

Mycosis Fungoides: Clinical and Therapeutic Review

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Mycosis fungoides is a cutaneously-derived malignant lymphoma which, without effective treatment, may run an unremitting, rapidly lethal course. Often beginning as a nonspecific skin eruption, easily misdiagnosed as a common eczema or psoriasis, the disease progresses through a plaque stage to the tumor stage with the appearance of the mushroom-like growths for which the entity was originally named. Because of the dismal outlook in uncontrolled cases, newer, more aggressive approaches to therapy are being developed and are being instituted earlier in the course of the disease.

The redundant and somewhat improbable epithet, mycosis fungoides, was first assigned to malignant lymphoma originating in the skin by Alibert in 1835,¹ and referred not to mistaken fungal infection, but to the mushroom-like appearance of the tumors. Although Alibert had first described the disease nearly 30 years earlier,² he initially believed he was observing an atypical variant of yaws and had referred to it as "pian fungoid" or the Latin equivalent, *Frambesia mycoides*.³ Through the years, the subject of mycosis fungoides has been surrounded by controversy and confusion, giving rise to a plethora of synonyms. Early classification placed the entity among granulomas, eczemas, exotic infections, and various neoplastic groups. One author, in fact, affirmed that "mycosis fungoides as an independent form of disease does not exist."⁴ The recent emergence of awareness of two distinct lines of lymphocytes has modified the nomenclature of lymphomas occurring in the skin. Mycosis fungoides is now considered to be a cutaneous re-

ticulosis associated with the proliferation of abnormal T-lymphocytes⁵⁻⁶ and which has the potential for metastasis to lymph nodes and internal organs.

While the distribution of cases of mycosis fungoides is worldwide, this form of malignancy is relatively uncommon, with less than 200 deaths per year attributed to it in the United States.⁷ The skin lesions commonly appear in the fifth decade of life but may begin at any time between the second and seventh decades.⁸ There is a slight predilection for males in most large series, and occurrence is somewhat less frequent in Negroes.⁹ The median time interval between the first appearance of skin lesions and a firm diagnosis of mycosis fungoides was four to ten years in several series.¹⁰ Although aggressive new forms of therapy may reverse the trend, the prognosis of the disease remains dismal, and if the patient lives long enough, he will probably die of it.¹¹ The median survival time for all patients following a histopathologic diagnosis is less than five years,¹⁰ but patients occasionally may live 15 to 20 years. The presence of tumors, ulcers, or lymphadenopathy further reduces the median survival to less than two years.¹¹ One hundred sixty of 165 patients with biopsy-proven mycosis fungoides, in one series, were dead at the end of an 11-year follow-up period.¹²

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Figure 1. Erythematous patches of premycotic mycosis fungoides simulating a benign dermatosis.

Clinical Features

Because a continuum of malignant progression falls under the classification of mycosis fungoides, the disease is most easily described when separated into three stages, even though the dividing line between stages is indistinct and often arbitrary. These include the premycotic or erythematous stage, the infiltrative or plaque stage, and the tumor of fungoid stage.¹³ In addition, the d'emblee type of mycosis fungoides in which tumors arise de novo without progressing through the initial stages, represents a controversial variant. Sezary syndrome, once considered a separate entity, now appears to be a leukemic form of the same malignant process.

In the initial premycotic or erythematous stage of mycosis fungoides, it is the multiplicity of presentations, often simulating common dermatoses, which precludes early diagnosis. The earliest lesions are frequently misdiagnosed as psoriasis, tinea corporis, or one of the forms of eczema (Figure 1). The term parapsoriasis designates the persistent erythematous, scaling, maculopapular eruption of this stage. Pruritis is a common symptom. Fever and arthralgia are variably present and may be significant.

The infiltrative or plaque stage of mycosis fungoides is marked by the appearance of lesions with palpable dermal substance (Figure 2). These plaques may arise within areas of premycotic in-



Figure 2. Infiltrative plaques of stage 2 mycosis fungoides.

volvement or at distant sites which had previously appeared normal. They are randomly distributed and often have figurate borders, at times surrounding islands of normal skin. The color varies from violaceous through brick red to a dusky tan.

In the tumor stage of the malignancy, nodules and tumors slowly develop within the borders of old infiltrated plaques. They generally have a red-blue color and a broad base which enlarges to 1 to 5 cm in diameter. They are firm in consistency and relatively painless while intact, although ulceration is common. The base may constrict with time, giving the tumor a mushroom-like appearance (Figure 3) for which the entity was named.

In approximately ten percent of patients, the tumor stage presents without progression through the first two stages. This type of mycosis fungoides was named "d'emblee" by Vidal and Brocq in 1885.¹⁴ The existence of this form has been brought into question because some of the early reported cases probably represented lymphosarcoma³ or exotic infections.¹³ The d'emblee type may take a fulminant progressive course resulting in rapid death.¹⁵

Pathology

The pathologic findings within the skin in mycosis fungoides, as would be expected, vary according to the stage of development of the disease. In the early erythematous stage, there may only be a relatively benign appearing lymphohistiocytic inflammatory infiltrate in the papillary and subpapillary portions of the dermis, so that a histologic diagnosis of mycosis fungoides cannot be made.¹⁶ The histologic findings in the infiltrative or plaque stage are usually diagnostic. A pronounced polymorphous cellular infiltrate contains a fairly high percentage of mycosis cells. The epidermis may contain Pautrier microabscesses, small collections of mycosis cells surrounded by a halo-like clear space. In the tumor stage, the polymorphous nature of the infiltrate is less pronounced as a higher proportion of mycosis cells with large, hyperchromatic nuclei are found. Extensive masses of these cells may occupy the dermis, at times penetrating into the subcutaneous tissue. Invasion of the epidermis results in destructive change, ending in ulceration.



Figure 3. Mushroom-like tumor.

The "mycosis cell" found in the skin and blood in this stage has been the subject of considerable recent research. Determining the precursor of this cell is important in correctly classifying mycosis fungoides among the cutaneous lymphomas and eventually understanding the cause behind its malignant transformation. Using electron microscopic identification, the cells were first demonstrated to be of probable lymphocytic origin¹⁷ and later to have T-cell membrane characteristics.⁶ Similar cells, morphologically indistinguishable from the mycosis cells, may also be detected in some non-lymphomatous dermatoses.¹⁸

In cases of mycosis fungoides with extension to extracutaneous organs, the lesions have a cellular composition which closely resembles that found in the skin. Mycosis cells are often observed in these metastatic sites and are of considerable diagnostic value. After lymph nodes, the most commonly involved viscera include, in order of decreasing frequency: lung, spleen, liver, kidney, thyroid, pancreas, bone marrow, and heart.¹⁹

Sezary Syndrome

Based on four previously reported cases, including three of his own, Sezary described what he considered to be a new cutaneous entity in 1949.²⁰ These original cases were all females and showed erythema; and edema of the skin, pruritis, and hyperkeratosis of the palms and soles were also present as well as lymphadenopathy.²¹ Recent series have shown the condition to affect both sexes equally. In addition to the clinical findings first reported by Sezary, alopecia, dystrophic nails, and hepatomegaly are also commonly observed.²²

The hematologic characteristics of the Sezary syndrome have attracted the most recent investigational interest, and, in fact, there now seems to be justification for considering this entity to represent the "leukemic" phase of mycosis fungoides. Sezary cells have been demonstrated in the circulation of one third of patients in either the plaque or tumor stage of mycosis fungoides,²³ and both

have been grouped together as "cutaneous T-cell lymphomas."²⁴ Sophisticated studies have shown the Sezary cells to be thymus-derived T-lymphocytes,²⁵⁻²⁸ or more specifically, a subset of T-cells programmed exclusively for "helper" interactions with B cells.²⁹ The latter finding, in part, explains some of the immunologic observations found in patients with this syndrome. Besides mycosis fungoides, Sezary syndrome may progress into malignant lymphoma, lymphosarcoma, or Hodgkin disease.²²

Treatment

Because of its appearance of relative benignity in the early, premycotic stages, mycosis fungoides has often been treated conservatively in the past,³⁰ until it advanced to a point where it could no longer be controlled. This approach is no longer tenable in light of present knowledge concerning the inevitable malignant progression of the disease. Early diagnosis is critical, and a very aggressive therapeutic assault is now advised. A number of antimetabolic modalities are currently being employed with varying degrees of success, and two of these, total skin irradiation with high-energy electrons and whole body application of mechlorethamine, have been shown to be extremely effective.³¹ A newer form of treatment using oral methoxsalen and long-wave ultraviolet light is in the preliminary clinical trial phase and appears promising.

Mechlorethamine or nitrogen mustard (HN₂) is an alkylating agent with exquisitely cytotoxic properties.³² It has been shown to be able to decrease both the number of cells and the percentage of atypical cells in the plaques of mycosis fungoides.³³ It is also capable of stimulating a brisk cell-mediated immune response within the skin. The suppressive effect of topically applied HN₂ on the skin lesions of the early stages of mycosis fungoides was first described in the American literature in 1959,³⁴ with subsequent reports^{35,36} confirming the proficiency of this form of treatment. In 1973, Van Scott and Kalmanson³⁷ outlined a specific schedule for the percutaneous administration of HN₂ based on their experience with a large series of patients. They also proposed a desensitization regimen for patients who developed sensitivity to the drug during the course of treat-

ment and a program for inducing immunologic tolerance prior to its initial topical use.

In the original report of 76 patients treated over four years, 50 percent were free of detectable lesions and 13 were in remission beyond two years. A follow-up report³⁸ included 14 patients who had developed tumors at some time in the course of their disease. In addition, new data from this series suggested that delayed hypersensitivity might play a beneficial role in eradicating the skin lesions. Intravenous HN₂ given in low doses has also proven of value in the induction of remissions in some patients with more advanced forms of the disease.³⁹ Principal side effects are related to the delayed hypersensitivity reaction and may include severe pruritis and blistering.

The alternative to HN₂ in the aggressive early treatment of mycosis fungoides is total skin irradiation with 2.5 MeV electrons. The proponents of electron beam therapy consider it to be the treatment of choice and the only curative approach to mycosis fungoides now available.³¹ The advantages of electron beam radiation include that it is easy to administer, covers the entire body surface, and is noninjurious to the deeper tissues of the body with most of the ionization occurring in the superficial layers of the skin.⁴⁰ It is also very effective, as revealed by a series of 132 patients described by Fuks et al^{41,42} in 1973. Fifty-eight percent of the patients in this series exhibited a complete remission of cutaneous manifestations; 14 patients had disease-free survivals of 3 to 14 years. As expected, the rate of remission was inversely proportional to the extent of the disease at the beginning of therapy, emphasizing the need for early detection and initial aggressive treatment. A common complication of this therapy is hyperpigmentation, which tends to improve with time. Edema of the skin, erythema, nail changes, and alopecia are also seen on occasion.

Since psoralen-long wave ultraviolet light (PUVA) was first established to be singularly effective in the treatment of psoriasis,⁴³ the application of this new method of treatment has been investigated in a number of other cutaneous diseases including mycosis fungoides. In one series,⁴⁴ nine patients were successfully treated for 16 to 28 months, with four cases achieving complete clinical clearing. In another group,⁴⁵ 8 of 12 patients treated with PUVA were cleared, but four patients with both plaques and tumors attained resolution

of the plaques only, again stressing the merits of early treatment. The incidence of relapses in patients thus treated as well as side effects of the PUVA regimen await future assessment. It is hoped that this new approach will join established treatment modalities in diminishing the futility that has faced clinicians in the past when caring for patients stricken with this insidious malignancy.

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