Skin Cancer: Back to Basics, Mycosis Fungoides

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ABSTRACT: Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma occurring when T-cell lymphocytes become malignant and proliferate as well as manifest in the skin. Most commonly, the disease affects the elderly population but has been seen in all ages. Presentations of MF include erythematous patches and plaques with fine scale anatomically favoring the buttocks, trunk, and extremities with complaints of significant pruritus. MF can mimic other benign inflammatory diseases such as atopic dermatitis or psoriasis. Skin biopsy of the rash for simple histology and immunophenotyping will aid in the differentiation from other diseases and confirm accurate diagnosis. Repeat biopsy is often required. A wide range of treatment options exist based on the extent of the disease and patient compliance. The prognosis is good with early detection and treatment. No cure currently exists for the disease, but a deeper understanding of triggers can guide prevention techniques and help develop targeted treatment modalities.

Key words: Mycosis Fungoides, Cutaneous T-Cell Lymphoma, Lymphocytes, Proliferation

Primary cutaneous lymphomas are the second most common type of non-Hodgkin lymphomas. Mycosis fungoides (MF) is a clonal proliferation of malignant helper T cell (CD4+) and the most common type of cutaneous T-cell lymphoma. The disease can be limited to the skin or can be at an advanced stage with significant nodal, visceral, or heme involvement (Larocca & Kupper, 2019). Skin manifestation of MF consists of the appearance of heterogenous lesions including plaques, patches, papules, and erythema. However, MF is referred to as the “great imitator” because of its overlapping clinical features with other dermatological conditions, as well as the presence of several variants, which differ greatly in clinical presentation (Hodak & Amitay-Laish, 2019). When MF develops into a systemic disease, it is known as Sézary syndrome, characterized by widespread generalized erythema and visceral involvement (Larocca & Kupper, 2019). Proper skin biopsy is an important diagnostic tool to provide diagnosis and guide appropriate therapy.

EPIDEMIOLOGY

MF is twice as common in men than women. Incidences of MF increase with age. The median age of diagnosis is 55–60 years (Wolff et al., 2017). In the United States, between 2000 and 2018, 14,942 cases of MF were diagnosed. Out of 8.55 per million of cutaneous T-cell lymphomas diagnosed in this time, five per million were attributed to MF, roughly 58% of the total cases (Stenger, 2022). Over the past 30 years, the average annual number of cases diagnosed worldwide has increased from 2.8 per million to five per million (Ghazawi et al., 2019). The disease is more prevalent in the Black population (Fitzpatrick Type V or VI) than the white population (Vaidya & Badri, 2022).

PATHOPHYSIOLOGY

The causes leading to MF are poorly understood but can be traced to environmental triggers and genetic factors (Ghazawi et al., 2019). Environmental factors include arsenic, benzene, and asbestos. These chemicals are also associated with multiple other malignancies including squamous cell carcinoma, acute myelogenous leukemia, and mesothelioma. Hydrochlorothiazide diuretics, immunosuppressants, and bacterial and viral agents are all additional external factors associated with MF (Ghazawi et al., 2019). T-cell lymphocytes function in the cell-mediated immune response. MF involves tumor cells originating from memory T cells or skin-specific CD4+ T cells. It is caused by a neoplastic proliferation of CD4+ T cells (Wolff et al., 2017). The neoplastic cells are targeted to the skin by the expression of cutaneous lymphocyte antigen. Two thirds of lymphomas are T-cell type (Vaidya & Badri, 2022).
CLINICAL PRESENTATION

Clinical presentation of the disease differs significantly depending on the stage of disease: patch, plaque, and tumor stages (Vaidya & Badri, 2022). Patch stage is the earliest presentation with erythematous or brownish scaly patches. Atrophic patches on the skin will resemble “cigarette paper” having a wrinkled appearance (Larocca & Kupper, 2019). Lesions may be satellite or clusters with variable diameters favoring the buttck and proximal thighs (sun-protected areas; Vaidya & Badri, 2022). Lesions can be superficial or mimic dermatophytosis (“mycosis”) and may thicken (Wolff et al., 2017). The plaque stage is characterized by the presence of larger lesions with evidence of infiltration. Lesions will be round, oval, arciform (progressive outer erythematous edge with inner scaly sides), annular, and disorganized in their distribution (Wolff et al., 2017). Figure 1 shows large widespread patches (photo credit to Margaret Bobonich, DNP, FNP-C, DCNP, FAANP). Earlier stages will spare sun-exposed areas, but at this stage, they may begin to affect the face and scalp. Tumor stage is the later stage of MF consisting of large erythematous purplish papules or nodules (Vaidya & Badri, 2022). Lesions can be with or without ulceration at this stage. Confluence can lead to widespread erythroderma (Wolff et al., 2017). As the lesions progress through the stages, lymph and visceral involvement increases (Vaidya & Badri, 2022). MF is often associated with significant pruritus. Some less common variants of MF include hypopigmented patches (more common in children) or poikiloderma (Vaidya & Badri, 2022).

Several clinical variants of the disease exist including follicular/folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin (Vaidya & Badri, 2022). Folliculotropic MF favors the head and neck and can be with or with mucinosis (increased mucin in the skin). Pagetoid reticulosis can be defined as localized patches and plaques with spread of neoplastic T cells with a similar pattern to Paget disease.

Granulomatous slack skin will have lax skin present in the major skin folds (Wolff et al., 2017).

As the disease progresses, it has the potential to develop into the systemic form known as Sézary syndrome. The naming of the syndrome derives from the circulating lymphocytes known as Sézary cells. MF experts refer to this phase as the leukemic, advanced form of the disease (Vaidya & Badri, 2022). Sézary syndrome is characterized by a classical triad of universal erythroderma with severe pruritus, peripheral lymphadenopathy, and atypical circulating lymphocytes in the skin and blood (Vaidya & Badri, 2022). Sézary syndrome can arise without warning or from preexisting MF (Wolff et al., 2017).

MF disproportionately affects skin of color and has a vastly different appearance (Nakamura et al., 2021). MF in skin of color is characterized by loss of the patient’s natural pigmentation network (see Figure 2; photo credit to Margaret Bobonich, DNP, FNP-C, DCNP, FAANP). Dermoscopy can improve the accuracy of MF diagnosis. Early diagnosis and improved clinical understanding can yield better patient outcomes for skin of color (Nakamura et al., 2021).

DIAGNOSIS

Diagnosis of MF can require the combination of clinical presentation, pathologic evaluation, and molecular studies (Larocca & Kupper, 2019). Because of the multiple differential
diseases associated with MF, skin biopsy is recommended as an early intervention (Vaidya & Badri, 2022).

Prompt diagnosis with a skin biopsy is the preferred method to ensure accurate diagnosis. Dermatopathologists continue to debate histopathologic features associated with MF. Timing of clinical presentation is difficult to correlate histologically because of variance in disease presentations. Several shave biopsies are often needed to accurately diagnose this disease (Semaan et al., 2021). Large, broad shave biopsies below the level of dermal epidermal junction is the preferred biopsy method. Indurated lesions would benefit from a punch biopsy (Semaan et al., 2021). A practitioner should choose a biopsy site that appears to be in early stages and is free from manipulation. The patient should avoid using topical steroids 2 weeks before shave biopsy (Semaan et al., 2021).

Epidermotropism, the presence of T cells in the epidermis accompanied by superficial dermal lymphoid infiltrates, is one of the debated diagnostic criteria among dermatopathologists (Hodak & Amitay-Laish, 2019). Attempting to bridge the gap and come together on diagnostic criteria, the International Society of Cutaneous Lymphomas has proposed a diagnostic algorithm combining histopathologic characteristics with clinical presentation (Hodak & Amitay-Laish, 2019). Sometimes repeat biopsy is recommended to establish the diagnosis, reassuring patients and providers when MF is slow to respond to treatments (Gilsen et al., 2019).

Additional blood testing can include complete blood count with differential and Sézary cell count, CD4 and CD8 T-cell counts, and T-cell receptor gene arrangement. Imaging such as chest x-ray, ultrasound of peripheral nodal groups, or magnetic resonance imaging can be performed to evaluate for potential lymphadenopathy (Vaidya & Badri, 2022). If clinically suspicious lymph nodes are present, a biopsy should be performed.

Several differential diagnoses exist for this disease process. The more common differentials include psoriasis, atopic dermatitis, seborrheic dermatitis, pityriasis rosea, and lichen planus. Less common differentials include vitiligo, pityriasis alba, tinea versicolor, and postinflammatory hyperpigmentation (Hodak & Amitay-Laish, 2019). MF is commonly misdiagnosed or diagnosed in later stages because of the common clinical presentation with other diseases. Skin biopsy and diagnostic workup is an important proactive intervention.

Patients may have a history of generalized eczematous or psoriasiform dermatitis before the diagnosis with MF (Gilsen et al., 2019). Light therapy, topical steroids, and immunosuppressants (used to treat other overlapping conditions) can dramatically change the way biopsied lesions will appear under the microscope. Early biopsy is essential with a repeat biopsy to ensure accurate diagnosis.

**FOLLOW-UP AND PROGNOSIS**

Prognosis is good for those diagnosed and treated early. Prognosis is related to the staging of the disease. Without treatment, Sézary syndrome is progressive, and patients can die from opportunistic infections (Wolff et al., 2017). The more progressed and advanced the disease, the poorer the prognosis for the patient (Gilson et al., 2019). Earlier stages can be treated with a combination of ultraviolet B or psoralen with ultraviolet A full-body light therapy, topical corticosteroids, and other oral immunomodulators (Larocca & Kupper, 2019). Patients should follow up with their dermatology provider every 3–6 months for treatment adjustments, symptom management, and evaluation for disease progression.

Late detection and progression may require chemotherapy or purine analogs (Larocca & Kupper, 2019). These patients will see a cutaneous oncology specialist regularly for their chemotherapy treatments and may require additional care with surgical oncology.

**CONCLUSION**

MF is the most common type of cutaneous T-cell lymphoma and mimics several other inflammatory dermatology conditions. Proper recognition of this disease can be a significant challenge for clinicians. Early skin biopsy and increased awareness with a high index of suspicion allow for targeted therapy options to be explored. This can prevent progression of the disease and allow for timely follow-up.

**REFERENCES**


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