Mycosis Fungoides in Puerto Rico: A 15-year Follow-up Retrospective Study

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Objective: To describe the patient population with mycosis fungoides (MF) in Puerto Rico in terms of demographics, disease course, and management.

Methods: We performed a retrospective chart review of patients with MF who were being followed at the University of Puerto Rico dermatology clinics from 1999 through 2016. Collected data included demographics, age at diagnosis, stage at diagnosis, follow-up time, treatment, and stage at the time of the study.

Results: A total of 53 patients were diagnosed with MF from 1999 through 2016, with a mean follow-up period of 89 months. Of those, 45% were male. At the time of diagnosis, 40% were at stage 1A, 53% were at stage 1B, and 7% were at stages 2 to 4. During data collection, 74% of the patients remained stable, 18% improved clinically, and 8% progressed in disease stage. The treatment modalities used included phototherapy, topical steroids, topical and systemic retinoids, methotrexate, topical and systemic chemotherapy, and interferon.

Conclusion: Our study reflects the chronic and indolent course of MF, which has an overall good prognosis if diagnosed at an early stage, as has been demonstrated in the recent literature. The information contained within this manuscript should contribute to the understanding and characterization of MF in patients in Puerto Rico. [*P R Health Sci J 2020;39:306-310*]

Key words: Mycosis fungoides, Puerto Rico, Staging, Treatment

Cutaneous T-cell lymphomas (CTCL) are a rare group of extranodal non-Hodgkin's lymphomas characterized by the initial localization of malignant T lymphocytes to the skin (1). The most common form of this heterogeneous group is mycosis fungoides (MF), accounting for approximately 55% of cases, while the much rarer form, Sézary syndrome, makes up approximately 5% (2).

MF usually affects individuals aged 55 to 60 years and has a male:female ratio of 2:1. The majority of patients are Caucasians (70%), followed by African Americans (14%), Hispanics (9%), and Asians (7%) (3). However, both younger ages at diagnosis and more advanced disease stages have been reported in African American and Hispanic individuals (4,5). It is hypothesized that MF is caused by chronic antigenic stimulation that leads to uncontrolled clonal expansion and the subsequent accumulation of T-cell helper memory cells in the skin. Other studies have suggested that infections by *Staphylococcus aureus* and immunosuppression may also play a role in its pathogenesis (3).

MF usually presents as well-defined, pruritic, erythematous patches that are distributed in non-sun exposed areas, including the breast, buttocks, lower trunk, and groin (3). These patches may then progress to infiltrative plaques and tumors. Most of those patients with disease limited to the skin have a good prognosis, with either disease remission or a chronic, non-progressive, indolent course, with normal life expectancy. However, a minority of patients may initially present with or ultimately progress to a more aggressive form. Therefore, prognosis is largely dependent upon the extent and type of lesions, extracutaneous manifestations, and the age of onset of the disease (6). Other prognostic factors include elevated lactate dehydrogenase, the histologic features of the folliculotropism, and large-cell transformation (7).

In order to determine the adequate treatment, the accurate staging of MF is required. The International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer proposed an updated staging classification, which evaluates for the type and extent of skin involvement (T), the degree of lymph node (N), visceral disease (M), and circulating Sézary cells in the peripheral blood (B). This information is then used to determine a given individual's clinical stage of disease (8).

As a general principle, patients presenting with an earlier stage or who have limited disease should be treated with skin-directed therapy, such as topical corticosteroids, mechlorethamine,

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The authors have no conflict of interest to disclose.

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topical retinoids, ultraviolet phototherapy, or localized radiotherapy. Systemic retinoids, recombinant interferons, chemotherapy, targeted immunotherapy, and hematopoietic stem cell transplantation are reserved for patients at advanced stages, with refractory cutaneous disease, or both (2).

Berlingeri et al (2007) reported 30 cases of MF in Puerto Rico (PR), from 1983 through 2002, with a mean follow-up of 70 months (6). Our aim was to evaluate and characterize the current MF patients in PR, comparing them (in terms of demographics, disease course, and management) with those patients who were described 15 years ago by Berlingeri and colleagues (6).

Patients and Methods

This is an institutional review board (IRB)–approved retrospective chart review study performed at lymphoma clinics at the University of PR, Medical Sciences Campus. Patients with MF at our clinics were identified by searching the school's electronic medical record database for relevant ICD9 and ICD10 codes (202.10-202.18 and C84.01-C84.09, respectively).

A preliminary list of 90 patients was obtained, of which 37 were excluded. The exclusion criteria included an individual's diagnosis of MF having been changed, having a CTCL diagnosis other than MF, and not having a follow-up period of at least 1 year. Fifty-three patients met the criteria for the study. The following variables were recorded: age, sex, town of residence, age at diagnosis, stage at diagnosis, follow-up time, treatment, and stage at the time of the study. Descriptive statistics were used in the analysis of the aforementioned variables.

Results

From 1999 through 2016, a total of 53 patients were diagnosed with MF in PR. The follow-up period ranged from 12 to 221 months (mean: 80 months). In 1999, only 1 case of MF was reported; from 2000 through 2008, 2009 through 2013, and 2014 through 2016, a total of 17, 14, and 21 new cases, respectively, were reported. In regard to gender, 24 (45%) cases were male, while 29 (55%) cases were female. The age at diagnosis varied from 24 to 75 years of age, with a mean age of 54 years. When classified by age group, 7 cases (13%) were younger than 40 years old, 29 cases (55%) ranged in age from 40 to 60 years, and 17 cases (32%) were older than 60 years old. Forty-six (87%) cases came from the eastern side of the island while 7 (13%) cases, came, from the western side of the island (Figure 1). At the time of diagnosis, 21 patients were at stage 1A of the disease, while 28 were at stage 1B, 1 was at stage 2B, 1 was at stage 3, 1 was at stage 3A, and 1 was at stage 4 (Table 1). Upon data collection, 20 patients were at stage 1A, 23 at stage 1B, 2 at stage 2B, 1 at stage 3, 1 at stage 3A, and 1 at stage 4; 5 were in remission (Table 1). Overall, 39 patients remained stable, 10 patients improved, and 4 patients progressed in disease stage (Table 1).

Table 1. Staging of Cases

Staging	At diagnosis N (%)	Study time N (%)
1A	21 (40)	20 (38)
1B	28 (52)	23 (43)
2A	0 (0)	0 (0)
2B	1 (2)	2 (4)
3	1 (2)	1 (2)
3A	1 (2)	1 (2)
4	1 (2)	1 (2)
Remission	0 (0)	5 (9)
Total	53	53

Stage 1A

Twenty-one patients (40%) were initially diagnosed to be at stage 1A; 12 were treated with topical steroids and Narrow-band Ultraviolet light B (NBUVB), 3 with topical steroids, only, and 6 with a combination of treatment modalities that included topical steroids, NBUVB and bexarotene, topical alkylating agents, retinoids, and Psoralen-ultraviolet light A (PUVA) or methotrexate, as necessary.

Eight achieved remission at some point during the disease course. Time to remission was from 7 to 56 months (mean: 23 months), and the remission period lasted from 1 to 44 months (mean: 16 months). Five of these patients received NBUVB and topical steroids; carmustine was added to the treatments of 2 patients, and 1 patient received only topical steroids. At the time of the study, 15 patients remained at this stage (1A), 3 progressed to stage 1B, and 3 were in remission.

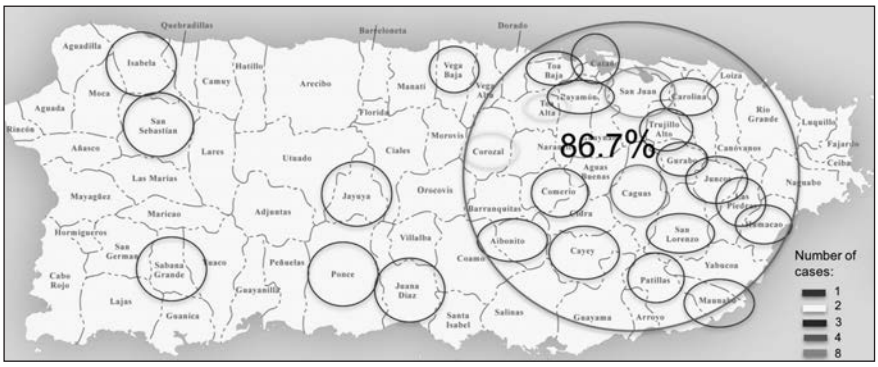

Figure 1. Geographic distribution of patients with MF

Stage 1B

Twenty-eight patients (52%) were at stage 1B, at the moment of diagnosis. Seventeen patients were treated with topical steroids and NBUVB. Four patients also received bexarotene, and 7 received different treatments, such as mechlorethamine, methotrexate, carmustine, PUVA, interferon, or a combination of any 2 or more of the previous. A total of 8 patients achieved

remission at some point during their disease course. The time to remission ranged from 7 to 56 months (mean: 25 months), and their remissions lasted from 1 to 19 months (mean: 8 months). Six patients received NBUVB combined with topical steroids, while the other 2 also received either bexarotene or carmustine and MTX. At the time of the study, 20 patients remained at stage 1B, 5 improved to stage 1A, 1 progressed to stage 2B, and 2 were in remission.

Stages 2 to 4

One patient was at stage 2B and was administered 8 different treatment modalities; this patient did not experience disease progression. Another patient, at stage 3, received topical steroids and methotrexate and experienced stable disease. One patient was at stage 3A and remained at this stage while being treated with a combination of topical steroids, bexarotene, and methotrexate. One patient was at stage 4 and was administered 6 different treatment modalities, including romidepsin; this patient did not experience disease progression.

Disease progression

During the course of their disease, 6 patients progressed in severity, with the timespan of their progression occurring over a period of 11 to 89 months (mean: 65 months). Four of these patients (67%) were male with a mean age of 52 years. They all received topical steroids combined with NBUVB, and other topical and systemic therapies were added as needed.

Treatment

Table 2 depicts the treatment modalities used. All the patients received topical steroids, 47 (89%) received NBUVB, and 5 (9%) received PUVA. One (2%) patient, who had a history of in situ melanoma, did not receive any type of phototherapy. Oral bexarotene was used by 13 (25%) patients, followed by methotrexate, which was used by 11 (21%) patients.

Table 2. Treatment modalities used in our population

Treatment	N (%)	Stage	Side effects
Topical steroids	53 (100)	1–4	
NBUVB	47 (87)	1	lupus (1)
Oral bexarotene	13 (24.5)	1, 3, 4	↑TG (5), ↑LFT (1), GI upset (2), muscle spasms (1), altered thyroid fn (1), dizziness (1)
Methotrexate	11 (21)	1–4	↑LFT (2), no response (2)
PUVA	5 (9)	1, 2, 4	
Topical mechlorethamine	5 (9)	1B	irritation (2)
Topical carmustine	5 (9)	1, 2B	
Topical bexarotene	3 (5.6)	1	ACD (1)
Interferon alpha-2b	2 (4)	1B, 2B	↑LFT (1)
Tazarotene gel	1 (2)	2B	
Acitretin	1 (2)	1	
Romidepsin	1 (2)	4	

ACD: Allergic contact dermatitis; fn: function; GI: gastrointestinal; LFT: liver function test; NBUVB: Narrow-band ultraviolet light B; PUVA: psoralen–ultraviolet light A; TG: triglycerides

Discussion

MF is a chronic condition with an overall good prognosis when diagnosed at an early stage. However, it can impose a significant economic burden and impact quality of life on those who suffer from it. We aimed to describe the patient population with MF in PR. A total of 53 patients were studied and followed for a mean period of 7 years. From this total, 39 patients remained stable, 10 improved, and 4 progressed during the disease course.

Our study showed there to be generally similar trends in new cases from 2000 through 2008, 2009 through 2013, and 2014 through 2016. An isolated case was diagnosed in 1999, likely because of both the retrospective nature of the study and the change from paper to electronic medical records. While a sustained increase in CTCL has been reported since 1970, our findings are more consistent with those presented by Korgavkar et al, which showed a stabilization of MF incidence in 1998 with a joinpoint year or statistically significant trend change in 1984 (9). While the cause of this trend change remains unknown, it could be due to improvements in physician detection or the true stabilization of incidence (9).

A majority of MF cases were identified as originating on the northern side of the island, mainly in the municipalities of San Juan, Carolina, Trujillo Alto, Bayamón, Gurabo, Juncos, Toa Baja, and San Lorenzo. These findings follow a similar trend of geographic clustering in different populations described in Texas, Saudi Arabia, and Kuwait (4). This clustering may be explained by an unknown environmental trigger (10). However, in our case, we believe clustering could be occurring because of referrals to our academic center, in San Juan (a city located in the northern part of the island). Therefore, additional studies are required for further geographic characterization.

Previous studies have shown that being older than 60 years old is considered a poor prognostic factor (7). Even though we were not able to measure overall survival due to the retrospective nature of the study, we did observe that 32% of our study population was older than 60 years old, and most of them were at an early disease stage during the study period and had no significant disease progression. Most of them were staged at 1A or 1B; 1 patient was at stage 3 and remained stable, while another experienced disease progression from 1A to 1B. We suggest that being a relatively older age (e.g., over 60 years) may not be a negative factor in our population.

Comparing our actual population with that described 15 years earlier by Berlingeri et al, we found that the average age at diagnosis was similar, 54 and 58, respectively (6). These results are parallel to those of other studies in the United States, which describe the average age at diagnosis as being from 55 to 60 years.

The vast majority (92%) of patients were diagnosed with stage 1 disease and either remained at that stage or improved, which is similar to what was observed by Berlingeri et al (6). In our study, 4 patients progressed during their disease course, with a mean time of 5 years—compared to 3 years observed in the

previous study (Table 3) (6). In the study population described by Berlingeri et al, three patients died from the progression of their lymphoma (6), while we did not observe any deaths. This finding is accounted for by the fact that we excluded patients lost to follow-up and were unable to register any deaths.

In regards to treatment, skin-directed therapies such as phototherapy continue to be the first-line treatment for early stage disease (5,6). Some studies recommend the use of PUVA over NBUVB for thick plaques or folliculotropic involvement because of the superior penetration by the former of the skin (8). However, PUVA's adverse effects may include the development of squamous cell carcinoma and melanoma. Therefore, NBUVB is often used as a first-line option for patients with early-stage disease because of its similar efficacy, wider availability, and decreased risk of cancer and other adverse effects, compared to PUVA.(11) Contrary to what was reported by Berlingeri et al (6), in our study, NBUVB was widely used over PUVA, reflecting its equal efficacy with diminished adverse effects. In addition, bexarotene and methotrexate were favored over more aggressive therapies, such as interferon and radiotherapy (Table 3) (6).

Table 3. Study comparison

Our study	Berlingeri et al 2007	
	(1999–2016)	(1983–2002)[1]
	N = 53	N = 30
	n (%)	n (%)
Mean age at diagnosis	54	58
Stage 1A or 1B disease	49 (92)	24 (80)
Remained stable or improved	49 (92)	24 (80)
Disease progression	4 (8%)	3 (10)
Lymphoma-associated deaths	0	3
Mean time to progression	5 years	3 years
Treatment modalities		
Multimodal therapy	53[a] (100)	29[b] (97)
Systemic retinoids	14 (26)	7 (23)
Methotrexate	11 (21)	2 (7)
Topical alkylating agents	10 (19)	3 (10)
PUVA	5 (9)	21 (7)
NBUVB	47 (89)	9 (30)
Topical retinoids	3 (6)	0 (0)
Interferon	2 (4)	8 (27)
Systemic chemotherapy	1 (2)	1 (3)
Radiotherapy	0 (0)	3 (10)
Systemic steroids	0 (0)	1 (3)
Electron radiation	0 (0)	1 (3)

[a]NBUVB and topical steroids, [b]PUVA and topical steroids

Our study has several limitations, such as its retrospective nature (with non-standardized documentation), its having a study population that was localized to 1 clinic, and its excluding of patients lost to follow-up. The study design and small sample size also contributed to the inability to both evaluate outcomes and include inferential statistics for further population comparisons. Finally, both Berlingeri et al's study and our study included patients evaluated from 1999 through 2002 at the same clinic. As such, there is a chance that there are some duplicated cases. However, in our study only 1 patient was identified during this timespan.

In summary, our results show the chronic and indolent course of disease, with an overall good prognosis at the early stages. These findings are consistent with those described by Berlingeri et al, whose data are from 15 years earlier (6). Similar to what was seen in the studies of Berlingeri et al (6) and Su et al (5), the majority of patients were in an early stage of disease, either 1A or 1B. Therefore, an early diagnosis and prompt treatment can significantly impact prognosis, thus reducing disease burden.

Resumen

Objetivos: Describir la población de pacientes con micosis fungoides (MF) en Puerto Rico en términos demográficos, evolución de la enfermedad y manejo. Métodos: Se realizó una revisión retrospectiva de los expedientes de pacientes con MF que se siguieron en las clínicas de dermatología de la Universidad de Puerto Rico entre el 1999 y 2016. Los datos recolectados incluyeron información demográfica, edad y estadio al momento del diagnóstico, tiempo de seguimiento, tratamiento y estadio actual. Resultados: Un total de 53 pacientes fueron diagnosticados entre el 1999 y 2016 con un período de seguimiento promedio de 89 meses. De esos, 45% fueron hombres. Al momento del diagnóstico, 40% se encontraba en estadio 1A y 53% se encontraba en estadio 1B, mientras que 7% se encontraba en estadios 2-4. Al momento del estudio, 74% permanecieron estables, 18% mejoraron y 8% progresaron de estadio. Las modalidades de tratamiento variaron desde fototerapia, esteroides tópicos, retinoides tópicos y sistémicos, metotrexato, quimioterapia tópica y sistémica e interferón. Conclusión: Los resultados reflejan el curso crónico e indolente de MF con un buen pronóstico cuando es diagnosticado en estadios tempranos, tal cual se ha demostrado en la literatura reciente. La información contenida en este manuscrito podría contribuir a la comprensión y caracterización de MF en pacientes puertorriqueños.

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