FEATURE ARTICLE

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Mycosis Fungoides in Skin of Color

Taylor Rager and Eden Lake

ABSTRACT: Mycosis fungoides is the most common primary cutaneous T-cell lymphoma. Although mycosis fungoides affects patients of all skin tones, mycosis fungoides has a higher incidence in patients with skin of color. Patients with skin of color who are diagnosed with mycosis fungoides have worse outcomes and poor prognosis compared with patients with lighter skin tones. Mycosis fungoides is difficult to diagnose in patients with skin of color as rare subtypes or clinical presentations are commonly seen in these populations. Increased awareness of the presentation of mycosis fungoides in skin of color and early detection could address the higher rates of morbidity and mortality in these populations.

Key words: Cutaneous T-Cell Lymphomas, Mycosis Fungoides, Skin of Color

Mycosis fungoides (MF) is a primary cutaneous T-cell lymphoma that has an insidious course and various subtypes. Diagnosis of MF is difficult to obtain as the various presentations can mimic inflammatory or infectious etiologies (Lebas et al., 2021). Although MF is found in patients of all skin types, MF is often diagnosed at an advanced stage in patients with skin of color and results in worse outcomes with limited treatment options (Nath et al., 2014). Early identification of MF in patients with skin of color could result in improved quality of life and address the higher incidence of advanced-stage MF in these populations (Martinez et al., 2021).

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EPIDEMIOLOGY

MF is the most common form of primary cutaneous T-cell lymphoma, with an incidence of 0.3–0.96 cases per 100,000 persons annually and comprising up to 50% of all cases of cutaneous T-cell lymphomas (Dobos et al., 2020; Miyagaki, 2021). MF has a male-to-female ratio of 2:1 and commonly presents in the fifth decade of life. Data from the Surveillance, Epidemiology, and End Results program reveal that the average age of diagnosis of MF was 51.5 years for Black Americans and 59.2 years for white Americans in 2004–2008 (Wilson et al., 2012). Patients with skin of color have a higher incidence of advanced-stage MF and worse outcomes in comparison with patients with lighter skin tones (Nath et al., 2014). Recent studies have suggested that MF in patients with skin of color goes undetected or misdiagnosed in the early stages, as Black American men are 3 times more likely to be initially diagnosed with Stage 2 MF than white American men with MF (Huang et al., 2019). In addition, a retrospective analysis of Americans with MF revealed that, even when accounting for stage, treatment course, and socioeconomic status, Black Americans with MF have a lower overall survival in comparison with white Americans with MF (Su et al., 2017). Because of the high incidence of advanced-stage MF in patients with skin of color, worse outcomes, and younger age of onset, further investigation into the pathogenesis of MF and the photoprotective effects of melanin is recommended to improve the detection of MF in these populations (Hinds & Heald, 2009; Su et al., 2017).

PATHOGENESIS

MF is defined as the malignant proliferation of CD4+ T cells with epidermotropism (Miyagaki, 2021). The exact mechanism in the development of MF is poorly understood but is likely because of a state of chronic inflammation that results in the maintenance of a favorable microenvironment for cancer growth (Jawed et al., 2014a). A skin homing mechanism of T-cells has been identified, in which resident T-lymphocytes within the dermis are thought to be activated by a stimulus, bind to chemokines,

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and undergo clonal expansion (Yumeen & Girardi, 2020). T-cells from patients with MF express cutaneous lymphocyte antigen and the chemokine receptors of CCR-4 and CCR-10, whereas CCR-7 is seen in the tumor stage of MF. The patients' immune response changes throughout the disease progression as the early stage of MF is marked by an elevation in the TH1 cytokines and advanced stage is marked by TH2 (Liu et al., 2021). Risk factors in the development of MF include underlying malignant hemopathies and immunosuppressive states, which further support the microenvironment that allows for the proliferation of MF.

CLINICAL FEATURES

MF has numerous subtypes that can all present with various severities depending on the stage in the disease. Although many unofficial variants or subtypes of MF have been described clinically, the World Health Organization recognizes three MF variants: folliculotropic, pagetoid reticulosis, and granulomatous slack skin (Willemze et al., 2005). The early stage of MF classically presents as pruritic patches in areas protected from sun exposure, such as the buttocks and hips (Lebas et al., 2021). In patients with skin of color, MF presents in various unofficial subtypes including classic MF, hypopigmented MF, folliculotropic MF, and verrucous MF. Recent studies have sought out to characterize MF in skin of color using clinical and dermoscopic features. Diagnosis of MF is largely based on clinical features; however, dermoscopic patterns could be utilized in deciding which lesions require biopsy (Bilgic et al., 2020). In patients with skin of color, classic MF is marked by pigmentary changes (Figure 1) with dermoscopic findings of pseudonetworks, geometric white lines, and white rosettes (Nakamura et al., 2021). Hypopigmented MF has a predominance in patients with skin of color, as most cases of hypopigmented MF are in young Black patients presenting in the early stages of I–IIA (Mitchell et al., 2021). Hypopigmented MF in skin of color is notable for loss of pigment network with patchy pink amorphous areas (Nakamura et al., 2021). Of note, patients of color with hypopigmented MF have better overall survival compared with patients of color with other forms of MF (Geller et al., 2020). Folliculotropic MF in skin of color is identified by follicular plugging, hyperpigmented/violaceous perifollicular halos, and perifollicular scale, whereas verrucous MF displays large multicolored amorphous structures, yellow gray ridges, and comedo-like openings (Nakamura et al., 2021). MF in skin of color is uniquely difficult to identify as it does not present with the same striking clinical findings as MF in patients with lighter skin tones. Additional studies are needed to further characterize the clinical and dermoscopic findings, as these patterns could be utilized as an indication for biopsy in a suspecting dermatology provider.

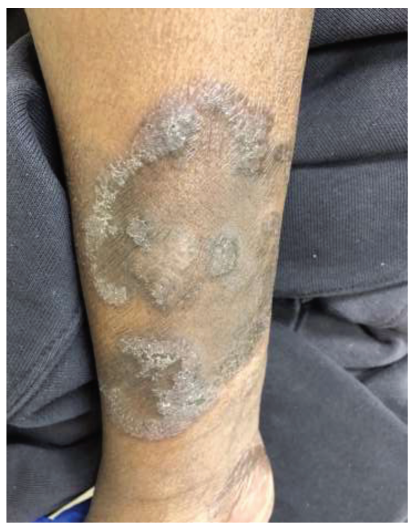

FIGURE 1. Scaly arcuate infiltrative hyperpigmented plaque.

DERMATOPATHOLOGY

Recent studies have sought out to histologically analyze MF in skin of color; classic MF in skin of color was described as an atypical, epidermotropic T-cell infiltrate; as an atypical lymphoid infiltrate that stained positive for CD8+ in hypopigmented MF; as a band-like infiltrate in the surficial dermis with intrafollicular atypical T-cells in folliculotropic MF; and as epidermal hypoplasia, hyperkeratosis with Pautrier microabscesses in verrucous MF (Nakamura et al., 2021). In immunohistochemical analysis of MF, tumor cells stain positively for CD3 and CD4 but negatively for CD8 (Miyagaki, 2021). Diagnosis of MF can also be suggested by a ratio of CD4/CD8 cells of greater than 4–6.

DIFFERENTIAL DIAGNOSIS

MF can mimic many diseases, the most common being inflammatory skin diseases including eczema and psoriasis (Lebas et al., 2021). Particularly in skin of color, MF can present as vitiligo, lichen planus pigmentosus inversus, actinic reticuloid, and progressive macular hypomelanosis (Hinds & Heald, 2009). In the early stages of MF, the lesions can present as numerous different inflammatory lesions, and multiple skin biopsies are often required for diagnosis. Diagnosis of MF requires a combination of a skin biopsy, clinical presentation, and immunohistochemical analysis. Diagnostic criteria for MF include a point system developed by the International Society for Cutaneous Lymphomas, in which clinical, histopathological, and immunopathological features are scored and 4 or more points indicates an MF diagnosis (Miyagaki, 2021). Table 1 displays the point system developed by the International Society for Cutaneous Lymphomas (Ryu et al., 2021). Early diagnostic criteria can be useful in the evaluation of patients with skin of color who present with inflammatory skin lesions concerning for MF. Recent studies have suggested

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TABLE 1. Early MF Diagnostic Criteria

Clinical	Histopathological	Molecular	Immunopathological
Persistent and progressive patches/plaques	Superficial lymphoid infiltrate		CD2, CD3, and CD5 in less than 50% of T-cells
With:	**With:**		
Non-sun-exposed region (+1)	Epidermotropism without spongiosis (+1)	Clonal TCR gene rearrangement (+1)	CD7 less than 10% of T-cells
Size or shape variation (+1)			
Poikiloderma (+1)	Lymphoid atypia (+1)		Epidermal discordance from the expression of CD2, CD3, CD5, or CD7 on dermal T-cells
Maximum Points:			
3	2	1	1

Note. MF = mycosis fungoides.

that eosinophilia may play a role in the diagnosis of MF in skin of color, as Black American patients with MF had a greater eosinophil blood count in comparison with white American MF patients (Zampella & Hinds, 2013).

TREATMENT AND DISCUSSION

Because of various presentations of MF, especially in skin of color, MF is often misdiagnosed as it can present as various skin diseases and therefore is diagnosed and treated at a later or more advanced stage. This delay in diagnosis and treatment is thought to contribute to the higher rates of mortality and morbidity in patients of color (Geller et al., 2020). The treatment options for MF are based on the subtype and stage of disease. The goal of treatment of MF is to address the patients' symptoms, such as pruritus, and slow the disease progression (Jawed et al., 2014b). In the early stages of MF, topical treatments such as corticosteroids, phototherapy, retinoids, and topical nitrogen mustard can be utilized. In later or more progressive forms of MF, systemic treatment such as retinoid therapy, biologics, chemotherapy, and stem cell transplants may be indicated (Hinds & Heald, 2009). Of the common subtypes of MF in patients with skin of color, the hypopigmented subtype is considered to be the easiest to treat and with the best prognosis (Geller et al., 2020). Light therapy with narrow-band UVB and corticosteroids are commonly used to treat hypopigmented MF, with most patients having some form of recurrence but little to no disease progression (Mitchell et al., 2021). Phototherapy is most beneficial in treating hypopigmented MF lesions, whereas hyperpigmented lesions are more difficult to treat with phototherapy as increased skin pigmentation can compromise the intended effect (Hinds & Heald, 2009). In addition, therapeutic levels may be difficult to determine in patients with skin of color, as phototoxicity is often visualized as skin erythema (Ware et al., 2020). Alternatively, topical nitrogen mustard can be utilized in patients with hyperpigmented MF lesions, who did not achieve remission after phototherapy; however, side effects often include hyperpigmentation (Hinds & Heald, 2009). Patients with advanced-stage MF can also be treated with immune-modifying medications or immunotherapies, and research suggests that initial treatment of advanced-stage MF with immunotherapy results in improved outcomes (Weiner et al., 2021). Although interferon alpha is an established immunotherapy for advanced MF, other immunotherapies such as chimeric antigen receptor T cells are being studied in clinical trials (Weiner et al., 2021). Antimicrobials can play an important role in the management of advanced MF as the skin can be prone to infectious agents, such as *Staphylococcus aureus*, as its defensive barrier is no longer functioning as it should (Jawed et al., 2014a).

CONCLUSION

Patients with skin of color are more likely to present with advanced-stage MF, which is more difficult to treat and often includes a combination of topical and systemic interventions (Huang et al., 2019). Early diagnosis of MF is difficult to obtain particularly in patients with skin of color as rare forms of MF are more common in theses populations. Early detection and diagnosis is crucial in the treatment of MF in patients with skin of color, as more aggressive initial treatment may be required for remission (Su et al., 2017). Close monitoring and regular follow-up appointments could address the racial disparities seen in MF prognosis (Huang et al., 2019). Further research is needed to explore the factors that lead to disease progression and presentation of MF in skin of color.

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