European Organization for Research and Treatment (WHO-EORTC) classification, PCTCLs are defined as T- and B-cell lymphomas with a dermatologic presentation and no signs of extracutaneous involvement when the diagnosis is made. MF makes up approximately 50% of PCTCLs [2]. MF in its 'classic' form (also known as the Alibert-Bazin type) presents as cutaneous patches, plaques or tumors [1,2]. On histology, the defining feature of classic MF is the presence of atypical CD4+ T-Cells with characteristic 'cerebriform' nuclei [1]. Several clinical and histopathological variants of MF have been described in literature. Clinical variants of MF often have overlapping histological features, and hence are not classified separately. However, there are three variants of MF which have drastically different clinical and pathologic features – these are the granulomatous slack skin (GSS), folliculotropic and pagetoid reticulosis (PR) subtypes [1].

Traditionally, MF has been very challenging to diagnose, for multiple reasons. Firstly, as discussed above, MF does not always present in its classic form, and has three distinct clinicopathologic variants. Secondly, even in its classic form, the skin lesions of MF can be extremely varied and may even mimic other benign dermatologic conditions such as atopic dermatitis, alopecia and eczema - leading to a misdiagnosis or a delayed diagnosis [1,2]. Thirdly, although skin biopsies have been the basis of diagnosis, the documented false-negative rate on histology is 40% and the false-positive rate is 44% [3]. This is primarily because the histological findings of MF in its early stages are often non-specific [4]. Furthermore, certain clinical conditions mimic MF histology, including its 'cerebriform' nuclei, and may lead to a false positive diagnosis [5].

As with most malignant conditions, the cornerstone of proper treatment and better prognosis is the ability to identify MF correctly and timely [6]. Once the disease becomes systemic, the prognosis is grim, with a survival rate of lesser than 30% at five years [7]. To facilitate early diagnosis, clinicians must be aware of the wide variety of disguises MF may adopt, both clinically and histologically. Current literature in this area comprises of several separate articles outlining the different variants of MF, its clinical mimickers and its histological mimickers [3,8-9]. However, no single article incorporates all three of the aforementioned components. In the current review, we concisely encapsulate all the variants of MF as well has the conditions it mimics clinically and histologically. Through this, we aim to provide clinicians with a holistic picture of MF and help them determine when to suspect this disease and steps to take in order to nail the diagnosis.

2. Early MF, classic MF, and variants

2.1. Early MF

In early stages, MF is particularly challenging to diagnose. This is due to its non-specific clinical appearance and complex histology, which often overlaps with the histology of other dermatoses. In early stages, classic histologic findings such as atypical lymphocytes and Pautrier microabcesses are present in < 10% and 25% of cases,

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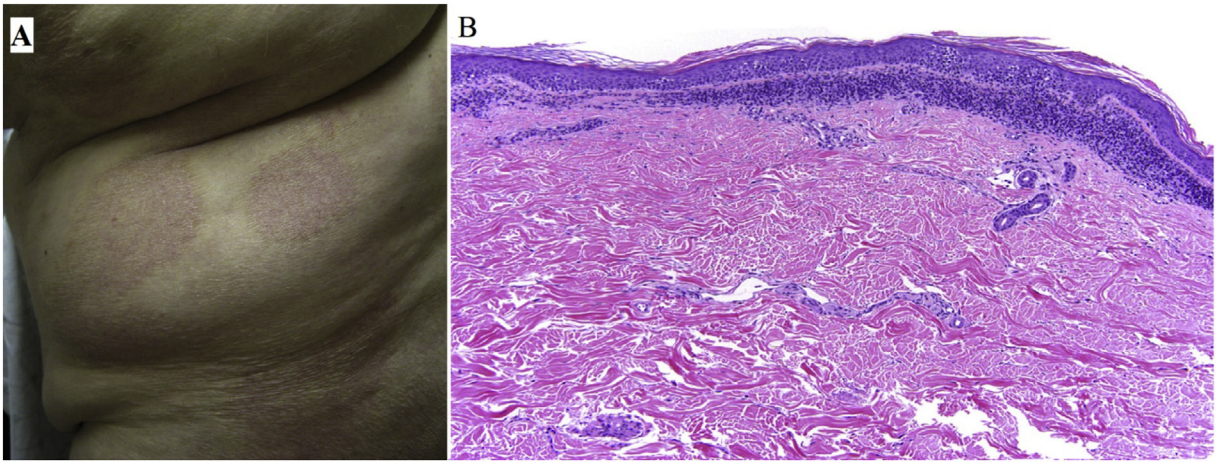

Fig. 1. Patch stage of classic MF. (**A**) Clinical presentation: Large erythematous patches can be seen on the trunk. (**B**) Histology: Band like infiltrates of lymphocytes in the papillary dermis, along with focal epidermotropism.
Reproduced with permission from Pincus LB. Mycosis Fungoides. Surg Pathol Clin. 2014 Jun;7(2):143–67 [76].

respectively. Even epidermotropism may not be present in 4% of cases, leading to low suspicion and false negatives [3,10]. Molecular analysis may assist in diagnosing early MF – for example, it has been reported that the *TOX* gene is a sensitive and specific marker, and can help differentiate early MF from benign conditions such as chronic dermatitis. The International Society for Cutaneous Lymphoma (ISCL) has designed an algorithm to help diagnose early MF (refer to Section 5 for more information) [11].

2.2. Classic (Alibert-Bazin) MF

Classic MF typically presents in 55 to 60 year old adults. This is the most common variant of MF, and accounts for approximately 90% of the cases [1]. It is divided into 3 stages: patch, plaque and tumor. Progression from patch stage to tumor stage is slow and may take years to decades [1,4]. It is essential to note that not all MF patients will develop all three stages. However, if only tumors are present - without a history of the preceding lesions - MF is highly unlikely and a different cutaneous T-Cell lymphoma should be considered [1]. Clinical manifestation of patch-stage MF (Fig. 1) includes asymmetric telangiectasias and macules that are erythematous in nature. Patches are usually present in the sun protected areas such as the breast in females and buttocks. The key histopathological feature in the patch stage of MF is proliferation of large pleomorphic lymphocytes at the dermal-epidermal junction area, focal parakeratosis and papillary dermis fibrosis [12]. Plaque stage (Fig. 2) is characterized as presence of reddish-brown, erythematous or scaling lesions. Histopathologically, this stage closely resembles the patch stage, however, it shows inter surface vascular changes such as infiltration of the upper dermis by lymphocytes that characteristically have hyperchromatic nuclei and nuclear membranes that are convoluted. Pautrier's microabcesses may also be seen. Tumors in the last stage of MF (Fig. 3) are seen as nodules measuring ≥ 1 cm in diameter. Histopathologically, this stage is characterized dense sheets of neoplastic lymphocytes that are present diffusely throughout the dermis [13].

Minor variants of classic MF may appear clinically different but have overlapping histologic features and a similar clinical course. Hence, these are usually not classified separately. A summary of the minor variants of MF and their presentations are given in Table 1. Major variants of MF are discussed below.

2.3. Granulomatous slack skin

This subtype of MF is rare, and has an indolent course. Clinically, it is characterized by pendulous folds of skin that develop over a pre-existing erythematous plaque. It typically involves the flexural areas, such as the inguinal and axillary region [14]. As the lesion matures it may become pedunculated. It typically affects individuals of a younger age group than classic MF and spread to an extra cutaneous site is infrequent. Histologically, GSS presents as infiltration of the dermis by macrophages and multinucleated giant cells (~10 nuclei per cell) [15]. Multi-nucleated giant cells show distinct lymphophagocytosis and

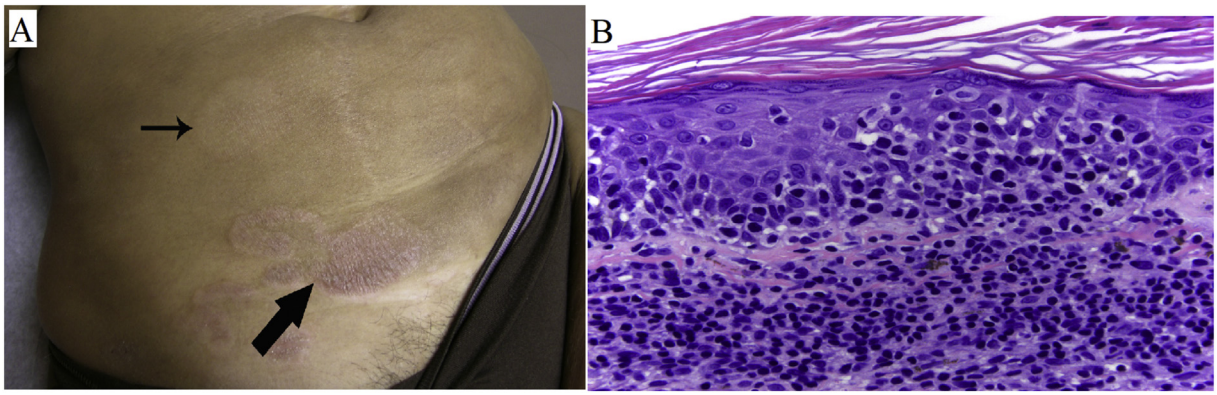

Fig. 2. Plaque stage MF. (**A**) Clinical presentation: Scaly plaques (thick arrow) and patches (thin arrow) can be seen. (**B**) Histological presentation: Hyperchromatic atypical lymphocytes can be seen in the upper dermis and in the epidermis.
Reproduced with permission from Pincus LB. Mycosis Fungoides. Surg Pathol Clin. 2014 Jun;7(2):143–67 [76].

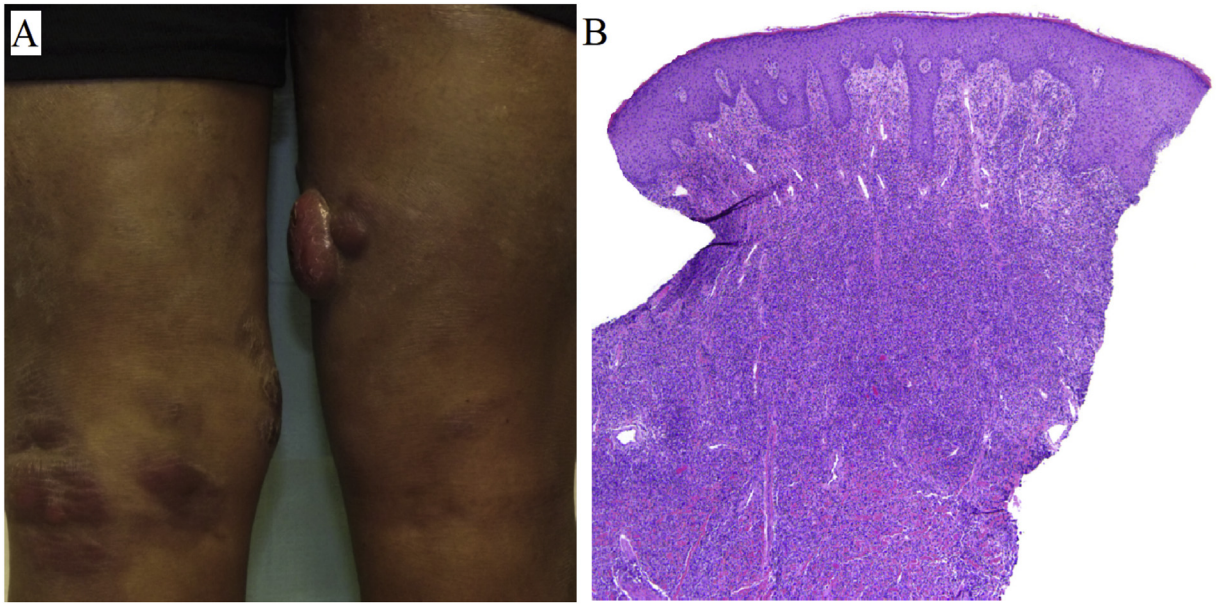

Fig. 3. Tumor stage MF. (**A**) Clinical presentation: A tumor can be seen along with accompanying patches and plaques. (**B**) Histologic presentation: A dense lymphocytic infiltrate is present throughout the dermis.
Reproduced with permission from Pincus LB. Mycosis Fungoides. Surg Pathol Clin. 2014 Jun;7(2):143–67 [76].

elastophagocytosis (leading to loss of elastic tissue). Atypical T-cells with cerebriform nuclei may also be present, as seen in Alibert-Bazin MF. Granulomatous MF is another variant of MF that has shared histological features (e.g. atypical T cells, diminished elastic tissue and presence of multi-nucleated giant cells) with GSS, and this makes their differential diagnosis difficult. However, granulomatous MF lacks the classic bulky skin fold seen in GSS. Treatment of GSS includes surgical excision, PUVA, radiotherapy and immunomodulatory therapy. However, treatment response is often unsatisfactory and long-term follow up is essential due to increased risk of a secondary malignancy [16].

2.4. Folliculotropic mycosis fungoides

FMF (Fig. 4) commonly occurs in adult males, presents in the clinic as lesions on the extremities, which are typically spared in classic MF. Lesions include follicular papules and erythematous plaques (maybe accompanied with alopecia), alopecic patches (maybe accompanied with scarring) or an acneiform lesion [17-19]. Histologically, FMF demonstrates the presence of atypical T-cells with hyperchromic cerebriform nuclei. These cells typically spare the interfollicular epidermis and are commonly seen in the follicular epithelium. Presence of mucin within the follicular epithelium may also be seen. FMF is usually misinterpreted as atopic dermatitis, rosacea or seborrheic dermatitis due to absence of atypical T cells from the epidermotropic region and absence of plaques and patches from the buttocks and trunk region [20]. Treatment for early stage of FMF includes PUVA or topical steroids. In patients with advanced FMF PUVA is combined with interferon alfa, retinoids or radiotherapy [21].

2.5. Pagetoid reticulosis

PR (Woringer-Kolopp disease) is a rare subtype of MF that occurs in both adults and children (Fig. 5). A lesion of PR is typically localized and consists of slowly progressive hyperkeratotic or psoriasiform plaques and patches with an elevated well-demarcated border and a central clearing. Ulceration and pain is present is some cases. These lesions are typically localized to the extremities. Histopathologically, PR generally presents as atypical cells assembled as a cluster or singly [22]. These Cd8+ cells with occasional cerebriform nuclei are characteristically located throughout the entire thickness of the epidermis. Prominent acanthosis and a corrugated epidermis are often found; and occasionally result in verrucous hyperplasia. An important histopathological differential is CD8-positive aggressive epidermotropic cytotoxic CTCL. Microscopically, cytotoxic CTCL may be seen as infiltration of the superficial layer with distinct pagetoid epidermotropism, mimicking PR. However, unlike PR, these individuals more commonly develop diffuse plaques, papules and tumors that are ulcerative in nature. Unlike classic MF, PR is not associated with spread to an extra cutaneous site. Treatment includes radiotherapy and surgical excision with good prognosis [23].

3. Dermatoses that MF may mimic clinically

MF is described as having similar clinical presentation as over a dozen different inflammatory dermatoses. In early stages, characteristic lesions of MF resemble an eczema with sharply defined borders, which may lead to a diagnosis of seborrheic, atopic, palmoplantar or dyshidrotic eczema [24]. Epidermotropism may also lead to clinical morphologies such as erythema multiforme, whereas folliculotropism may develop morphologies such as alopecia. Morphologies may also differ between individuals due to difference in biological responses. The overlapping clinical features of MF and other benign dermatoses often delays the diagnosis [25-26]. Application of topical steroids or immunosuppressing medications during this time may diminish the intensity of these lesions, thereby further delaying the diagnosis. In Table 2, we report the various dermatoses that MF may mimic clinically, which may aid clinicians and histopathologists suspect MF early before any systemic involvement. Fig. 6 displays few clinical examples of MF mimicking other dermatoses.

4. Dermatoses that MF may mimic histologically

Histological features of MF may not be distinct in all circumstances and possibly overlap with several benign inflammatory conditions such as secondary syphilis, arthropod bite reactions, chronic actinic dermatitis, chronic cutaneous lupus erythematosus, fungal infections or even other neoplasms such as melanomas (Table 3). For example, in early MF, Pautrier's micro abscesses and epidermotropism (the two

Table 1
Minor clinical variants of MF.

Variant	Clinical presentation	Histology
Hypopigmented	• Hypopigmented non-atrophic macules • Patches	• Epidermotropism • Lymphocytic infiltrates in the epidermis • Patchy parakeratosis
Granulomatous	• Hyperkeratotic patches and plaques • Poikilodermatous patches • Lacks the bulky skin fold characteristic of GSSS	• Granulomas that resemble sarcoidosis, with multinucleated giant cells • Lichenoid lymphocytes with interstitial histiocytes • Absence of giant cells, plasma cells, elastolysis and elastophagocytosis, when compared with GSSS
Bullous	• Vesiculobullous lesions, usually multiple	• Epidermotropism • Pautrier microabscesses • Atypical lymphocytes
Interstitial	• Patches • Verrucous plaques • Acanthosis nigricans like plaques • Perioral dermatitis	• Infiltration of the dermal interstitium by lymphocytes and few histiocytes
Poikilodermatous	• Hyperpigmentation • Hypopigmentation • Deep-red or brownish plaques • Atrophy • Telangiectasia	• Atrophic epidermis • Epidermotropism • Lichenoid infiltrate of neoplastic lymphocytes • Basal hydropic degeneration • Telangiectatic vessels • Keratinocyte apoptosis
Eruptive epidermoid cyst	• Comedones • Cysts • Widespread follicular eruption	• Band-like infiltration of mononuclear cells in the cyst wall • Upper dermal infiltrate • Cystic dilatation due to destruction of hair follicles
Syringotropic	• Polycyclic papules • Erythematous patches or plaques • Pin-head sized infiltrating papules	• Atypical lymphocytes in dermis • Sheet like epithelial island
Palmaris et plantaris	• Annual and hyperpigmented patches, plaques, pustules and ulceration • Nail dystrophy	• Dense band-like infiltrate located on the accrual surface
Solitary	• Small erythematous patch or plaque	• Epidermotropism of solitary lymphocytes • Band like infiltrate in the upper epidermis
Anetodermic	• Atrophic plaques with wrinkled surface	• Dense infiltration of lymphocytes, with some histiocytes • Sparse elastic fibres in the dermis
Ichthyosiform	• Comedo-like lesions • Follicular keratotic papules	• Orthokeratosis of epidermis • Thin granular layer • Lichenoid epidermotropic infiltrate of small cerebriform lymphocytes and histiocytes
Invisible	• Pruritis • NO cutaneous lesion	• Perivascular lymphocytic infiltrate • Clusters of atypical lymphocytes in the epidermis, with cellular pleomorphism
Pustular	• Pustular eruption	• Subcorneal pustules • Atypical mononuclear cells • Pautrier microabscesses • Epidermotropism
Papular	• Papules in the absence of patches	• Similar to classic MF
Verrucous	• Verrucous plaque • Surrounding poikiloderma	• Lichenoid and perivascular infiltrate of atypical lymphoid cells in the papillary dermis

GSSS = Granulomatous Slack Skin Syndrome

characteristics findings of MF) are usually not seen. In addition, treatment (systemic immunosuppressants and steroid therapy) for long periods for other pathologies before the biopsy usually leads to non-specific histopathological features in a specimen of early MF.

In most inflammatory conditions atypical lymphocytes are generally seen. In some circumstances, other inflammatory cells (such as eosinophils in the case of nodular variant of scabies) may also be seen - which closely resemble the plaque stage of MF. Thus, in such circumstance it is crucial to correlate the clinical picture with the immunohistology for the final diagnosis. Atypical lymphocytes are also seen in syphilis; however, the presence of plasma cells and equal number of B and T cells in syphilis can help rule out MF [27]. For patients complaining of pruritic rash (not commonly seen in MF), and a history of living in shelter homes, nodular variant of scabies should be suspected. Presence of mites along with infiltrative lymphocytes and possibly Pautrier-like micro abscesses on microscopy can possibly help narrow down the diagnosis to nodular variant of scabies [28]. Patients photosensitive to ultraviolet (UV) A and UVB radiation may have the risk of developing chronic actinic dermatitis. This condition also presents with Pautrier-like micro abscesses and possibly atypical hyperchromatic cells with cerebriform nuclei and spongiosis. However, CD8+ cells are commonly present in chronic actinic dermatitis, but rarely seen in MF [29]. One of the most challenging pathologies to differentiate from MF is vitiligo, as it resembles MF both clinically and histopathologically. Presence of low number of melanocytes on immunostaining, no clonal rearrangement on TCR genome analysis or retention of pan-T cell markers can help narrow down the diagnosis to vitiligo [30].

It is important to note that some malignancies may also present with epidermotropism and atypical lymphocytic infiltration of the epidermis and therefore mimic MF. Malignant melanoma is the most classic example of this. However, positive staining positive for S100 and HMB45 can help rule out MF [31]. The loss or decrease in the expression of T-cell-associated antigen CD7 can be a useful tool to diagnose MF. However, some have suggested that this clue maybe limited as some inflammatory conditions also have partial loss of CD7 [13]. Over the past few years, TCR sequencing has also shown success in discriminating MF from benign dermatoses. Further, this technique has also demonstrated value in evaluating response to therapy and disease recurrence [32].

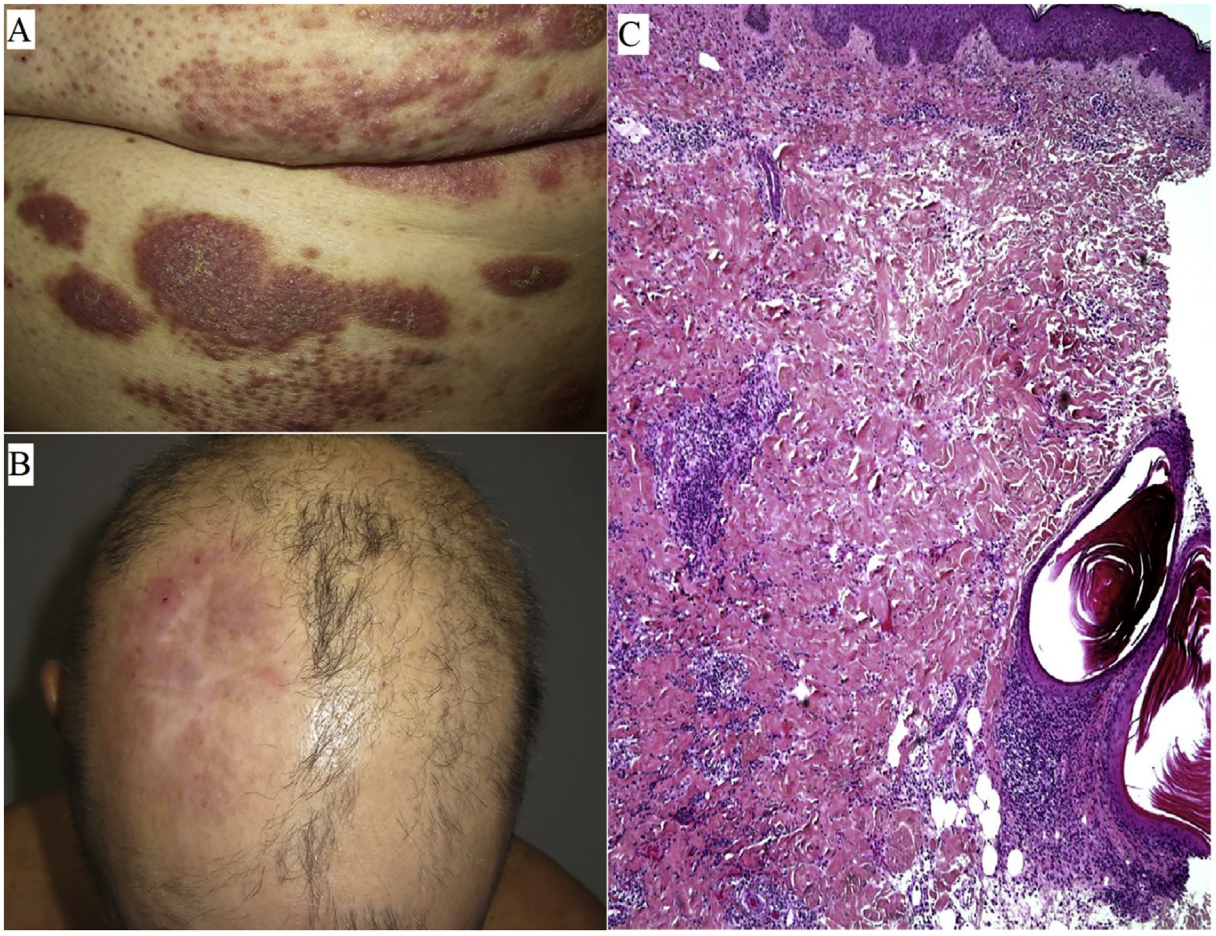

Fig. 4. Folliculotropic MF. (**A**) Clinical presentation: Follicle-based erythematous confluent plaques. (B) Clinical presentation: Patches resembling alopecia areata. (**C**) Histological presentation: Prominent perifollicular lymphocytic infiltration and accumulation of compacted keratin.
Reproduced with permission from Martínez-Escala ME, González BR, Guitart J. Mycosis Fungoides Variants. Surg Pathol Clin. 2014 Jun;7(2):169–89 [77].

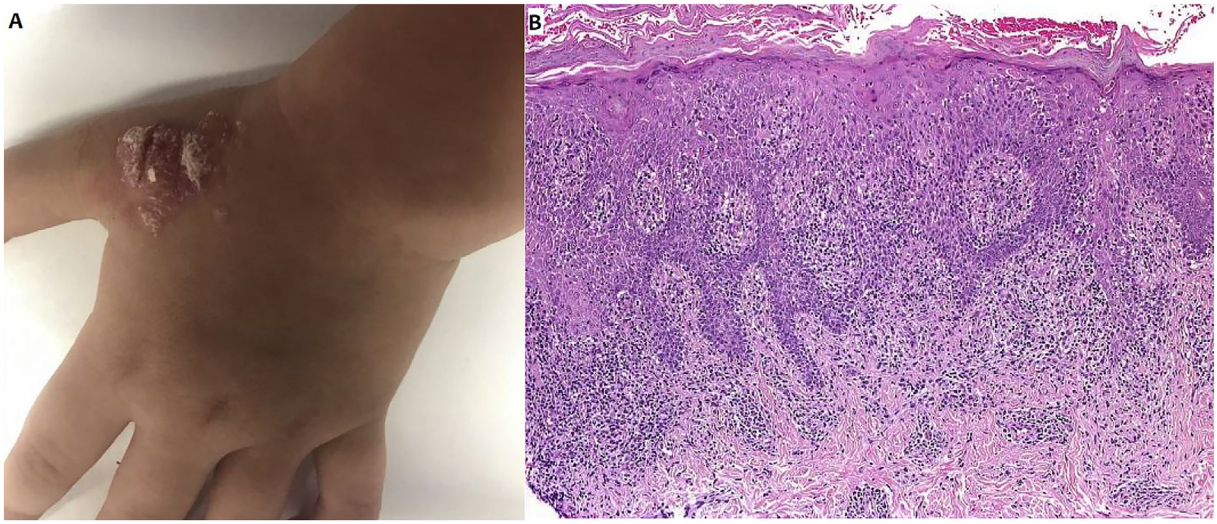

Fig. 5. Pagetoid reticulosis. (**A**) Clinical presentation: A typical presentation of PR; a slow-growing verrucous plaque on the dorsal surface a 2-year old girl's hand (**B**) Biopsy demonstrates epidermal hyperplasia, diffuse epidermotropism, and infiltration by small-to-medium sized atypical lymphocytes.
Reproduced with permission from Corbeddu M, Ferreli C, Pilloni L, Faa G, Cerroni L, Rongioletti F. Pagetoid reticulosis (Woringer-Kolopp disease) in a 2-year-old girl-Case report and review of the literature. JAAD Case Rep. 2018;5(1):104–107 [78].

Table 2
Dermatoses that MF mimics clinically.

Main clinical sign	Differential diagnosis	Reference
Eczematous	Seborrheic eczema	Van Doorn et al. [34]
	Atopic eczema	Kazakov et al. [35]
	Palmoplantar eczema	Goldberg et al. [36]
	Perioral dermatitis	Spieth et al. [37]
	Dyshidrotic eczema	Kempf et al. [38]
	Contact dermatitis	Spieth et al. [13]
Psoriasis (scaling)	Psoriasis vulgaris	Zackheim et al.
	Psoriasis palmaris	Spieth et al.
	Psoriasis palmoplantaris	Spieth et al.
	Tinea corporis	Chave et al. [39]
	Tinea pedum	Hubert et al. [40]
	Erysipelas	Brill et al. [41]
Erythematous	Erythema multiforme	Krebs et al. [42]
	Annular erythema	Lim et al. [43]
	Erythema annulare centrifugum	Zakheim et al. [8]
Hypopigmented	Pityriasis versicolor	Kazakov et al.
	Pityriasis alba	Whitmore et al. [44]
	Vitiligo	Ardigó et al. [45]
	Leprosy	Kazakov et al.
	Post-inflammatory hypopigmentation	Kazakov et al.
Hyperpigmented	Acanthosis nigricans	Wilemze et al. [46]
	Ashy dermatosis	Kazakov et al. [35]
	Pigmented purpuric dermatitis	Hanna et al. [47]
Alopecia	Alopecia areata	Burg et al. [48]
Bullous	Bullous pemphigoid	Kneitz et al. [49]
	Pemphigus vulgaris	Roenigk et al. [50]
	Bullous eruption	Roenigk et al. [51]
Hyperkeratotic	Verruca vulgaris	Goldberg et al.
	Keratosis lichenoides chronica	Bahadoran et al. [52]
	Ichthyosis	Kütting et al. [53]
Papular	Lymphomatoid papulosis	Kodama et al. [54]
Pustular	Pustulosis, palmoplantar	Ohkohchi et al. [55]
	Generalized pustulosis	Camisa et al. [56]
	Pyoderma gangraenosum	Ho et al. [57]
Granulomatous	Rosacea	Spieth et al. [37]
	Sarcoidosis	Bessis et al. [58]
	Necrobiosis	Woollons et al. [59]
Others	Seborrhoeic keratosis	Bazza et al. [60]
	Bowen's disease	Yoo et al. [61]
	Gangrene	Lund et al. [62]

5. The diagnostic approach

A stepwise diagnostic workup for suspected MF, as outlined below, may aid in reaching diagnosis before MF progresses into its advanced plaques, tumors or erythroderma stage.

- *A detailed history and physical*: The skin, lymph nodes, spleen and liver must be given special consideration during history and physical. Clinicians must be aware of the dermatoses that MF mimics, and high suspicion should be present when seemingly benign skin conditions fail to respond to medication [6]. The clinician should also provide a detailed clinical history to the histopathologist along with the biopsy sample, in order to aid the diagnosis.
- *Skin biopsy, and the role of the histopathologist*:
  - **Step 1 – Evaluating the clinical history**: While evaluating the biopsy sample, the histopathologist should be aware of key clinical features, such as sites of involvement, speed of progression, duration of symptoms and association with any past or present disease [33].
  - **Step 2 – Preparation and identification of pattern**: For ideal morphological evaluation, a segment must be 4 to 5 μm. Initially, a low magnification examination should be done to evaluate the distribution, extent of epithelial involvement and infiltrate architecture. This should be followed by intermediate magnification to identify characteristics cells and other features such as vascular invasion and presence of mucin. Lastly, high magnification is used to assess the morphology of the cellular composition [33]. The histology will vary based on the variant of MF being investigated (as discussed above). Notably, false negatives may arise during early stages when histologic features are non-specific. In order to avoid false positives, the pathologist should be cognizant of common cutaneous conditions that mimic MF in the lab, and findings should be interpreted with clinical correlation.
  - **Step 3 - Immunohistochemistry**: Ancillary immunohistochemistry and molecular studies should be done only if the diagnosis cannot be confirmed after the above-mentioned steps. Microscopic features can help provide an outline while selecting suitable antibody panels. A screening panel can be using in circumstances where clear microscopic features are not identifiable. Upon immunophenotyping, MF is classically CD4+ with a varying pattern surface marker loss involving CD2, CD3, CD5, CD7 and CD26. Loss of CD7 is most observed. On occasion, (20% of cases) a CD8+ pattern may be seen [6]. However, immunohistochemical findings should be interpreted only in context of other findings, as they are non-specific (for

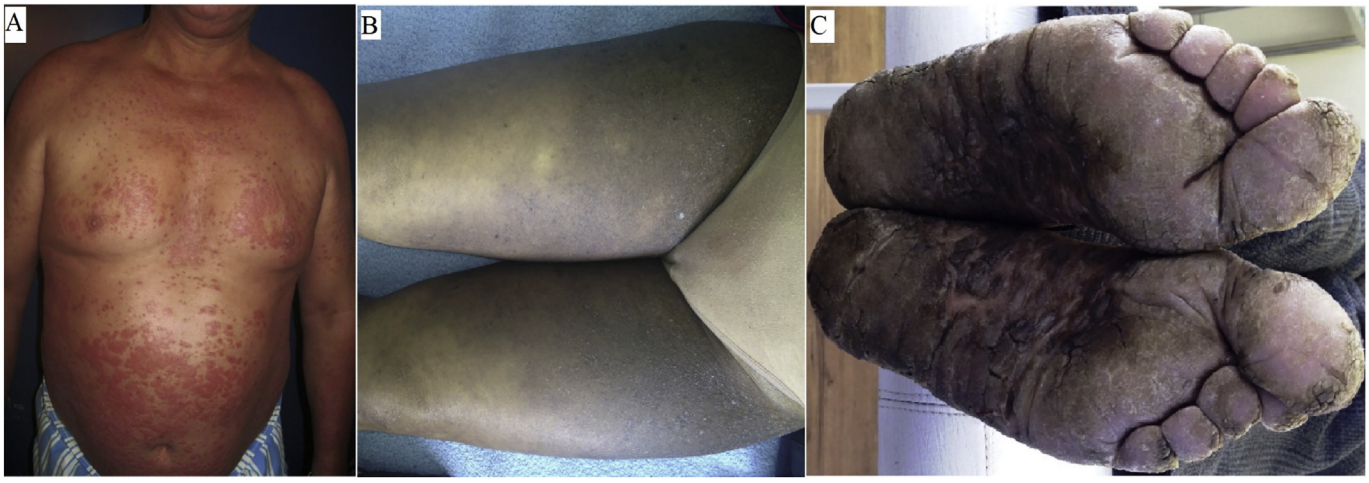

Fig. 6. Clinical mimickers of mycosis fungoides. (**A**) Mycosis fungoides that had initially been misdiagnosed as psoriasis; (**B**) **and** (**C**) Mycosis fungoides that had initially been misdiagnosed as eczema.
Reproduced with permission from Kelati A, Gallouj S, Tahiri L, Harmouche T, Mernissi FZ. Defining the mimics and clinico-histological diagnosis criteria for mycosis fungoides to minimize misdiagnosis. Int J Womens Dermatol. 2017 Jan 30;3(2):100–106 [79].

Table 3
Dermatoses that MF mimics histologically.

Disease	Possible histological findings	Key points for differential diagnosis	
		Clinical	Histological
Nodular variant of scabies [63]	• Infiltration of lymphocytes with eosinophils. • It may also present as Pautrier-like micro abscesses.	• Clearing after therapy for scabies.	• Presence of mite in the epidermis.
Malignant Melanoma [64]	• Epidermotropism and lymphocytic infiltration.		• Infiltration of CD8+ cells. S100 and HMB45 positivity of the cells of the melanoma.
Secondary syphilis [65]	• Lymphocytes with cerebriform nuclei infiltration of the epidermis. • Follicular mucinosis with folliculotropism.	• Rapid plasma reagin is positive	• Presence of plasma cells, polyclonal B and T cells (in equal proportion.
Persistent arthropod bite reactions [66]	• Numerous lymphocytes infiltrate the dermis. • There may also be presence of eosinophils and plasma cells (CD20+). • Epidermis maybe spared.	• Clinical history of an insect bite at the site of the lesion. • Classic clinical findings of MF on chest x-ray, abdomen + pelvis CT and blood studies will be absent.	• Presence of lymphoid follicles and germinal centers. Clonality may be absent.
Chronic actinic dermatitis [67]	• Pautrier-like micro abscesses. • May also see atypical hyperchromatic cells with cerebriform nuclei and spongiosis.	• Photosensitivity to ultraviolet (UV) A and UVB light.	• Papillary dermis thickening with collagen bundles lying parallel to the rete ridges in a vertical manner. • Increased and thick blood vessels Stellate fibroblast that are multinucleated • Presence of CD8+ cells (in contrast MF consist mostly of CD4+).
Vitiligo [68]	• Infiltration of the interstimulus and perivascular area with lymphocytes. • Invasion of the lymphocytes into the follicular epithelium and epidermis.		• Low numbers of melanocytes on immunostainin. • No clonal rearrangement on TCR genome analysis. Pan-T cell markers are retained.
Lymphomatous allergic contact dermatitis [69]	• Infiltration of lymphocytes in a band-like manner. • There may be also be presence of atypical mononuclear cells in a foci that may resemble Pautrier micro abscesses.	• Patch reaction to the allergen is positive.	• Presence of epidermal changes related to acanthosis, spongiosis or apoptosis. • A reactive process is favored with the presence of Langerhans cells (large cells with nuclei that is indented, large cytoplasm and stain positive for CD 1a).
Chronic cutaneous lupus erythematosus [70]	• Atypical lymphocytic infiltration of the epidermis.	• Good response to hydroxychloroquine therapy. • Lupus band test is positive of the lesioned skin. • Antinuclear antibody test is positive.	• Lupus erythematous characteristics features (several histocytes with polymorphous infiltration and polyclonal TCR rearrangement) maybe seen after several biopsy.
Infection by fungus [71]	• Lymphocytic (maybe atypical) infiltration in a band-like manner.		• Presence of dermatophyte or Candida infection on Periodic Acid-Schiff (PAS) examination.
Lichen Striatus [72]	• Lymphocytic infiltrate in a band-like manner. • Hyperchromatic lymphocytes spread out in a pagetoid pattern.		• Presence of CD8+ cells in the epidermis. • Focal parakeratosis. Spongiosis edema in the epidermis.
Pigmented dermatitis [73]	• Epidermal hyperplasia with infiltration by atypical lymphocytes. • Fibrosis of the papillary dermis.		• T cell gene rearrangement is negative with extravasation of red blood cells.
Lichen Sclerosis [74]	• Fibrosis of the superficial dermis. • Lymphocytic infiltration in a band-like manner with exocytosis into the lower epidermis	• White plaques in the perianal or vulvar region.	
Drug-induced pseudo lymphoma [75]	• Dermis consists of band-like infiltrate with cerebriform nuclei. • Epidermis may contain Pautrier like micro abscesses.	• Associated with certain drugs, especially antiepileptics such as carbamazepine, phenytoin and sodium valproate. • Diagnoses is confirmed when the skin lesions clear after discontinuing the drug.	• The infiltrate has a CD4:CD8 ratio of 1:1 that signifies a reactive process rather than MF.

example, CD7 loss may also be seen in spongiotic dermatitis) [4]. The literature supports repeat biopsies in ambiguous cases [11].

- **Step 4 – Clonality test**: In addition to MF, clonality test findings can support diagnosis of inflammatory or reactive process, and therefore, should be interpreted in relevance to histopathological and clinical features of the patient. Diagnosis of MF is supported by presence of marked CD4 and CD8 cells and absence of pan T-cell markers (CD5, CD7, CD3, CD2). Diagnoses of MF are further affirmed if such findings are present on epidermal lymphocytes rather than the ones present in the dermis. Loss CD7 and CD5 markers is often less prominent in inflammatory conditions when compared to MF.
- **Step 5 – T-Cell receptor gene rearrangement**: Although T-cell receptor gene rearrangement may assist in detecting MF, the results are neither specific nor sensitive, as several nonneoplastic processes in the skin such as lichen sclerosis and pseudo lymphomas may also be associated with clonal T cell proliferation.

- *Biopsy of enlarged lymph nodes*: should be conducted to evaluate disruption of node architecture and number of atypical lymphocytes. Furthermore, in dermatopathic lymph nodes, occult involvement may be assessed using immunophenotyping and PCR for T-cell clonality.
- *Blood tests*: A full blood count, liver function tests, and serum chemistries should be ordered. The following should be added in patients with suspected stage llB - IV disease: PCR to evaluate T-cell receptor gene rearrangement, soluble IL-2, LDH, and flow cytometry for the following markers: CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD26, and CD45RO [6].

Criteria	Score	Score Explanation
Clinical		
Basic • Persistent and/or progressive patches/thin plaques	2	Basic and 2 additional criteria
Additional • Non sun-exposed location • Size/shape variation • Poikiloderma	1	Basic and 1 additional criteria
Histopathologic		
Basic • Superficial lymphoid infiltrate	2	Basic and 2 additional criteria
Additional • Epidermotropism without spongiosis • Lymphoid atypia	1	Basic and 1 additional criteria
Molecular Biologic		
Basic • Clonal T-cell receptor gene rearrangement	1	For clonality
Immunopathologic		
• <50% CD2+, CD3+ and/or CD5+ T-cells • <10% CD7+ T-cells • Epidermal/dermal discordance of CD2, CD3, CD5 and CD7	1	For one or more criteria

Fig. 7. The International Society for Cutaneous Lymphoma Algorithm to Diagnose Early MF.
Reproduced with permission from Pimpinelli N, Olsen EA, Santucci M, et al. Defining early mycosis fungoides. J Am Acad Dermatol. 2005;53:1053–1063 [11].

Table 4
Staging of MF.

Skin	
T1	Limited patches and/or plaques covering < 10% of the skin surface T1a (patch only) vs T1b (plaque ±).
T2	Patches or plaques covering ≥10% of the skin surfaces.
T3	One or more tumors (≥1-cm diameter).
T4	Erythema covering ≥80% body surfaces.
Node	
N0	No clinically abnormal peripheral lymph nodes.
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2 (a = clone negative/b = clone positive)
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3 (a = clone negative/b = clone positive)
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 3–4 or NCI LN4 (a = clone negative/b = clone positive)
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation.
Visceral	
M0	No visceral organ involvement.
M1	Visceral involvement.
Blood	
B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells.
B1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2.
B2	High blood tumor burden: ≥1000/ul Sezary cells with positive clone.

- *Imaging*: In patients with suspected stages lA or lB, lateral and posteroanterior chest radiographs, and ultrasound of peripheral nodal chains should be considered. In those with possible stages llA – IV disease, computed tomography (CT) scan of the torso should be done, and a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan can be considered [6].

Given that neither clinical nor histologic findings are conclusive in early stage MF, an algorithm was designed by the ISCL in order to assist the diagnosis. This algorithm incorporates clinical, histologic, molecular, biologic and immunologic criteria, and is displayed in Fig. 7.

Once MF has been confirmed, it must be staged based on the criteria displayed in Table 4.

Declaration of competing interest

We report no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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