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Clone and Contradistinction—Mycosis Fungoides

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Abstract

Mycosis fungoides is a peripheral T cell lymphoma engendered from mature, post-thymic T lymphocytes representing with cutaneous patches, plaques, tumours and erythroderma. Mycosis fungoides demonstrates a 'bathing trunk' distribution wherein gluteal region, trunk and proximal limbs appear incriminated. Mycosis fungoides enunciates enhanced expression of Th2 gene along with Th2 associated cytokine production and activation of nuclear factor kappa B (NFkB). Lesions depict a band-like infiltrate of atypical lymphoid cells within papillary dermis with focal fibroplasia and Pautrier's micro-abscesses. Neoplastic cells display mature T cell phenotype and are immune reactive to CD45RO+, TCRβ+, CD2+, CD3+, CD4+, CD5+or CD7+. Photodynamic therapy, retinoids, targeted therapy, biologic therapy, radiation, chemotherapy or allogenic haematopoietic stem cell transplant may be adopted to treat mycosis fungoides.

Keywords: Peripheral T cell lymphoma, plaque, tumour, erythroderma

Mycosis fungoides is a peripheral T cell lymphoma engendered from mature, post-thymic T lymphocytes. The neoplasm manifests as cutaneous patches with subsequent emergence of plaques, tumours and erythroderma. Mycosis fungoides may additionally be designated as cutaneous T cell lymphoma. Mycosis fungoides (MF) is a diagnosis of exclusion and the lymphoma can be appropriately discerned with pertinent clinical, histological and molecular parameters. Clinically discerned mycosis fungoides necessitates concurrence with cogent histopathological and molecular features in order to exclude benign inflammatory disorders, aggressive primary cutaneous lymphomas or extra-cutaneous lymphomas involving cutaneous surfaces (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). The lymphoma exhibits an indolent clinical course with superior overall survival. However, disease progression may ensue with occurrence of fungating tumefaction, erythroderma and extra-cutaneous neoplastic dissemination. Advanced stage disease is associated with disease occurrence within lymph nodes, bone marrow and distant viscera. The disorder exhibits a male predominance and incriminates elderly individuals. Paediatric population delineates a hypo-pigmented variant. Median age of disease discernment is the fifth decade. Nevertheless, no age of disease

appearance is exempt (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019).

Characteristically, mycosis fungoides emerges within zones of photo-protection and depicts a 'bathing trunk' distribution wherein the gluteal region, trunk and proximal limbs appear incriminated. However, no site of disease incrimination is exempt (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019).

Of debatable pathophysiology, mycosis fungoides demonstrates significant clinical and immuno-phenotypic heterogeneity. In contrast to centric memory T cell phenotype encountered in Sézary syndrome, cell of origin is contemplated to be effector memory T cells which hone to diverse cutaneous sites. Mycosis fungoides confined to various cutaneous zones demonstrates cell of origin to be a tissue resident, memory T cell phenotype along with infrequently discerned migratory memory T cell phenotype (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Immunological milieu of mycosis fungoides (MF) enunciates enhanced expression of Th2 gene along with Th2 associated cytokine production. Nuclear factor kappa B (NFkB) is associated with B cell lymphomagenesis and may be constitutively activated within mycosis fungoides. Activation of signal transducer and activator of transcription (STAT), upregulation of cyclin and decimated RB1 may ensue in certain instances of mycosis fungoides (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Cytogenetic and comparative genomic hybridization (CGH) exemplify loss of chromosome 9p21including CDKN2a - CDKN2B genetic locus, especially within tumour stage and lesions of large cell mycosis fungoides (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). In contrast to B cell lymphomas, recurrent chromosomal translocations are exceptionally discerned within mycosis fungoides.

Exclusion of infection with human T-lymphotropic virus 1 (HTLV1) is mandated as adult T cell leukaemia/lymphoma may simulate initial representation of mycosis fungoides (MF). Genetic predisposition is indicated due to disease association with subtypes of human leukocyte antigen (HLA) or occurrence of exceptional, familial instances (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Certain drugs may engender T cell dyscrasias simulating mycosis fungoides wherein the condition may resolve upon withdrawal of offending agent (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Infrequently, drug induced T cell infiltrate may persist as mycosis fungoides despite withdrawal of offending agent (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019).

Mycosis fungoides may recapitulate spongiotic or psoriasiform dermatitis. The condition may wax and wane and definitive diagnosis may be delayed by several years or decades (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Initially, the disorder is confined to photo-protected cutaneous surfaces. Classically, conventional mycosis fungoides manifests as heterogeneous, erythematous, ezcematoid or psoriasiform patches with fine scaling and variable atrophy (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Enhanced possible occurrence of malignancies as synchronous lymphoma may ensue (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). The indolent mycosis fungoides may progress to infiltrative plaque, tumour stage and erythroderma simulating Sézary syndrome. Incrimination of lymph nodes and diverse viscera may occur with progressive disease. However, bone marrow involvement is exceptional. Advanced stage disease is associated with decimated T cell repertoire with consequent emergence of infection and disease associated mortality (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Mycosis fungoides demonstrates variants such as poikiloderma-like, hypopigmented, granulomatous, folliculotropic, syringotropic or palmoplantar mycosis fungoides (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019).

Upon microscopy, preliminary lesions may morphologically simulate common inflammatory cutaneous disorders (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). A band-like infiltrate of lymphoid cells appears confined to papillary dermis. Well configured patches and plaques exhibit band-like lymphoid infiltrate confined to papillary dermis admixed

with focal fibroplasia. Cytological atypia of infiltrating lymphoid cells may ensue. Besides, lymphocyte tagging upon dermo-epidermal junction and migration within epidermis as singular cells may be discerned. Pautrier's micro-abscesses may be articulated (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Intra-epidermal lymphocytes appear non concordant to spongiosis. Foci of epidermotropism along with or devoid of Pautrier's micro-abscesses may occur (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Lymphocytes with 'halo' appear confined to epidermis and dermo-epidermal junction, are imbued with hyperchromatic nuclei with irregular nuclear contour and delineate variable nuclear pleomorphism. Reticular fibroplasia can occur within dermis along with spacing between singular lymphocytes (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Lesions devoid of aforesaid features appear indicative of spongiotic dermatitis, drug hypersensitivity reaction and psoriasiform or interface dermatitis (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019). Tumour stage may demonstrate absence of epidermotropism along with incrimination of subjacent fibrous and adipose tissue. Large cell transformation is denominated as infiltrating cells displaying ≥ 4 times magnitude of small lymphocytes while constituting > 25% of comprehensive inflammatory infiltrate (Di Raimondo C, Han Z et al., 2021; Willemze R, Cerroni L et al., 2019).

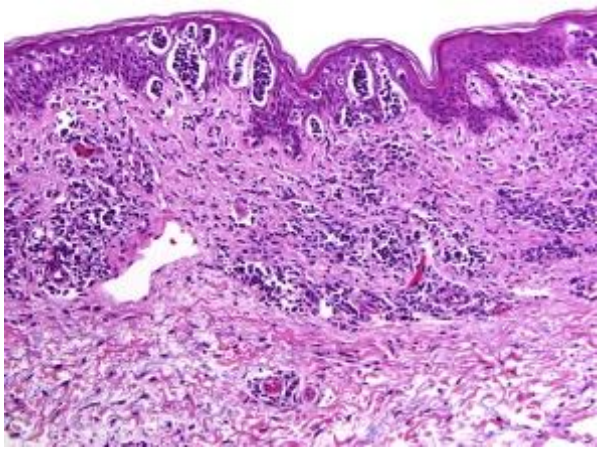

Figure 1. Mycosis fungoides with atypical lymphocytic infiltrate infiltrating papillary dermis with epidermal micro-abscesses and reticular fibroplasia

Source: Courtesy: Surgical pathology clinics

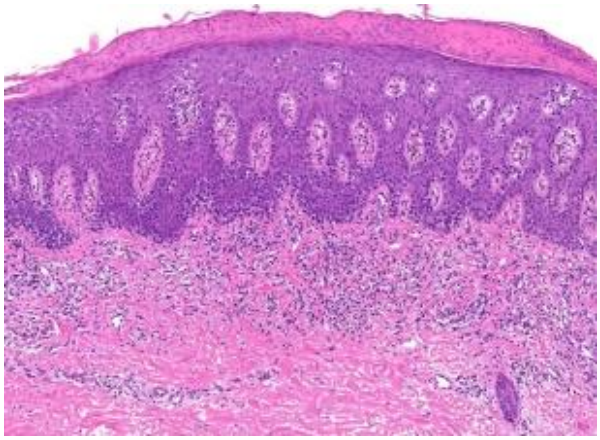

Figure 2. Mycosis fungoides delineating infiltration of atypical lymphoid cells within papillary dermis with foci of epidermotropism and reticular fibroplasia

Source: Courtesy: Pathology outlines

Table 1. TNMB classification of Mycosis Fungoides (MF) (Willemze R, Cerroni L et al., 2019; Patil K, Kuttikrishnan S et al., 2021)

Stage	T	N	M	B
IA	T1: patches and plaques<10%BSA T1a: patches only T1b: plaques only	N0: No palpable lymph nodes N0a: clone- N0b: clone+	M0: No visceral involvement	B0:<5%atypical peripheral blood lymphocytes B0a:clone-B0b:clone+ B1:>5% atypical lymphocytes

				&<1000/μL B1a:clone-B1b:clone+
IB	T2: patches and plaques>10%BSA T2a: patches only T2b: plaques only	N0	M0	B0-1
IIA	T1 or T2	N1:no evidence of MF (dermatopathic) N1a:clone-N1b:clone+ N2: early MF, aggregates of atypical cells, preserved nodal architecture N2a:clone-N2b:clone+	M0	B0-1
IIB	T3: tumour >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% atypical lymphocytes &<1000/μL
IVA1	T1-4	N0-2	M0	B2:>1000/μL atypical lymphocytes (Sézary cells)
IVA2	T1-4	N3: lymph nodes involved with loss of architecture	M0	B0-2
IVB	T1-4	N0-N3	M1: metastasis	B0-2

T category of TNM staging is contingent to percentage of incriminated cutaneous surface or body surface area (BSA) and neoplastic morphology as erythroderma, patchy, plaque or tumour stage. N category is described upon occurrence of dermatopathic lymphadenopathy, clone specific lymphoma cells and extent of regional lymph node involvement. M category denominates occurrence or absence of visceral involvement. Peripheral blood staging pertains to assessment of clone specific, quantifiable, anomalous lymphocytes or blood 'tumour burden'.

Mycosis fungoides demonstrates a variable immuno-phenotype which modifies with disease progression and transformation into large cells. Neoplastic cells display mature T cell phenotype and are immune reactive to CD45RO+, TCRβ+, CD2+, CD3+, CD4+, CD5+or CD7+. Immune reactive CD8+ is infrequently observed (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Mycosis fungoides is immune non-reactive to CD8-, TIA1, granzyme, Epstein Barr encoding region (EBER) or TCRẏ (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022).

Clonal rearrangement of T cell receptor may be beneficially discerned in instances of non-specific morphological enunciation of clinically indicated mycosis fungoides. However, assessment of

singular cellular clone may be effortless with procurement of recommended multiple tissue samples obtained from varying sites and disease stage (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Specific cellular clones can persist within T cell dyscrasias lacking diagnostic criterion of lymphoma.

Exclusions of conditions as inflammatory dermatitis occurring as spongiotic, psoriasiform or lichenoid variant, drug induced reaction or dyscrasias, cutaneous dissemination of extra-cutaneous peripheral T cell lymphoma, indolent cutaneous lymphoproliferative disorder or aggressive primary cutaneous lymphoma is mandated (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Erythoderma stage of mycosis fungoides requires segregation from conditions such as acute graft versus host disease, adult T cell leukaemia/lymphoma, atopic dermatitis, contact dermatitis, chronic actinic dermatitis, erythrodermic psoriasis, drug eruptions, paraneoplastic erythroderma, pemphigus, pityriasis rubra pilaris, psoriasis, Sézary syndrome or T cell prolymphocytic leukaemia. Patch or plaque stage of mycosis fungoides necessitate segregation from neoplasms such as adult T cell leukaemia/lymphoma, chronic actinic dermatitis, nasal subtype of extra-nodal NK/T cell lymphoma, interface dermatitis, lichenoid interface dermatitis, mycosis fungoides-like drug reaction, pityriasis rubra pilaris, primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma, primary cutaneous gamma delta T cell lymphoma, psoriasis, secondary cutaneous involvement by extra-cutaneous peripheral T cell lymphoma, secondary syphilis, spongiotic dermatitis, T cell prolymphocytic leukaemia or dermatophytes (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Tumour stage of mycosis fungoides mandates segregation from neoplasms such as lymphomatoid papulosis, primary cutaneous anaplastic large lymphoma, primary cutaneous CD4+ small/medium sized pleomorphic T cell lymphoproliferative disorder, primary cutaneous gamma delta T cell lymphoma, cutaneous B cell lymphoma, secondary cutaneous involvement with an extra-cutaneous peripheral T cell lymphoma or subcutaneous panniculitis –like T cell lymphoma (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Elevated serum lactate dehydrogenase (LDH) may be observed which is indicative of inferior prognosis and decimated survival (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Peripheral blood smear, flow cytometry and clone specific cellular evaluation is optimal in assessing peripheral blood disease (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Serologic evaluation of human T-lymphotropic virus 1(HTLV1) can efficaciously distinguish adult T cell leukaemia/lymphoma. Mycosis fungoides may be subjected to innumerable therapeutic strategies and clinical trials. However, adopted tailored therapy is contingent to clinical features, disease stage, comorbid conditions and prognostic outcomes (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Stratagem such as photodynamic therapy, retinoids, targeted therapy, biologic therapy, radiation, chemotherapy or allogenic haematopoietic stem cell transplant may be beneficially adopted (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Prognostic factors contributing to decimated survival are constituted of clinical stage IV disease, age > 60 years, large cell transformation or elevated serum lactate dehydrogenase (LDH) values (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Median survival of stage IA disease (< 10% BSA incrimination) with patches or plaques is ≥ 20 years (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022). Median survival beyond stage III (> 80% BSA incrimination and confluent erythroderma) is ~ 5 years (Patil K, Kuttikrishnan S et al., 2021; Giordano A & Pagano L., 2022)

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