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Disease evolution of patients with mycosis fungoides - a report of 30 cases

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Mycosis fungoides is the most common disease of the primary cutaneous T-cell lymphoma group. This is a retrospective study to evaluate the outcome of 30 patients with mycosis fungoides who were followed up for at least 3 years, 18 of them followed for 5 years and 9 of them followed for 7 years. A total of 10 patients achieved a sustained remission, 2 patients achieved a remission but then relapsed and three patients died from lymphoma-related death. It is concluded that the majority of the patients with T1 or T2 stage MF usually have a good prognosis. As a rule, those who do progress further in the disease have advanced stages at the moment of the diagnosis; the disease progression occurring during the first 3-5 years after diagnosis.

Key words: Mycosis fungoides, Primary cutaneous T-cell lymphoma, Outcome.

Primary cutaneous T-cell lymphomas (CTCL) encompass a group of lymphoproliferative diseases characterized clinically by presenting only with skin involvement at the time of diagnosis. Mycosis fungoides (MF) is the most common form of primary CTCL (1).

The typical clinical course of MF is the evolution of patches, plaques and tumors as described by the Alibert-Bazin model, (1,2) with initial lesions usually presenting on non sun-exposed skin.

This disease is clinically staged according to the type and extent of cutaneous lesions, lymph node clinical and/or pathologic abnormalities and the presence or absence of systemic involvement. The most widely used system of clinical staging is that described by Bunn and Lamberg in 1979 (3).

Most patients presenting with limited disease have a good prognosis with either disease remission or a disease which runs a chronic, indolent, non-progressive course having life expectancy similar to their age-matched controls. However, a minority of patients may either present initially with or progress to a more aggressive form of the disease. Prognosis of patients with MF is dependent upon extent and type of skin lesions, extracutaneous manifestations including lymphadenopathy (4-11) and age at onset of the disease (1,6).

In this study of cases we present the outcome of 30 patients with mycosis fungoides who were followed up for at least 3 years; 18 patients of them that followed for 5 years and 9 patients were followed for 7 years.

Patients and Methods

This retrospective study was performed at the Dermatology Clinics of the University of Puerto Rico. We included patients in which a diagnosis of MF was made between the years 1983 and 2002, and who had been followed up for at least 3 years. Patients with CTCL other than MF were excluded, as they are recognized to be distinct disease entities by WHO and EORTC (1).

Patients were diagnosed using clinical and histopathologic criteria. The histopathologic criteria used for diagnosis were those described by Sanchez and Ackerman (2) and later by Nickoloff, (12) namely the presence of atypical lymphocytes involving broad zones of the epidermis arranged as small nests or as single cells in a somewhat linear configuration along the epidermal side of the dermoepidermal junction, absence of microvesiculation, polymorphous mononuclear cell infiltrate in nonedematous papillary dermis and papillary dermal fibrosis with plasma cells and eosinophils.

Staging was determined using a clinical staging system (3) (Table 1). A complete medical history, physical examination, complete blood cell count, and skin biopsy were obtained to determine the stage of the disease in each patient. An abdominal CT scan, and in some cases a

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Table 1. TNM Classification for CTCL[3]

T: Skin suspicious	T_0	Clinically and/or histologically lesions
	T_1	Limited plaques, papules, or eczematous patches covering <10% of the skin surface
	T_2	Generalized plaques, papules, or erythematous patches covering >10% of the skin surface
	T_3	Tumors (1 or more)
	T_4	Generalized erythroderma
N: Lymph nodes	N_0	No clinically abnormal peripheral nodes, pathology negative for MF
	N_1	Clinically abnormal peripheral nodes, pathology negative for MF
	N_2	No clinically abnormal peripheral nodes, pathology positive for MF
	N_3	Clinically abnormal peripheral nodes, pathology positive for MF
B: Blood	B_0	<5% atypical circulating lymphocytes
	B_1	>5% atypical circulating lymphocytes (Sèzary's)
M: visceral organs	M_0	No visceral organ involvement
	M_1	Histologically proven organ involvement

lymph node biopsy, were obtained in the presence of lymphadenopathy. Further medical studies were obtained if the clinical picture suggested visceral involvement.

The following variables were recorded: age, sex, age at diagnosis, stage at diagnosis, stage at 3 years of diagnosis, site of early lesions and progression, treatment, other systemic or cutaneous diseases at time of diagnosis and previous cutaneous diagnoses. Stage at 5 and 7 years of diagnosis were recorded for those patients that were followed for that period of time.

Multiple regression analysis and correlation analysis were performed for the different variables studied.

Results

Our lymphoma clinic follows a total of about 100 patients. A total of 30 patients had sufficient data and sufficient follow up time to be included in this study. Table 2 depicts the patients' clinical characteristics. At the moment of diagnosis, the age of the patients varied from 24 to 84 years old (mean = 58). The follow up period ranged from 13 to 255 months (mean = 70.7 months). The patients received different treatment modalities. The main factor determining mode of therapy was stage of the disease. Other factors such as availability of patient for phototherapy and health insurance coverage guided management options in some cases. Twenty nine patients received multimodal therapy, most commonly PUVA and topical steroids. Twenty one patients received PUVA as part of their treatment, 20 patients were also on topical steroids. Other treatment modalities were systemic retinoids (7 patients), nbUVB (9 patients), IFNá (8 patients), topical alkylating agents (3 patients), radiotherapy (3 patients), systemic chemotherapy (1 patient), systemic steroids (1 patient), electron field radiation (1 patient) and methotrexate (2 patients).

Table 3 shows the evolution of the patients.

Three year follow-up – At the time of diagnosis, 10 patients were in stage T1 of disease, 14 were in stage T2, 5 in stage T3 and one in stage T4. Of the 30 patients, 11 were in remission, 9 patients were in stage T1, 5 in stage T2, 1 in stage T2N1, 1 in stage T4, and 3 patients had died of the disease after three years. Of the 10 patients that were on stage T1 at the time of diagnosis, 7 were in remission, 2 were still on stage T1, and one had died. Of the 14 patients who were on stage T2 at the time of diagnosis, 4 were in remission, 6 were on stage T1 and 4 were still on stage T2. Of the 5 patients diagnosed with stage T3 disease, 1 was on stage T1, 1 was on stage T2, 1 was on stage T2N1 and 2 had died to the disease. The patient who presented with stage T4 at the time of diagnosis responded well to therapy initially, but after three years he remained with T4 disease.

Five year follow-up - 18 patients were followed for 5 or more years. At diagnosis 5 of these patients were on stage T1, 10 were on stage T2 and 3 were on stage T3. At 5 year follow up, a total of 6 patients were in remission, 8 were on stage T1, 1 was on stage T2, and three had died of the disease. Of those patients initially diagnosed with stage T1, 3 were in remission, 1 remained on stage T1, and one had succumbed to the disease. Of the 10 patients initially diagnosed with stage T2 disease 2 were in remission, 7 were on stage T1 and 1 remained at T2 after 5 years. 2 of

Table 2. Clinical characteristics of the 30 patients studied divided by stage at diagnosis

	T1	T2	T3	T4	All
No. of Patients	10 (33.3%)	14(46.7%)	5(16.7%)	1(3.3%)	30(100%)
Age at DiagnosisMedian (Range)	72 (36-80)	52 (24-84)	60 (50-83)	N/A	59 (24-84)
Female Male Ratio	6:4	7:7	3:2	0:2	19:11
Duration of Follow-upMedian (Range)	48 (13-152)	67 (37-255)	52 (28-113)	N/A	55 (13-255)

Table 3. Disease Evolution for Each Patient

Patient up	Stage at dx	Stage at 3 years	Stage at 5 years	Stage at 7 years	total follow-(months)
1	T1	REMISSION	REMISSION	REMISSION	124
2	T2	T1	T1	T1	166
3	T2	T1	T1	T1	255
4	T2	REMISSION	-	-	44
5	T1	died of lymphoma	-	-	13
6	T2	T2	T2	-	60
7	T2	T1	-	-	42
8	T4	T4	-	-	43
9	T1	T1	-	-	48
10	T2	T2	-	-	37
11	T2	REMISSION	REMISSION	-	79
12	T1	REMISSION	T1	T1	152
13	T3	died of lymphoma	-	-	28
14	T2	REMISSION	REMISSION	-	71
15	T2	T2	T1	-	71
16	T1	REMISSION	-	-	46
17	T3	T2	-	-	58
18	T2	T1	T1	-	68
19	T1	REMISSION	REMISSION	-	69
20	T2	REMISSION	-	-	37
21	T1	REMISSION	REMISSION	REMISSION	90
22	T2	T1	T1	-	46
23	T1	REMISSION	-	-	47
24	T2	T1	T1	-	76
25	T3	T1	REMISSION	T1	113
26	T3	T2N1	-	-	38
27	T1	T1	-	-	38
28	T2	T2	T1	-	65
29	T1	REMISSION	-	-	45
30	T3	died of lymphoma	-	-	52

the patients initially diagnosed with stage T3 had died of the disease, and one was in remission after 5 years follow up.

Seven year follow up – A total of 9 patients were followed for 7 or more years. 4 of these patients were initially diagnosed with stage T1, 2 with stage T2, and 3 with stage T3. At 7 year follow up 2 patients were in remission, 4 were on stage T1, and 3 had died of the disease. Of those patients initially diagnosed with stage T1, 2 were in remission, 1 remained on stage IA, and 1 had died of complications of the disease at 7 years follow up. Both patients that had been diagnosed with T2 disease were on stage T1 after 7 years. 2 patients diagnosed with stage T3 disease had died due to disease progression. One patient diagnosed with stage T3 was on stage T1 after 7 years.

Discussion

This study analyzes the outcome of 30 patients with MF. For the period studied, there were a total of 10 patients who achieved a sustained remission, 2 patients who achieved remission but then relapsed (one was diagnosed at T1 and the other at T3, both relapsed to T1), and 3 lymphoma-related deaths.

During the first 3 years follow up period, 3 patients died of progression of their lymphoma. Although there was no statistically significant correlation between stage at diagnosis and prognosis, which could be due to our small sample size, it is important to note that 2 of the 3 lymphoma-related deaths had T3 disease at the moment of the diagnosis. Only 1 patient of those with T1 and T2 stage had progression of the lymphoma. Stage at diagnosis is a well established prognostic factor for patients with MF (4-6,10,11). Disease limited to the skin has been associated with patient survival similar to age-matched controls, while involvement of lymph nodes, blood, or any other organ rendering a more poor outcome for the patients. Some series have found that extent of skin involvement is the single most important prognostic factor, (5,9,11) showing thatnot only T1 and T2 patients do better than T3 and T4 patients, but stating that the thickness of the lesions (plaques versus patches) also conveys prognostic significance (11).

Except for the three lymphoma-related deaths, no other patient progressed to a more advanced stage during this period. The other 90% of the sample either achieved remission, improved their stage, or remained in the same stage. It should be noted that patients who progressed, did so within the first 3 years after diagnosis. This fact can be compared to the results of Kim *et al* (6) in which the patients who progressed from the lymphoma did so within the first 5 years of follow-up.

The age of the patient at the moment of the diagnosis is another factor that has been constantly implicated as an important predictor for prognosis of MF patients (5,6,13). Patients with an older age the time of at onset tend to do worse than those that are younger. Hamminga *et al* (5) found in their series that patients who were younger than 60 years at diagnosis survived longer than those diagnosed

at an older age. In our group, two of the three patients who progressed to an advanced stage of the disease had an older age than the mean age at the moment of diagnosis. This observation was not of statistical significance.

Treatment was not correlated with any specific outcome, which was expected for various reasons. First, treatment was not a controlled variable in the study. In addition, treatment options and guidelines have continued to change during the 20 year period from which the patients were selected. None of the different therapeutic modalities reported in the literature seems to affect the survival of MF patients (14,15).

Our study has the limitation of having a small sample size and those limitations inherent to record review studies, nevertheless our findings are consistent with those of larger series.

In summary, we conclude that the majority of the patients with T1 or T2 stage MF have a good prognosis with a disease characterized by either complete remission, or a disease which runs a chronic, indolent, non-progressive course. Patients at risk for progression are those diagnosed at more advanced stages, and those who progress usually do so during the first 3-5 years after the diagnosis.

Resumen

Micosis fungoides es el más común de los linfomas cutáneos primarios. Llevamos a cabo un estudio retrospectivo para evaluar la evolución de micosis fungoides en 30 pacientes que obtuvieron seguimiento clínico por lo menos de 3 años, 18 de ellos seguidos por 5 años y 9 de ellos seguidos por 7 años. Se observó remisión completa de la enfermedad en 10 pacientes. Dos pacientes tuvieron recaída luego de tener una remisión y 3 pacientes murieron por progresión del linfoma. Concluimos que la mayoría de los pacientes con micosis fungoides en estadío T1 o T2 tienen un buen prognóstico. Por lo general, aquellos pacientes que tienen una enfermedad progresiva son los que tienen un estadío más avanzado al momento del diagnóstico, y en estos casos la progresión ocurre dentro de los primeros 3 a 5 años luego del diagnóstico.

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