Henry Ford Hospital Medical Journal

Volume 19 | Number 2 Article 3

6-1971

Therapy of Mycosis Fungoides

Harvey G. Shapero

Henry Ford Hosp. Med. Journal
Vol. 19, No. 2, 1971

Therapy of Mycosis Fungoides

Harvey G. Shapero, M.D.*

Mycosis fungoides is best viewed as a cutaneous lymphoma. Over a period of years, it progresses through three stages—the first consisting of red scaly patches, the second of pruritic plaques, and the third of brownish-red tumors. The therapy of each stage is outlined, and several selected modalities are discussed in detail, including topical steroids, systemic steroids, localized superficial irradiation, topical nitrogen mustard, electron beam, and chemotherapy (alkylating agents and antimetabolites).

Mycosis fungoides (MF) is a pruritic cutaneous disorder best classified as a form of lymphoma. It is known for its steady progression interrupted by temporary remissions induced by therapy. Its course is long and usually continues over many years before death occurs. Clinically, it presents in three stages, each of which merits a different therapeutic approach:[1,2]

Stage I —Premycotic stage (erythematous, eczematous stage)
Stage II —Plaque stage (infiltrative stage)
Stage III —Tumor stage.

The premycotic stage is characterized by scaly erythematous patches which may be very pruritic. This stage may bear a strong clinical resemblance to nonspecific dermatitis, psoriasis or parapsoriasis. In the plaque stage, irregular but circumscribed areas of thickening and induration occur. Brownish red skin tumors which often ulcerate are the hallmark of the tumor stage. Many patients eventually develop visceral involvement, most commonly the lymph nodes, but also the spleen, liver, kidney, gastrointestinal tract or other organs. Symptoms such as fever, weight loss and anemia may indicate late disease with visceral involvement. Once stage III is reached, survival is usually less than 2-3 years.[3,4] Thorough clinical and laboratory evaluation is therefore mandatory. This should include hematological consultation with examination of peripheral blood and bone marrow. Lymphangiography, chest X-ray, liver scan, and tests of liver and kidney function are also valuable.

In contrast to other malignancies where early aggressive therapy offers the best chance of cure, most investigators[5,6] currently recommend a conservative therapeutic approach, realizing that therapy is only palliative and that the disease even untreated may progress very slowly. A notable exception, however, is Van Scott[7] who states: "There are compelling reasons why early treatment of M.F. should be *vigorously* pursued . . . postponement

*Department of Dermatology

Shapero

OUTLINE OF THERAPY

STAGE I (scaly red patches)

1. Symptomatic
   (Compresses, baths, emollients, antipruritics and antibiotics as necessary for secondary infection)
2. Topical steroids
   (With or without occlusion)
3. Ultraviolet light
4. Grenz irradiation
5. Topical nitrogen mustard

STAGE II (thickened plaques)

1. Measures as for Stage I
   (Intralesional steroids may be beneficial for small nodules or plaques)
2. Ionizing irradiation
   (Except for Grenz, limited to patients not readily responsive to above)
   a. Superficial x-ray (local lesions)
   b. Electron beam (widespread lesions)

Lesions not responding to the above, may be treated as for Stage III.

STAGE III (tumors)

A. When not rapidly progressive
   1. Measures outlined previously
B. When escapes from control
   1. Local superficial irradiation
   2. Electron beam
   3. Systemic chemotherapy

   } If previous measures fail, or if lesions are extensive.

C. Internal involvement
   1. Systemic chemotherapy (± radiation).

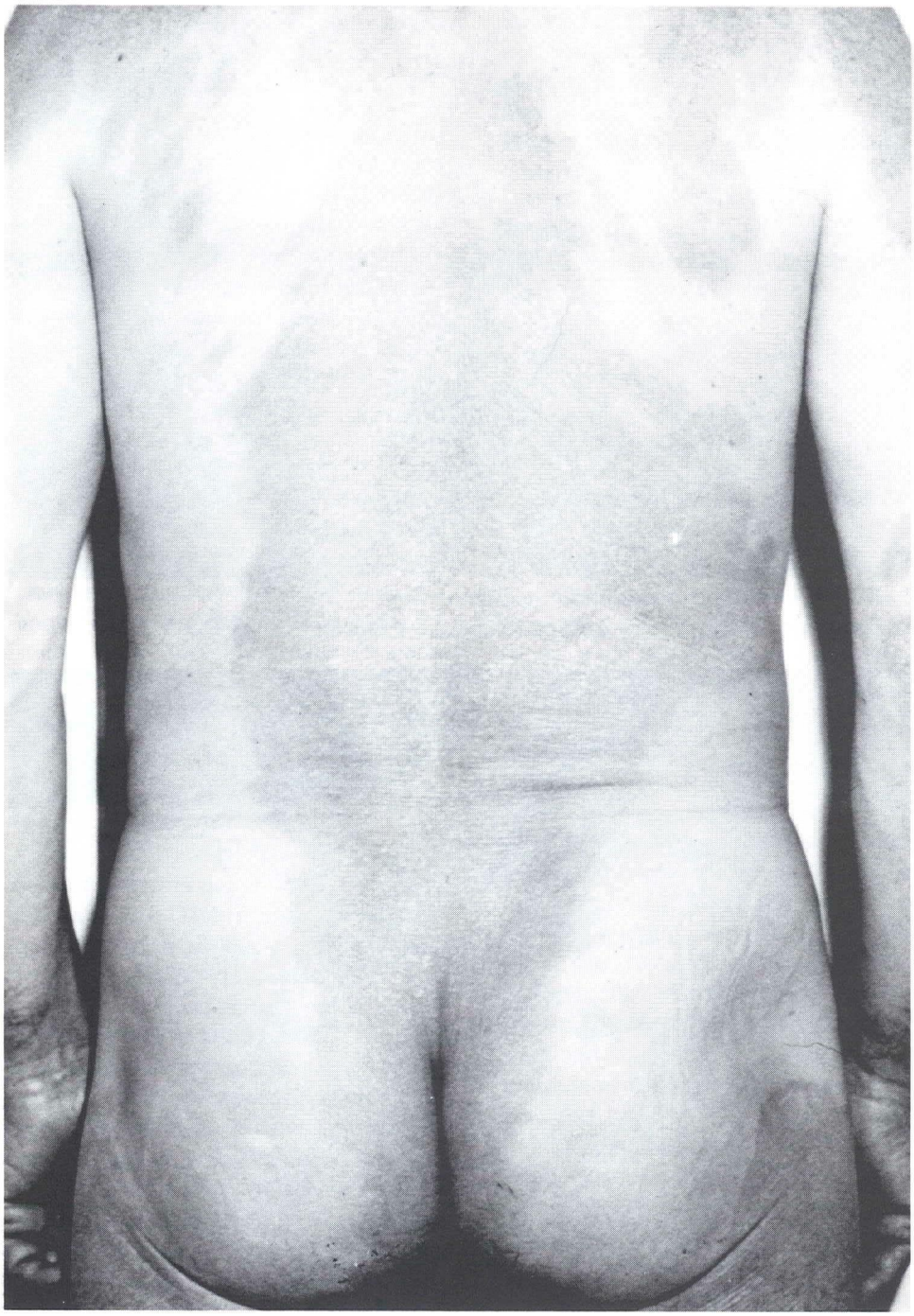

Figure 1

Erythematous scaly eruption of stage I.

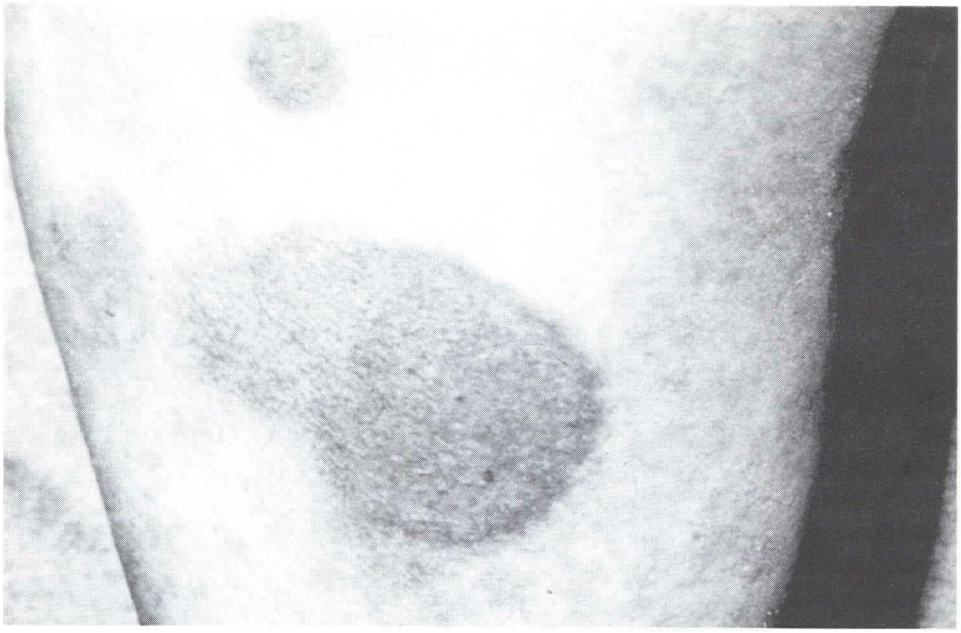

Figure 2
Thickened plaques of stage II.

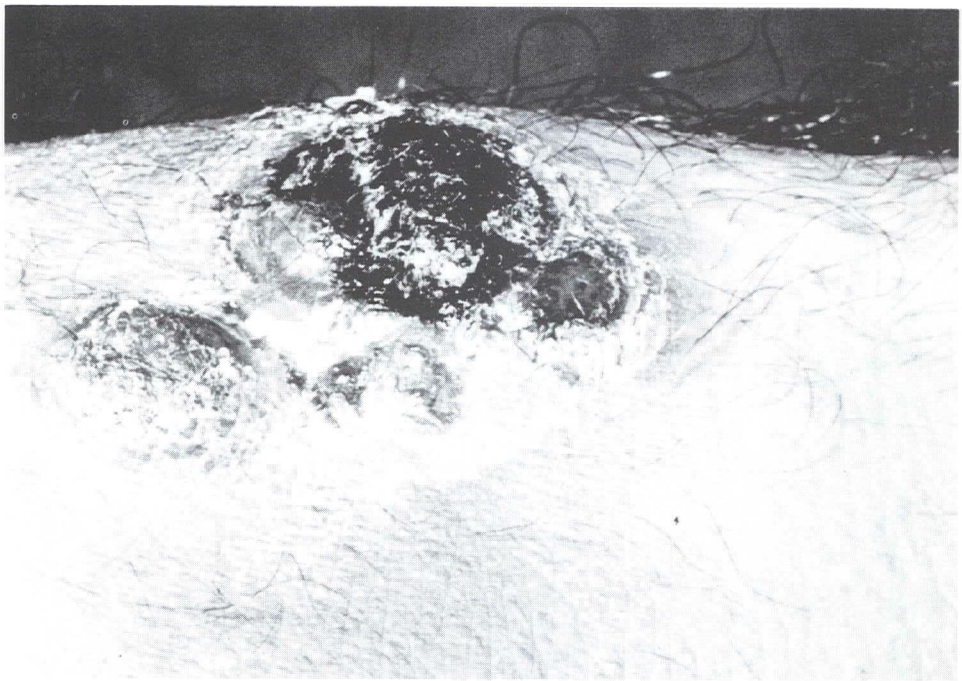

Figure 3
Cutaneous tumors of Stage III.

of aggressive therapy until later stages of the disease occurs, limits the final choice to chemotherapeutic drugs . . ."

Topical Steroids

Beneficial effects on MF have been reported with systemic steroids, intralesional steroids in infiltrated lesions and topical steroids. Farber treated 20 patients with varying concentrations of fluocinolone acetonide cream (0.01%, 0.025%, 0.2% and 1.0%). He found suppression of early and moderately advanced lesions with 0.2% and 1.0% concentrations. However, and more importantly, he found that continued applications of even 0.01% produced remissions lasting three months or longer in some patients, when plastic film occlusion technique was used at least 12 hours daily. In deeply infiltrated lesions, only 50% improvement was noted even with 0.2%. Subsequent intralesional triamcinolone acetonide gave good results in these sites (5 mgs/cc—about 1 cc per lesion).[8]

Systemic Steroids

Systemic steroids are occasionally used in *late* disease, in two instances. The first is in high dosage for a *short term* in which results are short lived. It may be useful symptomatically while another agent such as radiation or chemotherapy is taking effect. The second is in chronic low dosage in *combination* with radiation or chemotherapy if the response to these latter measures is only partial. Bluefarb feels that steroids should be reserved for patients who are debilitated or who have thrombocytopenia or hemolytic anemia. The dosage should be minimal.[5]

Local Superficial Irradiation

This is useful when the number of lesions are few. Recurrence is the rule, but re-treatment usually can be employed successfully. Bluefarb recommends 60-100 KV, 3-5 MA, 15-20 cm FSD and a HVL of 1.0-1.5 mm aluminum.[5] The sites are screened off to include a border (0.5-2 cm) of normal skin. Treatments can be given weekly. MF lesions are radio-sensitive, and often as little as 150-300r will be effective.

Grenz therapy, a very superficial form of irradiation, may offer symptomatic relief in early disease. Ultraviolet light may also be helpful in early MF.

Topical Nitrogen Mustard (mechlorethamine HCl)

The method consists of adding 10 mgs of nitrogen mustard (NM) to 50 cc saline or room-temperature tap water. This must be used immediately after mixing, as it degrades readily. The skin is cleansed of all greases and ointments. Wearing rubber gloves, the physician or nurse paints the entire skin with small gauze squares held with a hemostat. Precautions must be taken to avoid direct contact with the undiluted mixture, especially by the eyes or mucous membranes. The skin is kept moist for 15 minutes and the entire 50 cc is used. The skin may be dried with a towel or allowed to air dry. A soap-and-water bath is taken three hours later to remove NM degradation products.

NM may be applied daily for one week, then once weekly or as necessary for maintenance. If allergic contact dermatitis develops, therapy can still be continued but with a more dilute solution, such that only erythema and induration occurs.

No side effects have been reported

except for allergic contact sensitization[7,9,10] and some cutaneous pigmentation with continued use. No evidence of systemic toxicity has been shown such as nausea, diarrhea, ulcers or bone marrow depression. In fact, there has been no evidence of any significant systemic absorption.[7] Uninvolved areas of skin are not affected. Allergic contact dermatitis has been reported in 4 of 29 cases,[11] in 0 of 50 cases,[10] and in 1 of 11 cases.[9] Van Scott reported contact dermatitis in 6 of 21 cases,[7] but he used somewhat higher concentrations of NM.

Results have been encouraging. Roenigk and Haserick report favorable results in all of 50 cases to varying degrees, both clinically and histologically. Pruritus disappeared early. They emphasize that topical nitrogen mustard is not a cure but it induces remission.[9] Arundell reports that all of her 11 patients showed improvement in 4 weeks or less.[9] Van Scott reports complete remission of plaque stage MF in a majority of his patients. Resolution of tumors is also reported with intradermal injection, but not with topical NM in this stage of the disease.[7]

Most investigators do not recommend topical NM for the tumor stage of MF. A recent report, however, tells of 11 patients with recurrence subsequent to electron beam therapy in all of whom pruritus disappeared within one week and ulcers and plaques improved or disappeared in 2-4 weeks.[9]

Van Scott recently noted the most rapid clearing of clinical lesions in patients who became sensitized to NM.[7] In an earlier paper,[12] the majority of MF lesions, in six patients sensitized to DNCB (dinitrochlorobenzene) and AET (aminoethylthiuronium), cleared when the patients were treated topically with these substances to produce delayed hypersensitivity reactions. These agents were chosen only because they are potent sensitizers. He notes the normal ability of MF patients to produce both circulating antibodies and to develop delayed hypersensitivity. This contrasts with the impaired delayed reaction observed with other lymphomas. He also notes that the initial process of MF is identified by an infiltrate predominantly of normal lymphoreticular cells (the same cells commonly associated with delayed sensitivity). Only later do abnormal cells emerge in abundance. He suggests the possibility that early MF may be a cellular reaction to some unknown stimulus.

Madison and Haserick reported on 12 dermatoses treated topically with NM.[11] They found improvement in MF, Hodgkin's disease of the skin and in Bowen's disease; temporary improvement in parapsoriasis en plaque, and no improvement in lichen planus, plantar warts, seborrheic dermatitis and Sezary's syndrome. Resolution of psoriatic skin lesions, using topical NM, was recently demonstrated in seven patients.[13]

Electron Beam

Low megavolt electron beam therapy (1.5-2.5 mev) can be very helpful for extensive disease when whole body irradiation is desired. 200 rads every day to a total of 600-800 rads are recommended. When many lesions are present (ie, multiple scattered plaques) local regular superficial x-ray is cumbersome and hazardous because of marrow depression. It is here that electron beam therapy is most useful. Therapy can be given to the entire body surface

since the major ionizing effect is only 1-2 mm in depth and the maximal penetration 1 cm. Lesions thicker than 1 cm can be treated subsequently by conventional x-ray. Very advanced cases can be treated with concomitant chemotherapy. Responses are good; remissions vary from weeks to months. Electron beam therapy can be repeated several times at 3-6 month intervals.

The best review of this mode of therapy is a nine-year follow-up of 200 cases from the Massachusetts Institute of Technology and the Lahey Clinic.[4] They conclude that desperately ill patients can be salvaged for many months beyond the natural course of advanced disease.

Chemotherapy

Chemotherapy is clearly indicated when systemic manifestations are present. It may also be employed in stage III disease and in extensive stage II when other measures fail. Irradiation may be administered concomitantly. The drugs frequently used are the alkylating agents and antimetabolites.[2,3,6]

Alkylating Agents

Nitrogen mustard may be given intravenously. If used for long-term maintenance therapy, it should be used with caution because of hematopoietic toxicity.

Oral agents that have been used successfully include cyclophosphamide (Cytoxan—1-3 mgs/kg daily) and chlorambucil (Leukeran—0.1-0.2 mgs /kg daily). Although these may be used for long-term therapy, some prefer intermittent therapy to offset toxic effects, such as a course over 4-6 weeks. Approximately 50% of patients show objective improvement.

Bluefarb considers cyclophosphamide his first choice among chemotherapeutic agents for MF. He gives in the hospital 200 mgs daily IV by slow drip, then 50 mgs daily orally.[5]

Antimetabolites

1. Methotrexate appears promising but experience with it in MF is still limited. It has been found that the infiltrate of MF is relatively slow-growing; therefore, weekly methotrexate (50 mgs) can be successfully employed. If lesions tend to regain their size before the next dose, 25 mgs twice weekly is recommended, but only when a weekly regimen is ineffective, since more toxicity can be anticipated. Over half of a group of patients showed 50% regression with this regimen. Six of 30 showed complete remissions for 5-20 months.[6] Careful attention must be paid to pretreatment and followup of hepatic, renal and hematopoietic functions.

2. Triacetyl azauridine has also been reported to give beneficial results.[14]

Summary

Mycosis fungoides is a slowly progressive cutaneous lymphoma which is often complicated by visceral involvement. Thorough diagnostic investigation is therefore imperative, especially in late disease. This should include hematological evaluation, liver and kidney function tests and diagnostic x-rays including lymphangiography. The etiology is unknown and there is no specific cure. There are, however, a number of measures that offer prolonged remissions and substantial symptomatic relief. In early disease, these include general symptomatic care, topical steroids, ultraviolet light, Grenz irradiation

and topical nitrogen mustard. Later, superficial x-ray and electron beam therapy are helpful. When visceral involvement is detected, systemic chemotherapy becomes necessary. The most useful chemotherapeutic compounds are the alkylating agents and antimetabolites. Because of the chronic progressive nature of the disease, supportive psychotherapy is valuable.

REFERENCES

1. Lever, W. F.: *Histopathology of the Skin,* 4th ed, Philadelphia, Lippincott Co., 1967, pp 752-9.
2. Clendenning, W. E.: "Mycosis fungoides," in Maddin, S. (ed), *Current Dermatologic Management,* St. Louis, C. V. Mosby Co., 1970, pp 164-6.
3. Wright, J. E., et al: Observations on the use of cancer chemotherapeutic agents in patients with mycosis fungoides, *Cancer* 17:1045-62, Aug 1964.
4. Fromer, J. L., et al: Management of lymphoma cutis with low megavolt electron beam therapy, *Southern Med J* 54:769-76, Jul 1961.
5. Bluefarb, S. M.: "Treatment of mycosis fungoides," in Waisman, M. (ed), *Pharmaceutical Therapeutics in Dermatology,* Springfield, Charles Thomas Publishers, 1968, pp 83-6.
6. Haynes, H. A., and Van Scott, E. J.: Therapy of mycosis fungoides, *Progr Derm* 3:1-5, Mar 1968.
7. Van Scott, E. J., and Winters, P. L.: Responses of mycosis fungoides to intensive external treatment with nitrogen mustard, *Arch Derm* 102:507-14, Nov 1970.
8. Farber, E. M., et al: Treatment of mycosis fungoides with various strengths of fluocinolone acetonide cream, *Arch Derm* 97:165-72, Feb 1968.
9. Arundell, F. D., and Chan, W. H.: Mycosis fungoides. Topical use of nitrogen mustard in recurrent cases, *Calif Med* 109:458-61, Dec 1968.
10. Roenigk, H., and Haserick, J. R.: "Mycosis fungoides treated with topical application of nitrogen mustard," in Waisman, M. (ed), *Pharmaceutical Therapeutics in Dermatology,* Springfield, Charles Thomas Publishers, 1968, pp 87-91.
11. Madison, J. F., and Haserick, J. R.: Topically applied mechlorethamine on 12 dermatoses, *Arch Derm* 86:663-7, Nov 1962.
12. Ratner, A. C.; Waldorf, D. S., and Van Scott, E. J.: Alterations of lesions of mycosis fungoides lymphoma by direct imposition of delayed hypersensitivity reactions, *Cancer* 21:83-8, Jan 1968.
13. Mandy, S.; Taylor, J. R., and Halprin, K.: Topically applied mechlorethamine in the treatment of psoriasis, *Arch Derm* 103:272-6, Mar 1971.
14. Calabresi, P., and Turner, R. W.: Beneficial effects of triacetyl azauridine in psoriasis and mycosis fungoides, *Ann Intern Med* 64:352-71, Feb 1966.