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"HYPOPIGMENTED MYCOSIS FUNGOIDES: EPIDEMIOLOGICAL, CLINICAL, HISTOLOGICAL FACTORS AND TREATMENT RESPONSE IN A 48-CASE RETROSPECTIVE SERIES¨

TRABAJO DE INVESTIGACIóN CLÍNICO PRESENTADO POR:

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ABSTRACT

Background: Hypopigmented mycosis fungoides (hMF) is a rare mycosis fungoides subtype, therefore, epidemiological aspects and treatment response are not yet well established.

Methods: A retrospective cohort in a Dermatology reference center in Mexico City was done between 2007-2018 to determine the epidemiological, clinical, histological ad therapeutic aspects of this entity.

Results: 48 patients were included in this study; most of them were men (60%), with a mean age of 27.3 years. Phototype III was the most common phototype (68%). The trunk (89.6%) and upper extremities (89.6%) were the most affected body sites.

After starting treatment, 49.7% of the patients achieved complete remission, with an average of 8.87 months and an overall remission rate of 8.2% per 100 patients/month. PUVA and NBUVB treatments were associated with a higher percentage of remission (P 61.3%, p=0.029 and 100%, p=0.012 and, respectively). PUVA treatment proved to be the fastest to induce remission. 34% of the patients with a documented follow-up relapsed; with a mean relapse-free survival of 13.77 (IQR 4.4-22) months and an overall relapse rate of 0.89% per 100 patients/month.

Conclusions: In our sample, hMF was more frequent in men than in women; the rest of the clinical and epidemiological aspects were similar to the previous literature reported. PUVA was the most used therapy but NBUV showed a higher percentage of remission. The estimated time to remission was 8.87 months and we saw that irrespective of the treatment used, 34% of the patients relapse during follow-up.

INTRODUCTION

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma. First described by

Ryan et al. in 1973, hypopigmented mycosis fungoides (HMF) is one of the MF subtypes. Although it most commonly affects people in the second and third decades of life; [1,2] it accounts for 58-91% of MF cases in childhood.[3–7] This MF subtype is more common in phototypes IV-V, with no gender preference.[8] HMF has been reported to have a chronic but benign course a better prognosis than classic MF. [3,9] 24 25

It is clinically characterized by achromic or hypopigmented macules of different sizes and figures that can be covered by a fine scale. They are usually presented in nonexposed areas such as trunk and proximal extremities. Most cases are asymptomatic but some can be pruriginous.[3,10]

Clinical differential diagnosis includes hypochromic T-cell dyscrasia,[11] progressive macular hypomelanosis, vitiligo, indeterminate leprosy, parapsoriasis, lichen sclerous, pityriasis alba, idiopathic eruptive hypomelanosis, hypopigmented sarcoidosis.[12–14]

Diagnosis requires a clinicopathological correlation. The histologic study shows atypical lymphocytes with cerebriform-like nuclei, epidermotropism, Pautrier microabscesses and a lymphocytic infiltrate in the dermis.[12,16] Immunophenotype is typically positive for CD8.[2,15]

Regarding treatment, psoralen therapy and PUVA therapy have demonstrated complete remission in up to 90% of cases, with a mean response rate of 9.7 months.[2,17–19] NBUVB has also shown similar results.[17,20-23]

Currently, there are very few reports that document the clinical course of HMF, therefore the primary outcome was to describe the clinical characteristics and clinical course of the disease. The secondary outcome was to measure the relapse-free survival time after achieving complete remission.

MATERIALS AND METHODS

After approval by the Research and Ethics Committee of our center, we performed a

retrospective cohort study at the Phototherapy unit in ¨Centro Dermatológico Dr. Ladislao de la Pascua¨, Mexico City, over an 11 –year period from January 1st, 2007 to December 31st, 2018. Electronic charts were reviewed and 268 patients with MF were identified. Patients who possessed complete medical records, iconography and HMF diagnosis confirmed by clinical and histological exams were included. Patients with concomitant pigmentation disorders and people referred to other care facilities were excluded.

From the electronic charts, three parameters were measured:

1) Sociodemographic (gender, age, age at diagnosis)

2) Clinical manifestations (period with the disease, topography, treatment received, treatment duration, time to remission, relapse episodes).

3) Laboratory tests (histologic study, complete blood count). Not all patients had an x-ray or computed tomography because in our center there are no imaging labs.

Additionally, the following dates were recorded: the beginning of treatment, follow up visits, last follow up visit. During visits, the patient´s clinical status was classified into

1) with cutaneous dermatosis. 2) without cutaneous dermatosis.

We used SPSS v.19 and STATA 11.1 for statistical analysis. Disease-free survival was calculated from the time the patient showed no cutaneous manifestations until his/her last visit with no lesions. Time to remission was calculated from the beginning of treatment until remission of cutaneous lesions. Incidence of remission and relapse was reported by months-person. In order to evaluate the association between the sociodemographic, clinical and laboratory parameters with the remission rate at the end of the follow-up, a Kaplan Meier bivariate analysis, and a Cox analysis were used to estimate the hazard ratios, with a confidence interval of 95%. A P value less than 0.05 was considered statistically significant.

RESULTS

Cohort description

Forty-eight patients were identified. Sixty percent were men, with a mean age at diagnosis of 27.3 (SD +/- 14.6). Fitzpatrick´s phototype III (68.8%) and IV (31.1%) were the most prevalent. Topographically, trunk (89.6%) and lower limbs (89.6%) were the most affected sites, followed by upper limbs (72.9%), head (14.6%) and neck (14.6%).

Besides the hypopigmented macules, 18.8% presented erythematous plaques, 4.2% hyperpigmented macules and 10.4% infiltrated lesions/plaques. The total affected body surface was 28% (+/- 8) (Fig 1.)

Remission and treatment response rates

From all patients who were treated, 47.92% had a complete remission, with a mean time to remission of 8.87 months (IQR 6.3-13.8) and a global remission rate of 8.2% per 100 persons/month. The treatments associated with a faster remission were psoralen therapy and PUVA therapy, 61.3%, and 38.7%, respectively (p= 0.006) with a tendency to statistical significance for survival analysis with an HR 3.8 (CI 95 % 0.87-17, p = 0.075). (Table 1) (Fig 2). An optimal dose-response was seen after 19 or more PUVA sessions, with a tendency to statistical significance (61.9% vs 38.1% p= 0.08) (Fig. 3). Home treatment with PUVA therapy proved to be less effective than other treatments, with a lower probability to induce remission (22% vs 77.8, p=0.012).

Relapse and relapse rates

The global frequency of relapse rate was 34.78% with a free survival relapse rate of 13.77 months (IQR 4.4-22) and a global relapse rate of 0.89% per 100 persons/month. The multivariate analysis didn´t show any clinical findings, laboratory tests or any treatment to have a predictive value for remission or relapse rates.

DISCUSSION

The primary outcome was to determine the epidemiologic characteristics of HMF patients in a Mexican dermatology reference center between 2007 and 2018. We are aware that HMF affects younger people than classic MF. In our study, the mean age was 27.3, which is consistent with the literature reported before. (1,2,7,14). Data regarding sex distribution in hMF are highly heterogeneous, in our study we found a male predominance with 60.4% of the cases.(1,2,8,14,15) According to previous reviews, we observed that the predominant phototypes affected in the Mexican patients were phototype III and IV, in contrast to classic MF which is usually seen in lighter phototypes. (2,8,15). However, it is important to consider that this could also be due to the high prevalence of these phototypes in the Mexican population.

As described in the previous literature, the most affected topography was the trunk and lower extremities, with hypopigmented macules all of the cases. (1,7,16,25). The mean affected body surface was 28% +/- 8%, to our knowledge this data was not reported in the previous literature.

The secondary outcome was to analyze the therapy used, time to remission, the percentage of patients to achieve complete remission and relapse rate. The mean time to complete remission was 8.7 months and about half of our patients showed remission after starting treatment. It is known that hMF responds appropriately to PUVA, topical steroids and NBUVB because of its good prognosis and stage at which the diagnosis is done. PUVA treatment (combined with or without any other treatments) showed to be more effective compared to the rest of the treatments used in this study. Nineteen sessions with PUVA showed to be beneficial for the patient to achieve complete remission compared to patients who were exposed to a lower dosage. When our patients find it difficult to attend

our care facilities and it is not possible to treat them with PUVA in our center, we use heliotherapy instead (sunlight irradiation). Heliotherapy did not show to be as effective as the rest of the treatments to achieve complete remission.

Of all patients who achieved complete remission (47.8%), the global frequency relapse rate was 34.8%, with a disease-free average of 11.7 months, hence the importance of clinical follow up of patients over time. We didn´t find any clinical, histological or laboratory findings to have a predictive value for relapse rate.

Our findings must be interpreted in the context of the study; even though we did not find any larger series in the literature regarding hMF than the described on this paper, its retrospective nature and small sample size show us the necessity of future research to elucidate the characteristics and the treatment response of this disease.

In conclusion, the epidemiological and clinical findings shown in our study are similar to those found in previous literature. Among all treatment options used in this study, PUVA therapy showed to be more effective than the other ones. Nineteen or more sessions of PUVA therapy tended to the statistical significance to better induce complete remission than fewer sessions and could be suggested as a cut-off point in which this treatment starts to be beneficial for the clinical remission of the disease. Despite its indolent course, all patients with HMF should be periodically monitored because relapse is quite common.

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TABLES

Frecuency of Remission According to Therapy

Treatment	No remission		Remission		P value
	Number	Percentage (%)	Number	Percentage (%)	P
Topical Steroids	1	25	3	3	0.257
Systemic steroids	25	52.1	23	23	NS
Immunosupressive therapy	25	52.1	23	23	NS
Heliotherapy	14	77.8	4	4	**0.006**
PUVA	12	38.7	19	19	**0.012**
19 sessions of PUVA	8	38.1	13	13	**.087**
NBUVB	0	0	4	4	**0.029**
Calcineurin inhibitors	0	0	2	2	0.132
Topical retinoids	1	50	1	1	0.952
Oral retinoids	1	100	0	0	0.332

Table 1. Frequency of remission according to therapy. PUVA showed 61.3% of remission vs. 38.7%, compared to the rest of the treatments. Heliotherapy showed less efficacy for remission (22.2% vs 77.8% p=0.012).

FIGURES

Figure 1. Clinical characteristics of hypopigmetned mycosis fungoides. a. Numerous hypocromic macules on trunk and right arm b. Acromic macule, poorly delimited, on buttocks c. acromic macules on proximal segment of lower extremities d. Acromic macules on the back of the limbs.

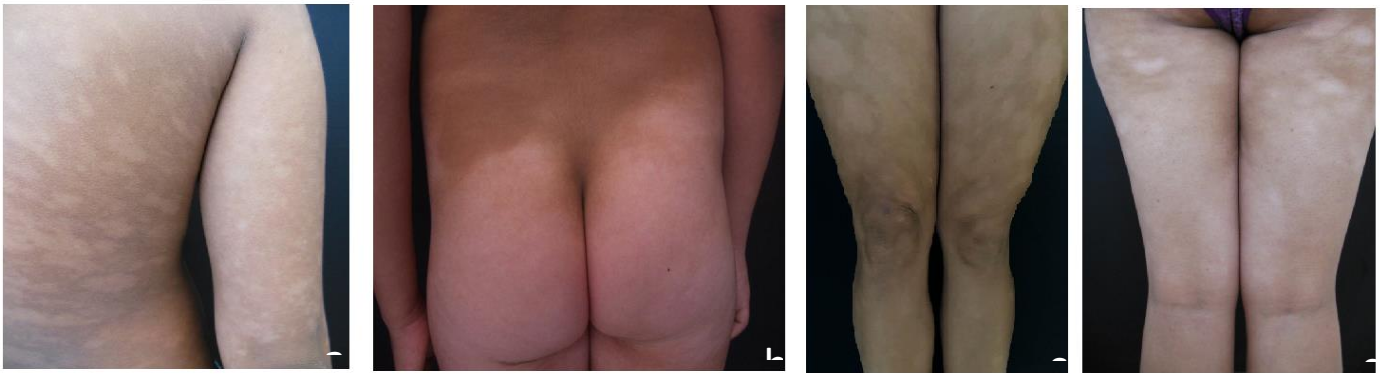
Figure 2. Kaplan Meier analysis demonstrates a superior remission rate over time using PUVA therapy compared to other treatments HR 3.8 (IC 95% 0.87 - 17, p=0.075)

PUVA: Psoralen and UVA light.

Figure 3. Kaplan Meier analysis comparing the number of PUVA sessions. Patients who were treated with more than nineteen PUVA sessions showed a better response to treatment compared to people with less than 19 sessions (61.9% vs. 38.1%, p=0.08).

PUVA: Psoralen and UVA light

Figure 1.



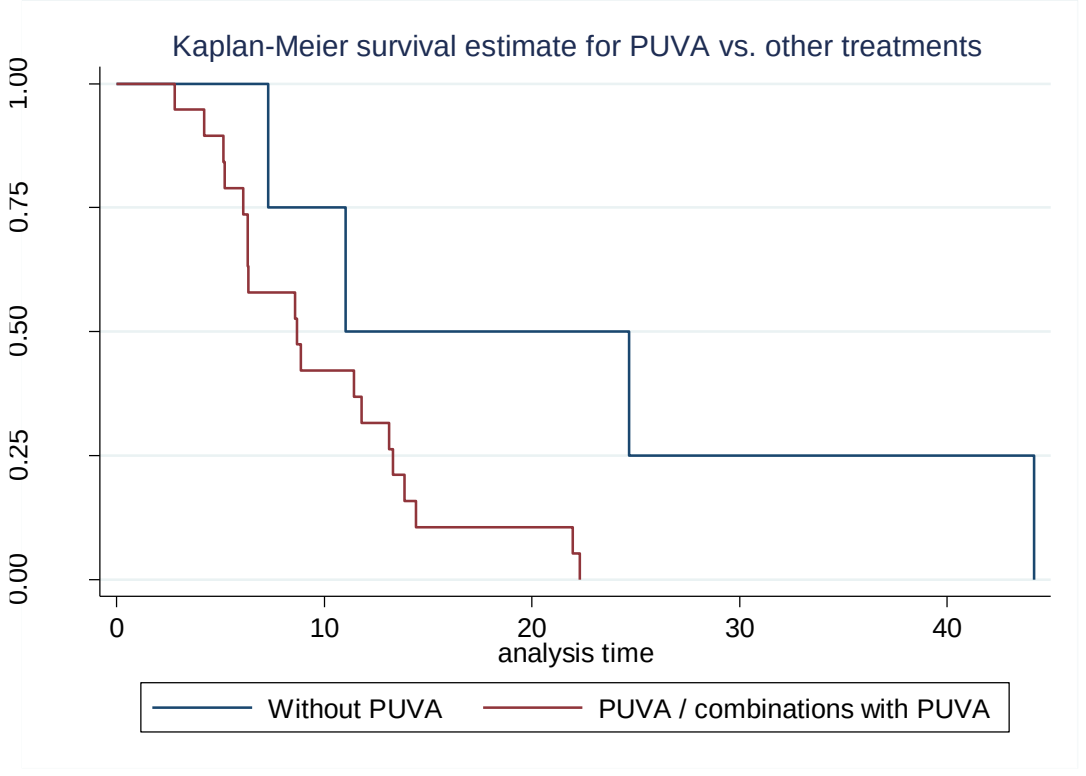
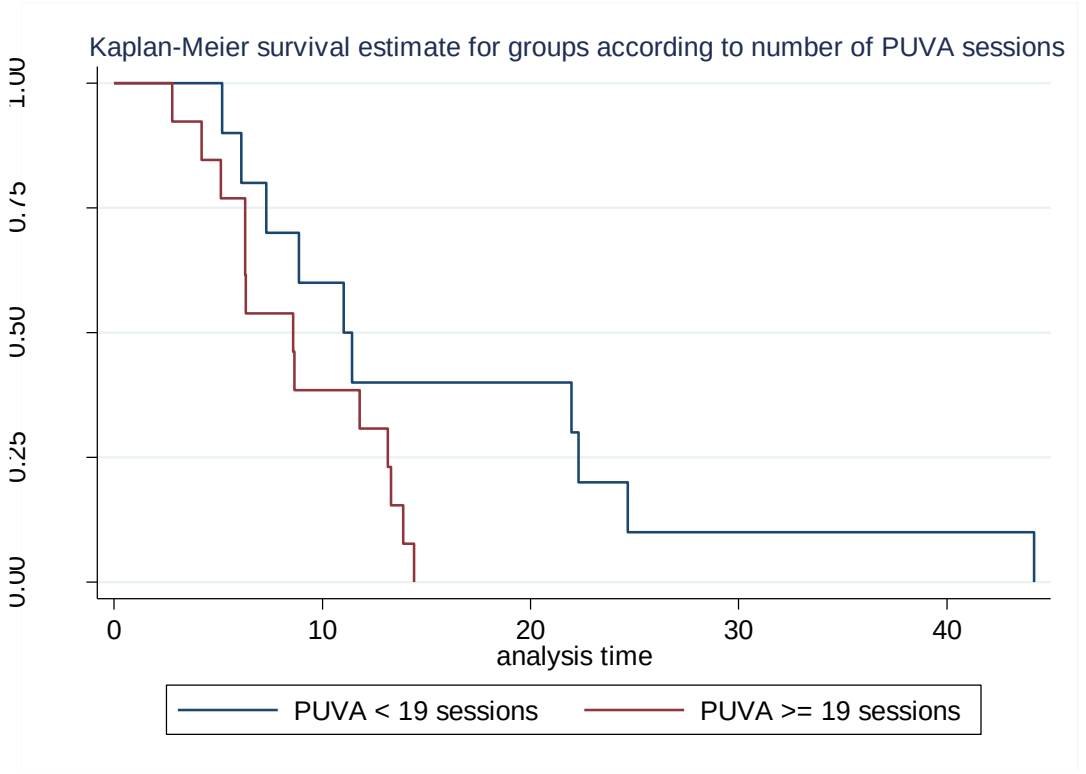


Figure 3.


Kaplan-Meier survival estimate for groups according to number of PUVA sessions
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
analysis time
PUVA < 19 sessions
PUVA >= 19 sessions