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Atypical Variants of Mycosis Fungoides

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ABSTRACT

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and it is characterised by specific histological features. MF is in a spectrum of disorders which includes Sezary syndrome and other CTCL subtypes. Clinically and histopathologically it can imitate other T-cell mediated dermatosis hence making its diagnosis difficult. Due to different prognosis and difference in treatment strategies other subtypes of CTCL must be differentiated from MF. MF is a clinically indolent low-grade lymphoma which is seen in people aged between 55-60 and it's seen more commonly in men (2:1 ratio). Meanwhile other subtypes of MF like folliculotropic variant may show relatively a more aggressive course and our treatment strategy may differ.

Keywords: Mycosis fungoides, Cutaneous T-cell lymphoma, Phototherapy, PUVA

Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and it is characterised by specific histological features [1]. MF is in a spectrum of disorders which includes Sezary syndrome and other CTCL subtypes. Clinically and histopathologically it can imitate other T-cell mediated dermatosis hence making its diagnosis difficult [2]. Due to different prognosis and difference in treatment strategies other subtypes of CTCL must be differentiated from MF. MF is a clinically indolent low-grade lymphoma which is seen in people aged between 55-60 and it's seen more commonly in men (2:1 ratio). Meanwhile other subtypes of MF like folliculotropic variant may show relatively a more aggressive course and our treatment strategy may differ [3,4].

MF Subtypes

Folliculotropic MF (FMF)

FMF has a broad spectrum of clinical presentations. Varying from patches, infiltrative plaques to tumours, prurigo nodularis or keratosis pilaris like lesions [5]. These lesions tend to contain the

follicles frequently causing alopecia and in the paediatric population it tends to accompany hypopigmented patches and plaques. FMF preferentially involves the head and neck region however it can sometimes involve the trunk or the extremities [6]. Patients with FMF have significant pruritus which may be overlapped by *S. aureus* infection [7].

Histologically FMF presents with perifollicular infiltrates around the infundibulum sparing the bulbar region and the epidermis showing folliculotropism instead of epidermotropism. Immunohistochemistry shows in almost all cases a CD4+ phenotype. Clinical presentation of FMF depends upon the clinical presentation hence when located on the scalp it could cause alopecia which could be mistaken as alopecia areata, trichotillomania and cicatricial alopecias. It could present as follicular spiky papules resembling keratosis pilaris, lichen spinulosus, pityriasis rubra pilaris and lichen planopilaris. FMF is known as an aggressive variant of MF based on many series it is correlated with quick disease progression and worse outcome similar to tumour-stage MF. The estimated five-year survival is 94% for early-stage FMF while it's 69% for tumour-stage [8].



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Management of FMF is based on its aggressive behaviour and it is treated as such. Due to the perifollicular infiltrates being harder to target by skin-based therapies alone so it should be emphasized that narrow band UVB phototherapy cannot penetrate and target deep adnexal components of FMF hence psoralen and ultraviolet A (PUVA) is the first choice of treatment of early stages of FMF [9]. However, in later stages it could be combined with systemic retinoids like bexarotene or interferon (IFN). In late stages single agent chemotherapy like gemcitabine or histone deacetylase inhibitors like vorinostat and romidepsin may be used [10].

Pagetoid Reticulosis (PG)

PG or Woringer-Kolopp disease is a localised variant of MF. It is characterised by localised, slow growing patches or plaques located mainly at the distal extremities. These lesions are hyperkeratotic or psoriasiform in appearance. Histopathology shows a verrucous or psoriasiform hyperplasia with intraepidermal (pagetoid) diffusion of highly epidermotropic, abnormal lymphocytes seen in dispersed nests or throughout the epidermis. The neoplastic lymphocytes are CD3⁺ and express CD4^{+/-} and CD8^{+/-}. It is a benign disease which is treated locally with success by excision or radiotherapy [11].

Granulomatous Slack Skin (GSS)

GSS is an uncommon clinicopathological subtype of MF. It is characterised by slow growing of large, infiltrated drooping folds of atrophic skin in the intertriginous areas (axilla and groins).

Histopathology reveals many features resembling MF however the number of multifocal giant cells in GSS is larger displaying 20-30 nuclei per cell which is quite pathognomonic for GSS. Elastophagocytosis, elastic fibre loss and engulfment of lymphocytes are additional findings. Neoplastic lymphocytes mainly express CD4⁺ and CD8⁺. Depending on the stage of the disease PUVA, topical mustard, radiotherapy and systemic chemotherapy can be used however patients with GSS need a lifelong observation for secondary lymphoid malignancies the main culprit being Hodgkin's disease [12].

Granulomatous MF (GMF)

Granulomatosis could be detected in many of the MF cases either as initial presentation or in later stages of the disease. The pathogenesis of granulomatosis in MF is unknown although it is known that in other disorders it is mediated by Th1 and Th2 cells. Treatment of CTCL with IFN or bexarotene might also induce granuloma formation. GMF is a histopathologic subtype of MF that may be found in histological sections from patients with classical, poikilodermous, hyperpigmented or FMF. In some instances the clinical characteristics may suggest granulomatous disease as it may mimic granuloma annulare or sarcoidosis. Pathologic criteria for GMF includes granuloma formation or numerous giant cells with

histiocyte rich infiltration and loss of elastic fibres. Diagnosis of GMF may be difficult due to granulomatous component obscuring the abnormal lymphocytic infiltrate. Epidermotropism which is a major pathological evidence of MF may not be found in all cases [13].

GMF is associated with rapid disease progression and irresponsiveness to skin directed treatments so systemic treatment is a must. Individuals with GMF are also prone to developing secondary malignancies like Hodgkin's disease so frequent follow ups is a must [14].

Poikilodermatous MF (PMF)

Poikilodermous MF is a clinical variant of patch stage MF characterised by atrophy, telangiectasia and pigmentary changes. It is usually located around the gluteal region, breasts and hips and is frequently associated with classical and other subtypes of MF.

Histopathology reveal features of MF together with poikiloderma like epidermal atrophy, basal hydropic degeneration, pigment incontinence and telangiectasia. Immunophenotyping shows an overexpression of CD8⁺ cells. PMF is a mild variant of MF usually showing benign behaviour and responds to phototherapy [15].

Hypopigmented MF (HMF)

HMF is a variant of MF affecting people with dark skin and children or adolescents [16]. Hypopigmentation in HMF is due to loss of melanocytes in the lesional skin due to cytotoxic T-cells like in vitiligo. Clinical features of HMF includes irregular round shaped hypopigmented patches and plaques and this may be the only manifestation of MF or seen together with other variants like classical MF. In children the hypopigmented lesions may be accompanied by early folliculotropic lesions. Histopathology reveals many similarities with classical MF, HMF is highly epidermotropic composed of atypical lymphocytes, decreased melanin in stratum basale of the epidermis and melanophages. Compared to classical MF HMF is mainly composed of CD8⁺ lymphocytes [17].

Due to its slow indolent course and its lack of signs or symptoms multiple biopsies may be needed for definitive diagnosis. HMF is extremely responsive to phototherapy and resulting in favourable prognosis [16].

Hyperpigmented MF (HPMF)

HPMF is a rare subtype of MF seen mainly in darker individuals [18]. It presents itself with hyperpigmented patches or plaques with ill-defined borders and variable amounts of scaling and skin atrophy. These lesions may be lone or accompanied by different types of MF. Histopathology shows features of classic MF together with vacuolar degeneration of basal keratinocytes and basal hydropic degeneration. Immunohistochemistry shows in most of the HPMF cases a CD8⁺ phenotype. These cytotoxic T-cells cause vacuolar

degeneration resulting in interphase dermatitis and marked melanin incontinence. HPMF has an indolent clinical course similar to of early-stage MF with good response to phototherapy [19].

MF Palmaris et Plantaris (MFPP)

MFPP is a rare histopathologic variant of MF. Specific involvement of the palms and soles are seen in MFPP, these lesions tend to be bilateral and are characterised by erythematous hyperkeratotic patches and plaques covered in fissures or scales. These lesions may be accompanied by ulcerative lesions and dystrophic nails [20].

Histopathologically usual features of MF are found in MFPP but due to the spongiotic dermatitis seen in MFPP correct diagnosis might be difficult. Immunophenotyping and T-cell clonality must be analysed to confirm the diagnosis. The differential diagnosis of MFPP includes dermatophyte infections, eczema or palmoplantar psoriasis [21].

MFPP is considered as stage 1A MF and is treated as such giving positive clinical response to skin directed therapies like topical steroids, topical bexarotene, radiotherapy and phototherapy [22].

Pigmented Purpuric Dermatitis (PPD)-like MF (PPDMF)

PPDMF is a rare variant of MF characterised by purpuric lesions. This version of MF is reported in both adults and children, it could be seen as a lone manifestation or it could be together with other unusual subtypes of MF. Histopathologically PPDMF shows similar features to that of MF including epidermotropism with atypical lymphocytes together with the presence of siderophages typically seen in PPD [23].

Major characteristic that separates PPDMF from PPD is the distribution of the lesions. While the lesions of PPD are located mainly on the lower extremities the lesions in PPDMF is located throughout the body and may be accompanied by other types of MF lesions or large-plaque parapsoriasis. Also, in PPDMF classic patterns of MF could be seen like larger numbers of atypical lymphocytes and papillary dermal fibrosis easing the diagnosis [24].

Bullous MF (BMF)

BMF is a rare subtype of MF usually appearing a couple of months after the onset of MF or SS. The bullae in BMF tend to be tense or flaccid making it difficult to differentiate from bullous pemphigoid or pemphigus. These bullae may transform to ulcers in time effecting predominantly the trunk or the limbs. Histopathologically the blisters may be subcorneal, intraepithelial or subepidermal accompanied by typical histopathology of MF. This subtype is usually associated with a poor prognosis [25].

Other clinicopathological variations include interstitial MF, syringothrophic MF, papular and pityriasis lichenoides chronica like-MF. MF and it's subtypes could easily be mistaken as other T-cell mediated dermatosis so lesions refractory to long term

treatment should be followed up closely and biopsied if lymphoma is suspected [2,4].

Conclusion

Other extremely rare clinicopathological variations of MF include interstitial MF, syringothrophic MF, papular and pityriasis lichenoides chronica like-MF. MF and it's subtypes could easily be mistaken as other T-cell mediated dermatosis so lesions refractory to long term treatment should be followed up closely and frequently biopsied if lymphoma is suspected.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: B.E., Design: B.E., Data Collection or Processing: Ö.A., T.K.U., Analysis or Interpretation: Ö.A., T.K.U., Literature Search: D.D.A., Ö.A., T.K.U., B.E., Writing: D.D.A., B.E.

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