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Patch, Plaque, Tumour - Mycosis Fungoides

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Abstract

Mycosis fungoides is a frequent cutaneous lymphoma contributing to an estimated half (50%) of the emerging dermal lymphomas. As an epidermotropic primary cutaneous T lymphoma (CTCL), it may comprise of miniature or medium sized lymphocytes containing cerebriform nuclei and a T helper cell immune phenotype, although variants of a cytotoxic T lymphocyte (CTL) component may commonly arise. "Mycosis Fungoides "as a terminology is restricted to classical manifestation of a disorder characterized by the appearance of patches, plaques and tumours or the diverse cutaneous disorders with an identical clinical evolution. The prevalence of mycosis fungoides is at an estimated 60% of cutaneous tumours, though the incidence may be augmented in the Africans. The lesions may depict a prominent regional variability. Elderly and adult individuals may be frequently incriminated with a male predominance (M:F: 2:1), although children and adolescents may similarly manifest the cutaneous lymphoma

Keywords: Mycosis fungoides; Lymphoma; Chronic dermatosis; Cutaneous

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Introduction

Mycosis fungoides is a condition of obscure aetiology. Chronic dermatosis may accompany the disorder. An extensive exposure to diverse allergens or a genetic predilection may be elucidated in specific instances. Viral infections have not been implicated in the genesis of mycosis fungoides. The condition may appear subsequent to a solid organ transplant, thereby implying an immune suppressive aetiology in disease evolution [1].

Disease characteristics

Mycosis fungoides as a disorder may be categorized into three distinct stages: I) patch stage, ii) plaque stage and iii) tumour stage. The prolonged clinical course may be undulating and extends over a period of months or decades. The majority (>90%) of the initial lesions of mycosis fungoides may not depict an extra cutaneous manifestation of the disease [1-3]. Mycosis fungoides may exhibit plaques, patches or tumours appearing singularly or as commingled lesions [1,2]. Although patches classically delineate the preliminary form of mycosis fungoides, they may be frequently admixed with adjunctive plaques and tumefaction. The progressive stage or the remitted, extensive lesions may reoccur with subsequent reappearance of patches, plaques or tumours. i) The typical patches of mycosis fungoides may be generalized or localized, variegated, enlarged erythematous lesions predominantly arising in the sun protected zones, especially buttocks and the female breasts. A variable scaling may ensue; contingent to the preceding therapeutic remedies undertaken [1]. ii) The plaques of mycosis fungoides may signify an indiscriminately infiltrative, variously scaled, erythematous or reddish-brown lesion. The classical patches may appear to be contiguous with the plaques or may arise at adjunctive body sites [6]. The plaques of mycosis fungoides may necessitate a demarcation from the flattened tumefaction. Dusky or dark-skinned individuals may generate greyish or silver hued patches and plaques with a diminished erythema [1] (iii) Tumefaction contingent to mycosis fungoides may be solitary and localized or disseminated and concomitant to the classic patches or plaques or appear as singular tumour in the absence of adjunctive lesions. Tumour ulceration may be frequent. Tumour progression with mycosis fungoides may be divaricating, the tumours may quickly evolve within a few weeks or may be comparatively indolent. Partially retrogressed tumours may be frequent [1]. The mucosa may be infrequently implicated in patients with preliminary mycosis fungoides, though commonly involved with the progressive phase. Enhancing erythroderma may be delineated in mycosis fungoides, which mandates a distinction from the classic Sezary syndrome [7]. The two conditions may be generically associated in cutaneous T cell lymphomas (CTCL) [1] **(Table 1)**.

Histological elucidation

Classically, mycosis fungoides may be categorized into three distinct stages: premycotic, mycotic and tumorous. The premycotic stage may delineate the scaling skin to be erythematous and pruritic. Thematic diversity in the clinical formulation of the disorder may be characterized by solitary, follicular granulomatous, pustular, bulbous, hyperkeratotic, verrucous and hypopigmented variants [2]. Lesions such as large plaque parapsoriasis may transform into mycosis fungoides in a significant number of instances. The non-confirmatory microscopic morphology of the premycotic stage may depict a picture akin to chronic nonspecific dermatitis accompanied by psoriasiform alteration of the epidermis. The infiltrative plaques may arise within the mycotic stage with the histological delineation of a dermal polymorphous inflammatory infiltrate which may exhibit a miniature quantity of definitive, a typical lymphoid cell. The cells may enunciate a dermal invasion (Partier's micro-abscesses) or may congregate within the epidermal basal layer (with the absence of spongiosis, the feature may suggest the emergence of mycosis fungoides). The lymphoid infiltrate may surround the hair follicles with a concomitant follicular mucinosis [2]. The tumorous stage may be defined by intense infiltrates of aberrant lymphoid cells which may distend the dermis. The categorical, definitive cell of mycosis fungoides may be a miniature or a medium sized lymphocyte with a cerebroid nucleus. The nuclear character may be typified by a markedly irregular nuclear outline with a thick nuclear membrane, a feature elucidated with thin paraffin embedded sections, the cerebroid cells may demonstrate a phenotype of T helper lymphocyte $CD4^+$ though occasional $CD8^+$ cytotoxic/suppressor or anomalous phenotypes of T lymphocytes may be exhibited [2]. Malignant lymphocytes within the advanced tumour stage may manifest the appearance of CD15. The characteristic histopathology enunciates an epidermotropic proliferation of variable, pleomorphic T lymphocytes (cerebriform cells) which may configure typical intra-epidermal aggregates (Pautrier's micro-abscesses). Micro abscesses may be the designated morphological indication of disease, though may be absent within preliminary lesions, tumefaction stage along with diagnostic biopsies acquired in the therapeutic phase [2]. The assiduous categorization of the histological criterion of preliminary mycosis fungoides may be achieved with an appropriate clinical and pathologic concordance [1] **(Figures 1-6)**. Numerous histological configurations of inflammatory dermatosis may simulate the preliminary lesions, thus an accurate categorization on histopathology may be challenging. The early lesions of mycosis fungoides may depict a focal, lichenoid or a band like inflammatory infiltrate arising in the fibrotic papillary dermis with a prominent component of mature, miniature lymphocytes [7,8]. The lymphocyte aggregates may singularly articulate the phenomenon of "epidermotropism". However, 'Pautrier' micro-abscesses may be infrequent. Constituent 'halo lymphocytes' (cells with enlarged nuclei circumscribed by a minimal halo) may be aligned along the epidermal basal layer (basilar epidermotropism),

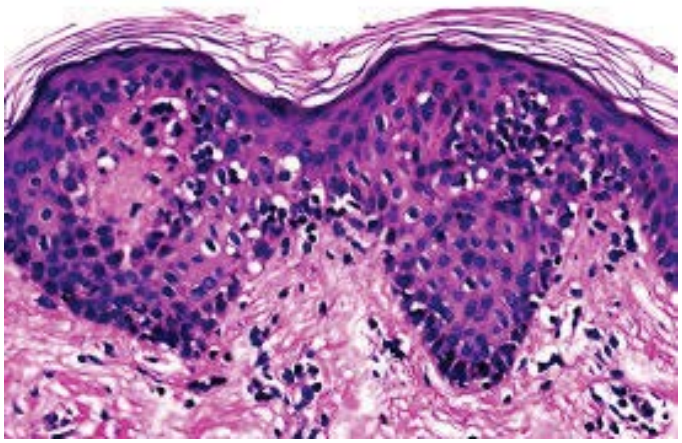

Figure 1 T lymphocytic infiltrate in the upper dermis.

Table 1 Classification of cutaneous T cell lymphomas [5].

Cutaneous T cell and NK cell lymphomas
Mycosis Fungoides (MF)
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sezary Syndrome
Adult T cell Leukaemia Lymphoma (ATLL)
Primary cutaneous CD30+ lympho-proliferative disorder
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid Papulosis
Subcutaneous panniculitis like T cell lymphoma
Extra-nodal natural killer/T cell lymphoma nasal type
Hydroa vacciniforme like lympho-proliferative lesion
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma (provisional)
Primary cutaneous γ/δ T cell lymphoma
Primary cutaneous CD4+ small/medium sized T cell lympho-proliferative disorder (provisional)
Primary cutaneous acral CD8+ T cell lymphoma (provisional)
Primary cutaneous peripheral T cell lymphoma

Numerous intra-epidermal lymphocytes may be elucidated with concomitant, mild epidermal spongiosis (disproportionate epidermotropism). The aforementioned features may provide crucial evidence in the diagnosis of the preliminary disorder [8]. Atypical histological manifestations of preliminary mycosis fungoides may be 1) the occurrence of significant spongiosis 2) modifications of dermo-epidermal junction with the emergence of numerous necrotic keratinocytes, thus simulating the histology of erythema multiforme 3) prominent incontinence of the melanin pigment with concurrent melanophages within the papillary dermis 4) extravasation of erythrocytes, identical to a histology of lichen aureus and 5) a conspicuous dermal oedema [1]. "Poikilodermatous" mycosis fungoides may be described on histology as an epidermal flattening with a concomitant lichenoid inflammatory infiltrate with vascular dilatation of the papillary dermis [1]. Plaque stage of mycosis fungoides may be characterized by a dense, band like inflammatory infiltrate of small lymphocytes situated within the upper dermis [9]. Epidermotropism may manifest along with Pautrier's micro-abscesses. Morphologic emergence of miniature and/or medium sized pleomorphic lymphocytes (cerebriform cells) may be predominant, though enlarged cells may appear infrequently [1]. Tumour stage of mycosis fungoides may be enunciated by a nodular or diffuse inflammatory infiltrate localized within the entire dermis with extensions into the subcutaneous fat. Aspects such as angio-centricity and angio-destruction may exceptionally coexist and simulate a NK/T cell cytotoxic lymphoma. Extensive incrimination of subcutaneous fat may resemble a subcutaneous panninculitis like T cell lymphoma. Tumefaction stage may be identical to a primary or secondary cutaneous natural killer (NK)/T cell lymphomas. Preponderant, enlarged lymphocytes within the inflammatory infiltrate of the progressive stage along with immunoblasts, mammoth pleomorphic cells or giant anaplastic cells may appear [9,10]. The categorization into an 'enlarged cell' variant may depict the constituent of mammoth lymphocytes to be greater than 25% of the inflammatory infiltrate or the emergence of a nodular configuration of enormous lymphocytes [1] **(Figures 7-10).** Though the transformed, enlarged lymphocytes may usually be discerned in the tumefaction stage of mycosis fungoides, aggregates of enormous lymphocytes may concurrently be demonstrated within the plaques or patches of the disorder **(Tables 2-5)**.

Genetic modifications

The malignant lymphocytes of mycosis fungoides may frequently be of the α/β memory T helper phenotype (with T cell receptor genes). They may also delineate a TCR β^+, TCR γ+, a cluster of differentiation $CD3^+$, $CD4^+$, $CD5^+$, $CD8^-$, $CD45Ro^+$ and a T cell intracellular antigen (TIA) [10,11]. The tumefaction stage may depict an absence of pan T cell antigens ($CD2^-$, $C3^-$, $CD5^-$). Indicators of a cytotoxic phenotype such as TIA^{-1}, granzyme B and perforin may be lacking in the classic mycosis fungoides [1]. However, a minimal depiction of T cytotoxic lymphocyte immune phenotype may emerge (TCR β^+, TCR γ-, $CD3^+$, $CD4^-$, $CD5^+$, $CD8^+$, TIA^{1+}) or an alternative phenotype of TCR β^-, TCR γ+, $CD3^+$, $CD4^-$, $CD5^+$, $CD8^{+/-}$ & TIA^{1+} may be exhibited. Paediatric instances of mycosis fungoides may describe a $CD8^+$ phenotype.

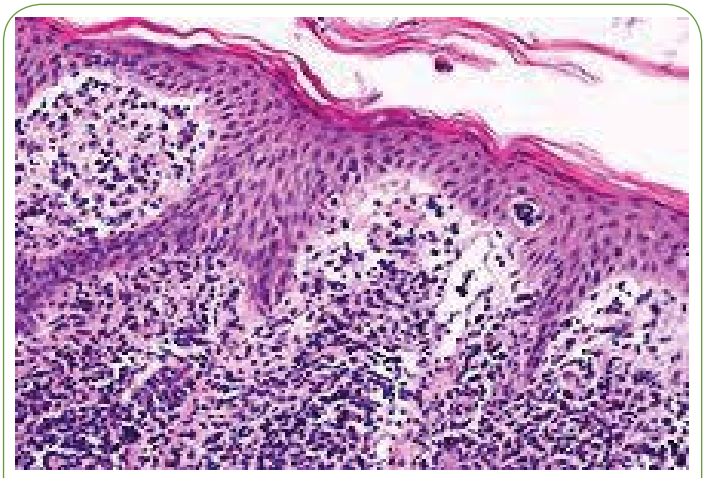

Figure 2 The appearance of classic Lutzner's cells.

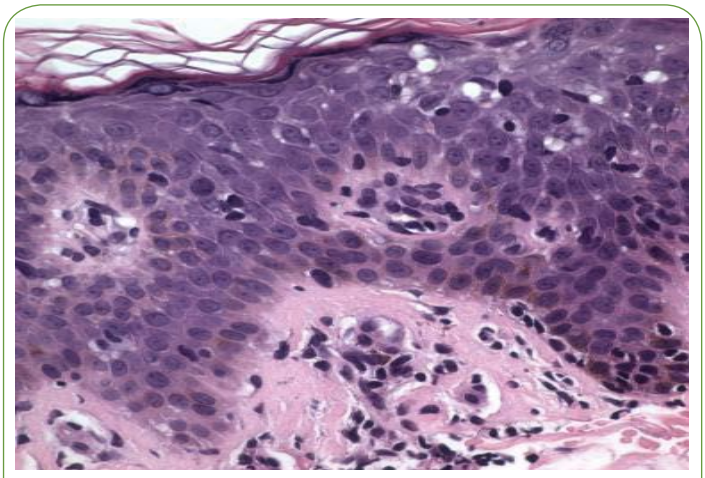

Figure 3 Large, atypical lymphocytes within the papillary dermis.

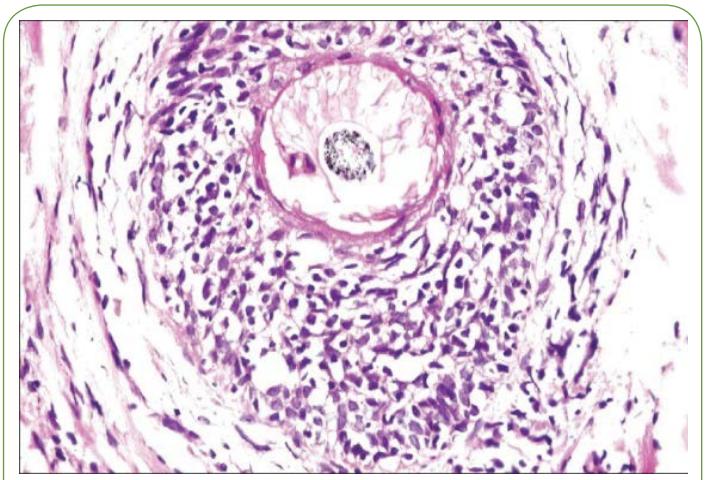

Figure 4 Folliculotropic variant of mycosis fungoides.

An anomalous $CD4^+/CD8^+$ or a $CD4^-/CD8^-$ phenotype may be elucidated infrequently with preliminary mycosis fungoides and rarely with the progressive variant [11,12]. Histological assay of the tumefaction may detect the appearance of cytotoxic proteins in previously non-reactive instances. $CD56^+$ immune

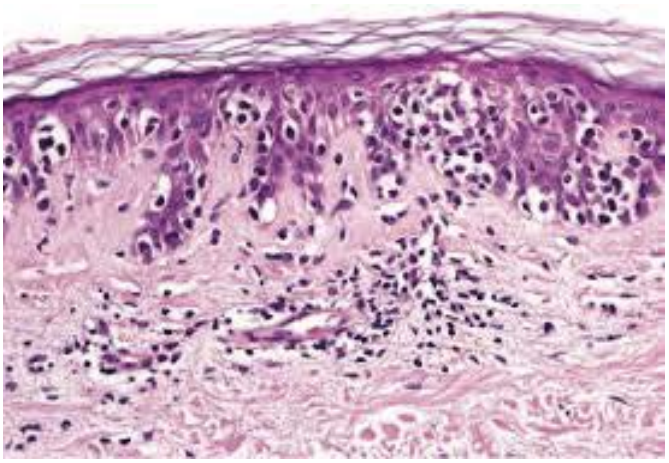

Figure 5 Pautrier's micro-abscesses and a dermal inflammatory ingression.

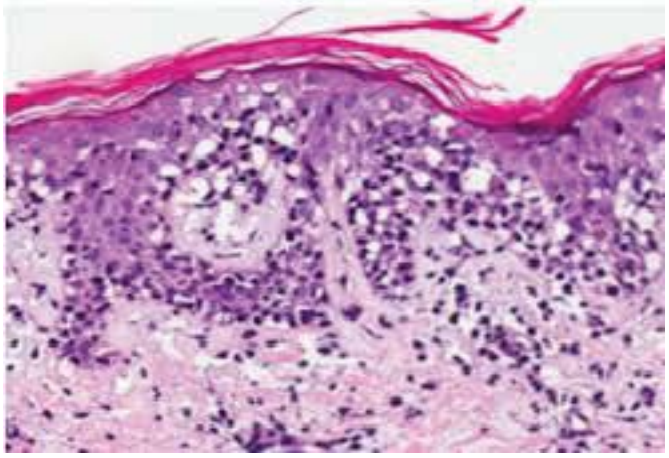

Figure 6 Patchy, dermal aggregates of T lymphocytes.

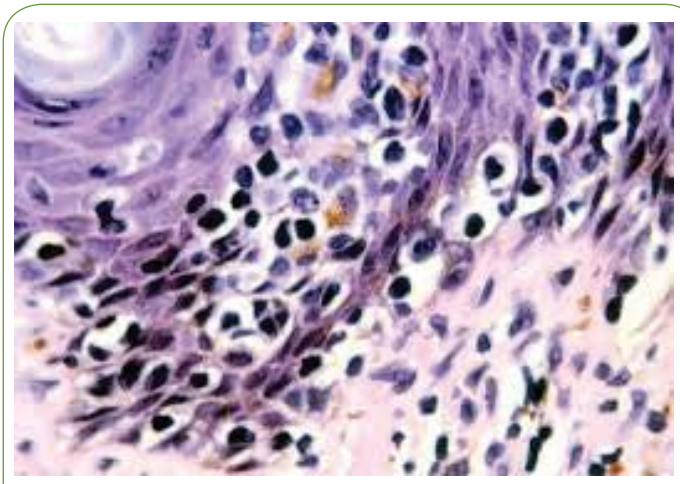

Figure 7 Halo lymphocytes scattered within the epidermis and dermis.

reaction may be exceptional in classic mycosis fungoides. Clinical or prognostic deviation betwixt the T helper lymphocyte or T cytotoxic phenotype may be absent [7]. An evaluation of T cell cytotoxic immune phenotype with clinical attributes of the lymphoma may eliminate the adjunct cytotoxic T cell lymphomas (CTCL) such as the cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T cell lymphoma, cutaneous γ/β T cell lymphoma or cytotoxic lymphomatoid papulosis [1]. Phenotypic and histological diversity may be delineated from the specimens obtained from a singular patient within a short duration. The programmed cell death protein (PD1) immune stain may be reactive in a proportion of patients. Certain instances may depict a comprehensive T follicular helper phenotype (TFH) [12,13]. $PD1^+$, $BCL6^+$ B cell lymphoma, chemokine ligand (CXCL) 13^+ and $CD10^+$ immune phenotypes may be demonstrated. Langerhans cells and associated dendritic reticulum cells may be augmented in the preliminary phase and may simulate a Langerhans Cell Histiocytosis. The intra-epidermal collections of langerhans cells may resemble a 'Pautrier's' micro-abscess. However, these cells a man immune react to $CD1a^+$ instead of a CD3. The lesions may be challenging to differentiate from the instances of lymphomatoid contact dermatitis [1]. The transformed, enlarged, malignant T lymphocytes of mycosis fungoides tumefaction may exemplify the CD30 antigen. In instances of established mycosis fungoides, a diagnosis of an enlarged cell neoplasm such as anaplastic large cell lymphoma or lymphomatoid papulosis with CD30 elucidation may be considered only with characteristic lesions [1]. IRF 4 translocations may be absent in a majority of mycosis fungoides, whereas primary cutaneous large cell anaplastic lymphoma may enunciate the translocation [14]. Anomalously elucidated B cell antigen CD20+ may be described within the malignant T lymphocytes. Innumerable immune reactive $CD20^+$ B lymphocytes, configuring germinal centres, may be exhibited in the progressive lesions of mycosis fungoides. The predominantly B lymphocytic infiltrate may conceal the malignant T lymphocytic character of the disorder, which may be misrepresented as a B cell lymphoma [13,14]. Cutaneous variants of composite lymphoma may be delineated (composite lymphomas signify lesions with the histological attributes of two disparate lymphomas in a singular biopsy specimen) Frequently, the two concomitant cutaneous lymphomas may enunciate a mycosis fungoides and a B cell chronic lymphocytic lymphoma [1] **(Tables 6A and 6B)**.

Molecular modifications

T cell receptor (TCR) gene rearrangements may be employed for the elucidation of T cell clones. The genetic assay may be beneficial with the skin biopsy of preliminary mycosis fungoides and may provide a great diagnostic assistance [2]. The TCR genes may depict a clone specific rearrangement in a majority of the mycosis fungoides lesions. The proportion of reactive instances may be incident to the technique of TCR determination. Genetic sequencing may enhance the sensitivity and specificity of the investigated TCR with appropriately delineated malignant clones [6]. Somatic mutation may be discerned within various constituents of TCR signalling pathway, situated within the T helper cell 2 (TH2) differentiation related genes, within genes evading the growth suppression interceded by the transforming growth factor β (TGF β) and within genes which induce resistance to apoptosis intervened by the TNF receptor super-family (TNFRSF) [3,8]. Activation of the Janus Kinase 3 (JAK3) mutation

Table 2 Tumour node metastasis blood (TMNB) classification of Mycosis Fungoides [4].

Stage	T	N	M	B
I A	T1: patches and plaques in < 10% BSA T1a: patches only. T1b: plaques only	No: no palpable nodes or histological evidence of MF. N0a: clone negative. N0b: clone positive	M0-: no visceral involvement	B0< 5% atypical peripheral blood lymphocytes and < 250 cells/µL. B0a: clone negative B0b: clone positive B1 > 5% atypical peripheral blood lymphocytes, betwixt 250- 1000cells/µL B1a: clone negative B1b: clone positive
IB	T2: patches and plaques in > 10% BSA T2a: patches only. T2b: plaques only	N0	M0	B0-1
IIA	T1 or T2	N1: no histological evidence of MF (dermatopathic) N1a: clone negative N1b: clone positive N2: early involvement with MF, aggregates of atypical cells with preservation of nodal architecture. N2a: clone negative N2b: clone positive	M0	B0-1
IIB	T3: tumours or lesions>1cm diameter with deep infiltration	N0-2	M0	B0-1
IIIA	T4: erythroderma > 80% BSA involved	N0-2	M0	B0
IIIB	T4: erythroderma	N0-2	M0	B1->5% circulating atypical lymphoid cells though < 1000cells/µL
IVA1	T1-T4	N0-2	M0	B2> 1000cells/µL of circulating atypical lymphoid cells (Sezary cells)
IV A 2	T1-T4	N3: lymph node involvement with effaced architecture	M0	B0-2
IV B	T1-T4	N0-N3	M1-metastasis	B0-2
On flow cytometry as per EORTC guidelines, an elevated T lymphocyte count ≥10,000/µL may indicate a worse outcome than stage B2.				

Table 3 Inter observer concordance of staging of lymphoma [16].

Stage	Observer 1	Observer 2	Ƙ	Percentage agreement
Stage I	12.1%	11,3%	0.93	96.4%
Stage II	15.7%	17.4%	0.90	94.8%
Stage III	28.7%	33.0%	0.89	94.6%
Stage IV	43.5%	38.3%	0.88	94.0%
Overall			0.90	94.9%

Table 4 Inter observer concordance of response assessment of lymphoma [16].

Stage	Observer 1	Observer 2	Ƙ	Percentage agreement
Progressive disease	28.7%	30.4%	0.94	97.1%
Stable disease	26.1%	23.5%	0.90	95.0%
Partial response	23.5%	22..6%	0.96	98.1%
Complete response	11.3%	13.1%	0.87	93.3%
Overall			0.91	95.8%

Table 5a First line treatment of mycosis fungoides stage IA, IB and IIA [5].

Expectant policy (T1a)
Skin directed therapy (SDT) Topical corticosteroids (T1 a and T2a)
Ultraviolet B (T1a and T2a)
Psoralen ultraviolet A (PUVA)
Localized radiotherapy (localized MF including pagetoid reticulosis)
Mechlorethamine

Table 5b Second line treatment of mycosis fungoides stage IA, IB, IIA [5].

Systemic therapies (cyclosporine, interleukin2, monoclonal antibodies,adenosine/purine analogues)
Retinoids (Bexarotene, Aliretinoin)
Interferon α
Total skin electron beam (TSEB-chiefly T2b)
Low dose methotrexate

may be targeted with particular drugs. Integral activation of STAT 3 and inactivation of CDKN2A/p16INK4a with PTEN may accompany the evolution of the disease [1] **(Tables 7A and 7B)**.

Clinico-pathological variants

Apart from the characteristic stages of the disease, numerous variants of mycosis fungoides as classified by the World Health

Table 6a First line treatment of mycosis fungoides stage IIB [5].

Systemic therapies (cyclosporine, interleukin2, monoclonal antibodies,adenosine/purine analogues)
Retinoids (Bexarotene, Aliretinoin)
Interferon α
Total skin electron beam (TSEB)
Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine)
Low dose methotrexate
Localized Radiotherapy

Table 6b Second line treatment applicable for stage IIB [5].

Poly-chemotherapy (cyclophosphamide, hydroxydaunorubicin, oncovin, predisone CHOP or combination chemotherapy)
Allogeneic stem cell transplant

Table 7a First line treatment in mycosis fungoides stage IIIA and IIIB [5].

Systemic therapies (cyclosporine, interleukin2, monoclonal antibodies,adenosine/purine analogues)
Retinoids (Bexarotene, Aliretinoin)
Interferon α
ECP (Extracorporeal photopheresis)
Low dose methotrexate
Total skin electron beam (TSEB)

Table 7b Second line treatment of mycosis fungoides stage IIIA and IIIB [5].

Monontherapy (gemcitabine, pegylated liposomal doxorubicine)
Allogeneic stem cell transplant

Organization- European organization of research and treatment of cancer (WHO EORTC) for cutaneous lymphomas along with the World health Organization (WHO) 2017 classification of the tumours of haematopoietic and lymphoid neoplasm may be described, particularly the folliculotropic mycosis fungoides (FMF) or pilotropic variant, localized pagetoid reticulosis, Woringer Kolopp disease and granulomatous slack skin [1] **(Figures 11-14)**.

Para-psoriasis en plaques

The accurate description of para-psoriasis and its correlation to mycosis fungoides may be obscure. Evolution of small patch para-psoriasis (SPP) to progressive mycosis fungoides may ensue. Majority of the small patch para-psoriasis lesions may develop a protracted clinical course with frequent remissions and relapses. However, the disease may not actively progress, thus the clinical intervention may be moderate [14]. On the contrary, a large patch para-psoriasis may simulate a mycosis fungoides on clinical and histological grounds and may confirm a preliminary evidence of the lymphoma [1] **(Table 8)**.

Syringotropic mycosis fungoides

The particular variant is exceptional and displays aspects simulating a folliculotropic mycosis fungoides. A typical and distinctive incrimination of the eccrine glands may ensue, frequently accompanied with pilotropism. The lesions may be solitary or frequently widespread with a prognosis identical to FMF [1] **(Table 9)**.

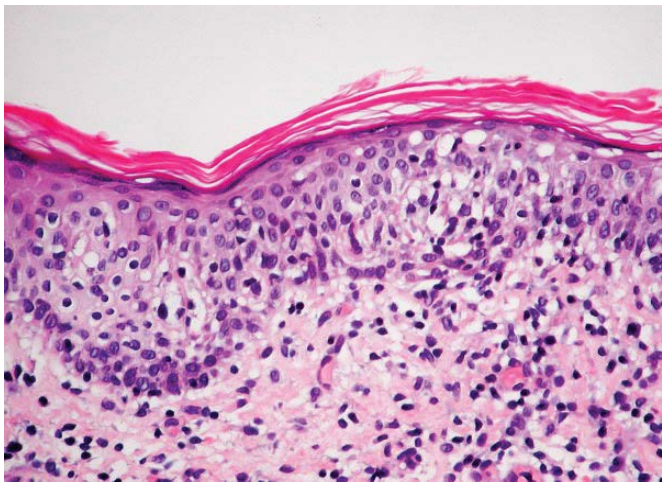

Figure 8 Genesis of Pautrier's micro-abscess with dermal disposition.

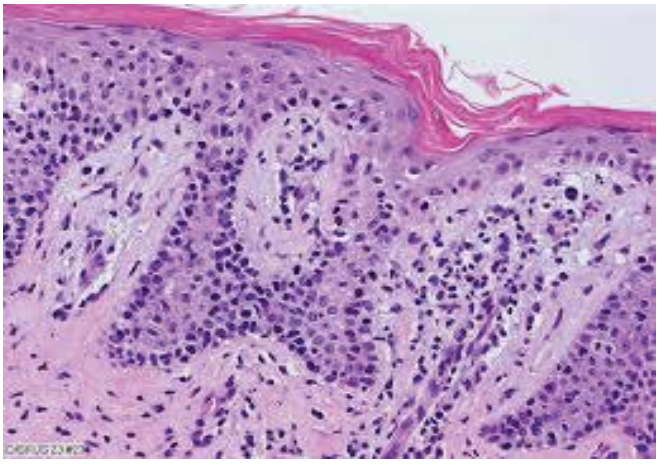

Figure 9 Prominent micro-abscess with disseminated T lymphocyte infiltrate.

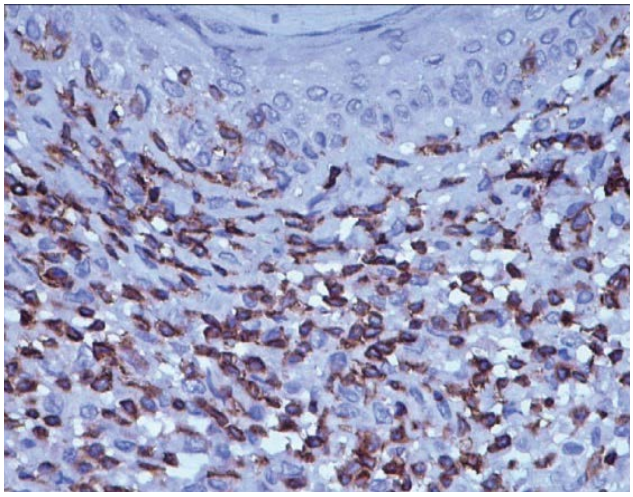

Figure 10 CD3+ immune reactive dermal T lymphocytes.

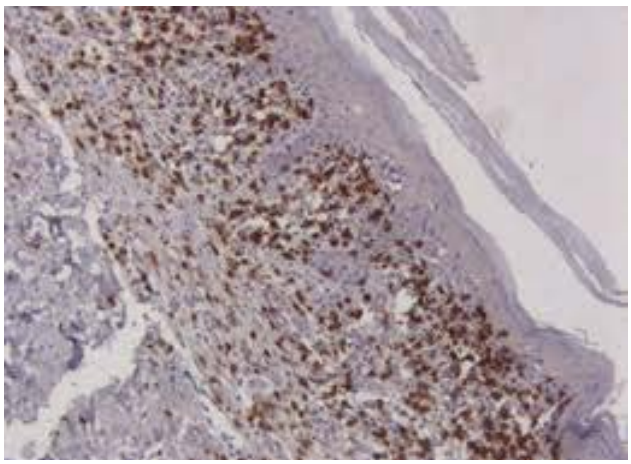

Figure 11 CD8+ immune reactive epidermal and interface T lymphocytes.

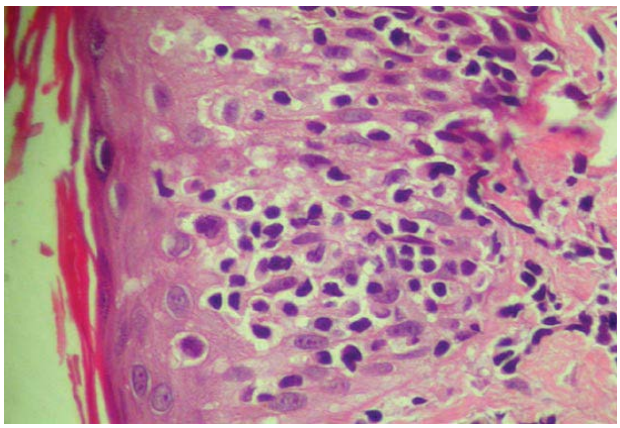

Figure 12 Hypo-pigmented variant with dispersed T lymphocytes.

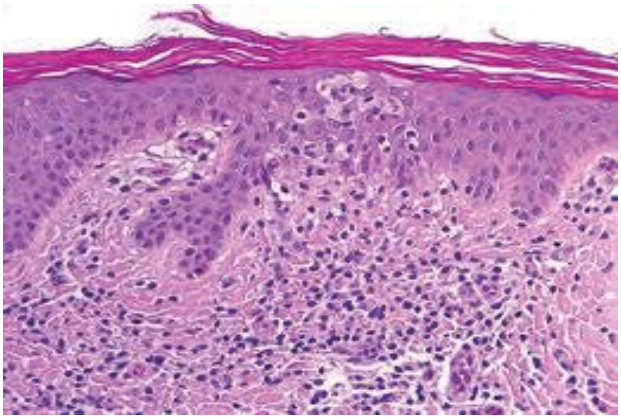

Figure 13 Ichthyosiform variant with dense, dermal collections of T lymphocytes.

Interstitial mycosis fungoides

It may be described as a variant which classically depicts a dermal infiltrate of lymphocytes dividing the collagen bundles, a configuration which resembles inflammatory dermatosis

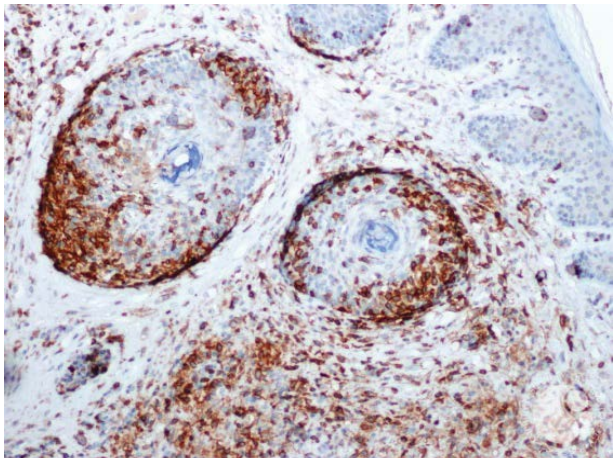

Figure 14 Folliculotropic mycosis fungoides with CD3+ immune reactive T lymphocytes.

Table 8 Treatment of mycosis fungoides stage IVA and IVB [5].

Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, cyclophosphamide, hydroxydaunorubicin, oncovin, predisone -CHOP and CHOP like poly-chemotherapy)
Radiotherapy (TSEB and localized)
Alemtuzumab (chiefly in B2)
Allogeneic stem cell transplantation

Table 9 Maintenance therapy following remission of mycosis fungoides [5].

ECP (Extracorporeal photopheresis)
Interferon α
Low dose methotrexate
Mechlorethamine
PUVA (Psoralen ultraviolet A)
Retinoids (Bexarotene, Aliretinoin)
Topical corticosteroid
Ultraviolet B

such as an interstitial granuloma annulare, inflammatory stage of localized scleroderma or an interstitial granulomatous dermatitis. Flattened tumefaction of mycosis fungoides may lack the characteristic clinical aspects such as 'epidermotropism' and a band like dermal inflammatory infiltrate, thereby engendering a misdiagnosis. A few collagen fibres may be circumscribed by the malignant lymphocytes, thereby mimicking the 'rosette' pattern discerned with the interstitial granulomatous dermatitis (the collagen fibres may be encompassed by histiocytes in such lesions of inflammatory dermatosis [12,14] A majority of the interstitial cells may be T lymphocytes, with a cytotoxic immune phenotype in an estimated half (50%) the instances. Granuloma annulare may exceptionally co-exist with inflammatory infiltrates of pseudo-lymphoma, although an authentic granuloma annulare may be described with mycosis fungoides [1].

Divergent diagnosis

Mycosis fungoides necessitates a distinction from innumerable benign and malignant disorders with identical clinical and pathologic attributes. Various lymphomas may delineate 'epidermotropic' inflammatory infiltrates especially the cutaneous

γ/δ T cell lymphoma, cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma, lymphomatoid papulosis, cutaneous anaplastic large cell lymphoma, cutaneous counterparts of extra-nodal natural killer (NK)/T cell lymphoma, nasal type T cell lymphoma, Sezary syndrome and adult T cell leukaemia/ lymphoma (ATLL) [1]. Epidermotropic inflammatory infiltrates may exceptionally appear with B cell lymphomas. Cutaneous inflammation delineating a distinctive epidermotropism may mandate a suitable immune phenotypic examination along with an in-situ hybridization for the detection of Epstein Barr virus [9,10]. A categorization of mycosis fungoides may be accepted in endemic regions of human T lymphotropic virus (HTLV 1) following exclusion of a concomitant HTLV 1 infection, as the cutaneous elucidation of ATLL may be identical to mycosis fungoides on clinical and histological grounds. An assiduous history taking with a precise coordination of the clinical features may be mandated to eliminate a diagnosis of mycosis fungoides from a cutaneous cytotoxic lymphoma [1]. Innumerable benign inflammatory conditions may also require a demarcation from mycosis fungoides such as lichenoid keratosis, lymphomatoid eczematous dermatitis, lymphomatoid drug eruptions and the inflammatory stage of lichen sclerosus. Apart from a definitive diagnosis of localized pagetoid reticulosis, a description of solitary mycosis fungoides may be acknowledged with categorical clinical/histological confirmation [1]. A discernment of preliminary mycosis fungoides may be a challenging feat on histology alone and a clinical concordance may be pre-requisite. Extensive therapy may be administered prior to a histological elucidation of early mycosis fungoides, thereby engendering a non-diagnostic morphology (therapy resistant dermatitis). A prominent 'epidermotropism' and Pautrier's micro-abscess may be contemplated as the two distinctive histological parameters for detecting preliminary mycosis fungoides, though they may be absent in a majority of instances [11,13]. An immune phenotype of early lesions may not be typical and may resemble the immune reactions of several inflammatory dermatoses [1]. The absence of T cell associated antigen CD7 may aid the detection of the disorder, although benign inflammatory T lymphocytes may also depict a deficit of CD7. Molecular analysis of the T cell receptor (TCR) genetic rearrangement may be advantageous in demarcating mycosis fungoides from benign dermatoses. The emergence of an identical clone of malignant lesions from divergent locations may support a diagnosis of mycosis fungoides, in contrast to an inflammatory dermatosis. Genetic sequencing of the T cell receptor may permit a superior elucidation of T cell infiltrate, contrary to a standard polymerase chain reaction (PCR). Analysis of TCR sequencing depicts the malignant component to be limited to 10% of the entire T lymphocytic infiltrate, thus a histological manifestation of malignancy may be challenging to discern [1].

Radiographic evaluation

Whole body imaging in lymphomas may provide constitutive information for therapeutic purposes such as an assay of the baseline disease, a precise tumour staging, adopting efficacious therapeutic strategies, evaluation of treatment response and discerning disease relapse. A positron emission tomography (PET CT) or a computerized tomography scan with 18 fluorodeoxy glucose (FDG PET CT) may be employed for response assessment in various lymphomas [14]. Criterion for lymphoma staging generally applicable may be Stage I: incrimination of a single lymph node/site, Stage II: involvement of multiple lymph nodes or groups appearing ipsilateral to the diaphragm, Stage III: implication of lymph node groups above and below the diaphragm and Stage IV: a non-contiguous, extra nodal emergence such as in the liver, lung or bone marrow etc. [14]. The "Lugano Criterion" of assessment of therapeutic response with the assistance of computerized tomography (CT) may incorporate aspects such as a) complete radiologic response with the nodes ≤ 1.5 centimetre in the magnitude of longest diameter along with elimination of indicators of lymphoma on computerized tomography (CT) b) a partial remission displaying a 50% or greater reduction in the tumour burden **(Table 3)**. c)a stable disease which signifies a declined in the tumour burden beneath 50% of existing disease d) a disease progression, a contemporary lesion or an augmentation of the lymph node enlargement or a recent extra-nodal lymphoma [14]. Thus, whole body computerized tomography (WBCT) may be considered as a decisive and predictable imaging modality necessitated for staging of a lymphoma along with evaluating the therapeutic response. Apart from the aforementioned Lugano criterion, the guidelines of therapeutic response evaluation criterion in solid tumours (RECIST) may categorize parameters such as a minimal magnitude of quantifiable lesions, the exact number of emerging lesions, the imaging techniques employed and the non-specified parameters requisite for assaying the tumour burden [15]. The first version of RECIST criterion categorically standardized and magnified the assessment of therapeutic response. Application of RECIST study may be beneficial for choosing the target lesions according to the magnitude, quantification, situation and accessibility of the lesions **(Table 4)**. Since the introduction of RECIST, the defined criterion may be adaptable and extensively employed for appropriate clinical trials and may provide a frequent and competent methodology of assessing therapeutic response with lymphomas [15].

Prognostic indications

Inferior prognostic outcomes may be delineated with widespread plaques or tumours accompanied a disseminated erythema and lymph node enlargement. The number and morphology of the malignant T lymphocytes and the concentration of epidermal langerhans cells as detected on the biopsy may be concordant to the clinical course of the disease [16]. However, a conclusive derivation on a singular histo-pathological specimen may be inadequate. An estimated half to two thirds (50% to 65%) of instances of mycosis fungoides on the skin may demonstrate the implication of lymph nodes and internal viscera [2]. The intrinsic disease may be categorized as mycosis fungoides on account of the polymorphism of the inflammatory infiltrate with the accompanying T lymphocytes with cerebroid nuclei. The internal inflammatory infiltrates may congregate within the lymph nodes, lung, spleen, liver, kidney, bone marrow, central

nervous system or ubiquitously. A primary extra cutaneous lesion may also appear within the lymph node or internal organs. Sepsis may be elucidated as a frequent terminal complication **(Tables 5A and 5B)** [2]. The stratification of various individuals with the proliferation index (PI) in mycosis fungoides may be delineated as the early stage (stage IA- IIA) and the late stage (stages IIB-IVB). Attributes such as male sex, age greater than 60 years, the appearance of plaques, the variant of folliculotropic mycosis fungoides (FMF) and nodal indicators of NX (not assessable)/ N1 may be categorised as early stage disease. Aspects such as male sex, age beyond 60 years, lymph node stage N2/N3, blood category B1/B2 and metastasis M1 may characterize the late stage disease [4].

Discussion and Conclusion

Autonomous evidence of a poor prognosis and indeterminate survival may incorporate stage IV disease, age of disease emergence beyond 60, a large cell transformation, the appearance of folliculotropic variant of mycosis fungoides (FMF) and an elevated serum lactate dehydrogenase (LDH) [16]. The specified risk indicators may formulate three distinct proportions of 5year survival for stage IIB-IVB: a low risk fraction at 68%, an intermediate risk segment at 44% and a high-risk category at 28%. Particular prognostic evidentiary elements, beyond the staging system, may delineate a favourable prognostic outcome with co-existent poikiloderma, an association with lymphomatoid papulosis and a juvenile age of onset [4].

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