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RESEARCH ARTICLE

Study of the prevalence of Hypopigmented Mycosis Fungoides among Patients Presenting Hypopigmented Lesions

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ABSTRACT

Background: Hypopigmented mycosis fungoides (MF) is a variant of primary cutaneous T-cell lymphoma. Although the prognosis of hypopigmented mycosis fungoides is excellent, the diagnosis is usually missed.

Objective: The study aimed to identified the prevalence of patients with hypopigmented mycosis fungoides presenting hypopigmentation in Phramongkutklao Hospital, Bangkok, Thailand. We also reported the characteristic of hypopigmented mycosis fungoides among patients presenting hypopigmentation and compared clinical presentations between patients with a diagnosis of hypopigmented mycosis fungoides and patients with other diagnoses

Materials and Methods: We conducted a retrospective among 56 patients presenting hypopigmentation and receiving skin biopsies at Division of Dermatology, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand between January 2016 to December 2021. The data parameters including demographic data, clinical manifestations (symptoms, size and morphology of the lesions, e.g., scale, margin, erythema, atrophy, mottled hypopigmentation, involved body surface area and distribution, histopathologic reports, special stains, final diagnosis, further investigations, treatments, follow-up duration and result of the treatments were recorded.

Results: The prevalence of hypopigmented mycosis fungoides among patient presenting with hypopigmentation was 16.1%. Compared with patients with other diagnoses, patients with hypopigmented mycosis fungoides usually had lesions with ill-defined margins (P-value=0.045) and presence of atrophy lesion (P-value=0.023).

Conclusion: The prevalence of hypopigmented mycosis fungoides involved 16.1% of patients presenting hypopigmentation. The presence of ill-defined margins and atrophic lesions led to suspected hypopigmented MF in our study. This data could be useful in epidemiologic information and might be adapted when choosing lesions for biopsy to diagnose MF.

Keywords: Hypopigmented mycosis fungoides, hypopigmentation, prevalence

Introduction

Primary cutaneous lymphomas are a group of cutaneous T-and B-cell lymphoma that present in the skin without evidence of extracutaneous disease at the time of diagnosis.[1,2] In general, Cutaneous T-cell lymphomas (CTCLs) usually present approximately 75-80% in contrast to primary cutaneous B-cell lymphomas which present approximately 20-25% of all primary cutaneous lymphomas.[1,2]

Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphoma which account almost 60% of. CTCLs.[1,2] Generally, classic MF usually occur in old age (median age at diagnosis 55-60 years) and patients present with well-defined border erythematous patches, plaques predilection in sites of covered areas in the body (buttock, trunk, proximal portions of extremities).[1,3,4-7] The lesions can progress to tumor lesions in the late stage. A diversity of clinical presentation has been reported such as granulomatous, pustular, purpuric, hyperkeratotic, verrucous, bullous, invisible, follicular, and ichthyosiform.[4,8]

Hypopigmented MF (HMF) is a variant of MF which are frequently reported among dark-skinned and Asian patients.[4,8] Most of the report cases occurred in young age which usually occur in the 20-30-year-old of age at the time of diagnosis.[4-7,9]

The clinical manifestations in HMF are hypopigmented to depigmented lesions and mainly distributed on buttock, trunk and proximal portions of extremities.[4,10] The HMF has good prognosis. The disease is slow progression usually in patch stage and without systemic involvement.[4,8,12]

The diagnosis and classification of MF are defined by WHO-EORTC.[2] No accurate criteria have been established to diagnose hypopigmented MF. Combined clinical presentations, histopathologic features and possible immunohistochemical stains are required. Histopathologic features constitute the main criteria for diagnoses including the presence of disproportionate epidermotrophism, tagging of lymphocytes along the basal layer, haloed lymphocytes, convoluted lymphocytes, Pautrier's abscessed, larger epidermal lymphocytes, wiry dermal collagen, eccrine infiltration, folliculotropism, follicular mucin, monomorphous infiltrates and atypia of dermal lymphocytes.[4,11]

The immunohistochemical analysis frequently involves mainly CD8+ cell epidermotrophism, in contrast with classic MF predominating CD4+ neoplastic cells.[4]

Although the prognosis of hypopigmented MF is excellent, the diagnosis is usually missed. A number of patients with hypopigmented MF are misdiagnosed as vitiligo, leprosy, postinflammatory hypopigmentation, progressive macular hypomelanosis, hypochromic pityriasis versicolor etc.[12,13] Misdiagnosis leads to delayed treatment.

In this study, we report the prevalence of patients with hypopigmented MF presenting hypopigmentation in Phramongkutklao Hospital, Bangkok, Thailand. The knowledge will constitute one of the statistical resources to estimate the possibilities of hypopigmented MF among patients presenting hypopigmentation which may help lead to more effective diagnostic measures and treatments.

Material and Methods

STUDY DESIGN

We conducted a retrospective study from January 2016 to December 2021. The patients were recruited from the Division of Dermatology, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand.

INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria comprised adult patients (age ≥20 years old) presenting cutaneous hypopigmented lesions and receiving a skin biopsy at the Division of Dermatology, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand. We excluded patients without histopathologic reports and with incomplete medical records.

DEFINITION AND DATA COLLECTION

Hypopigmented MF cases were defined as patients presenting hypopigmentation and a histopathological diagnosis of MF along with the WHO classification of tumors of hematopoietic and lymphoid tissue 4th edition.[14] Complete remission was defined as repigmentation of all lesions and negative skin biopsy for at least three months.[15]

Recurrence was defined as new hypopigmented lesions during remission and positive skin biopsy for mycosis fungoides.[15]

The medical records, clinical photography and histopathologic records (examined and reported by two board-certified dermatopathologists) were reviewed and data were collected.

The data parameters comprised demographic data, clinical manifestations (symptoms, size and

morphology of the lesions, e.g., scale, margin, erythema, atrophy, mottled hypopigmentation, involved body surface area and distribution, histopathologic reports, special stains, final diagnosis, further investigations, treatments, follow-up duration and result of the treatments.

STATISTICAL ANALYSIS

The data were reported as number (%), mean ± standard deviation or median (interquartile range). Comparison between patients with hypopigmented mycosis fungoides and patients with other diagnoses was statistically analyzed using Independent samples t-test, Mann-Whitney U test, Chi-square test or Fisher's exact test.

Results

We enrolled 56 patients presenting hypopigmentation and receiving skin biopsy in our division. Their mean age of onset was 41.1 ± 18.6 years and male to female ratio was 5:2. Demographic data of patients presenting hypopigmentation are shown in Table 1.

Table 1: Demographic and clinical characteristics among patients presenting hypopigmented lesions

Characteristic	Total (n = 56)	Hypopigmented mycosis fungoides		p-value
		Yes (n = 9)	No (n = 47)	
Sex				0.100
Male	40 (71.4)	4 (44.4)	36 (76.6)	
Female	16 (28.6)	5 (55.6)	11 (23.4)	
Age (years)	41.1 ± 18.6	39.6 ± 15.6	41.4 ± 19.2	0.790
Symptoms				
Hypopigmented to depigmented patches	56 (100.0)	9 (100.0)	42 (100.0)	NA
Itch	7 (12.5)	1 (11.1)	6 (12.8)	0.999
Pain	0 (0)	0 (0)	0 (0)	NA
Numbness	0 (0)	0 (0)	0 (0)	NA
Duration (months)	6 (3 - 24)	5 (2 - 12)	9 (3 - 24)	0.494
Morphology				
Scale	9 (16.1)	2 (22.2)	7 (14.9)	0.626
Margin				**0.045**
Well-defined	18 (32.1)	0 (0)	18 (38.3)	
Ill-defined	38 (67.9)	9 (100.0)	29 (61.7)	
Erythema	33 (58.9)	4 (44.4)	29 (61.7)	0.464
Atrophy	2 (3.6)	2 (22.2)	0 (0)	**0.023**
Mottled hyperpigmentation	12 (21.4)	3 (33.3)	9 (19.1)	0.385
Telangiectasia	5 (8.9)	2 (22.2)	3 (6.4)	0.178
Size				0.603
<5	32 (58.2)	6 (75.0)	26 (55.3)	
≥5	2 (3.6)	0 (0)	2 (4.3)	
Variable (both < 5 cm and ≥5 cm in the same patient)	21 (38.2)	2 (25.0)	19 (40.4)	
Distribution				
Trunk	48 (85.7)	8 (88.9)	40 (85.1)	0.999
Head and neck	14 (25.0)	3 (33.3)	11 (23.4)	0.676
Proximal upper limbs	36 (64.3)	8 (88.9)	28 (59.6)	0.136
Distal upper limbs	22 (39.3)	5 (55.6)	17 (36.2)	0.294
Proximal lower limbs	24 (42.9)	6 (66.7)	18 (38.3)	0.151
Distal lower limbs	15 (26.8)	3 (33.3)	12 (25.5)	0.688
%BSA				**0.250**
<10	18 (32.7)	1 (12.5)	17 (36.2)	
≥10	37 (67.3)	7 (87.5)	30 (63.8)	
Previous hypopigmented MF	8 (14.3)	4 (44.4)	4 (8.5)	**0.017**
Time to biopsy (months) from onset	7.5 (3 - 24)	5 (2 - 12)	9 (3.5 - 24)	0.488
Underlying diseases	20 (35.7)	3 (33.3)	17 (36.2)	0.999
HT	8 (14.3)	2 (22.2)	6 (12.8)	0.602
DM	5 (8.9)	2 (22.2)	3 (6.4)	0.178
DLP	10 (17.9)	2 (22.2)	8 (17.0)	0.656
CKD	1 (1.8)	0 (0)	1 (2.1)	0.999
Malignancy	4 (7.1)	1 (11.1)	3 (6.4)	0.514
Other skin diseases/conditions	5 (8.9)	1 (11.1)	4 (8.5)	0.999
Provisional Diagnosis				
Hypopigmented mycosis fungoides	50 (89.3)	9 (100.0)	41 (87.2)	0.575

Characteristic	Total (n = 56)		Hypopigmented mycosis fungoides				p-value
			Yes (n = 9)		No (n = 47)		
IGH	1	(1.8)	0	(0)	1	(2.1)	0.999
PLC	2	(3.6)	1	(11.1)	1	(2.1)	0.298
Vitiligo	5	(8.9)	1	(11.1)	4	(8.5)	0.999
PIH	15	(26.8)	0	(0)	15	(31.9)	0.094
PMH	7	(12.5)	0	(0)	7	(14.9)	0.583
Contact leukoderma	1	(1.8)	0	(0)	1	(2.1)	0.999
Other	1	(1.8)	0	(0)	1	(2.1)	0.999

Data are presented as number (%), mean ± standard deviation or median (interquartile range).

P-value corresponds to [t]Independent samples t-test, [m]Mann-Whitney U test and [f]Fisher's exact test.

**BSA = body surface area, HT = hypertension, DM = diabetes mellitus, DLP = dyslipidemia, CKD = chronic kidney disease, IGH = idiopathic guttate hypomelanosis, PLC = pityriasis lichenoides chronica, PIH = post inflammatory pigmentary change, PMH = progressive macular hypomelanosis*

Of the 56 patients, 9/56 patients (16.1%) received a diagnosis as hypopigmented MF. Other diagnoses consisted of postinflammatory pigmentary change (20/56 patients; 35.7%), followed by progressive macular hypomelanosis (11/56 patients; 19.6%), vitiligo (3/56 patients; 5.4%), idiopathic guttate hypomelanosis (2/56 patients; 3.6%) and others (6/56 patients; 10.7%), as shown in Table 2.

Table 2: Final diagnosis among patients presenting hypopigmented lesions

Diagnosis	N	(%)
Final Diagnosis		
Hypopigmented mycosis fungoides	9	(16.1)
IGH*	2	(3.6)
PLC*	0	(0)
Vitiligo	3	(5.4)
PIH*	20	(35.7)
PMH*	11	(19.6)
Contact leukoderma	0	(0)
Other	6	(10.7)

**IGH = idiopathic guttate hypomelanosis, PLC = pityriasis lichenoides chronica, PIH = post inflammatory pigmentary change, PMH = progressive macular hypomelanosis*

All the patients with hypopigmented MF (9 patients), their mean age was 39.6 ± 15.6 years old. Male to female ratio was 4:5. Four of 9 patients (4/9 patients, 44.4%) received a diagnosis of recurrent hypopigmented mycosis fungoides.

All patients (9/9 patients; 100%) presented hypopigmented to depigmented patches of whom 8/9 (93.3%) patients were asymptomatic. Only 1/9 patients (11.1%) presented itchy hypopigmented to depigmented patches, while no patients experienced pain or numbness at the lesions. Mean duration of onset was five months (1 to 120 months).

According to lesion morphologies, all patients exhibited ill-defined margin (9/9 patients; 100%). Erythema, atrophy, mottled hyperpigmentation and telangiectatic change were observed among 4/9 patients (44.4%), 2/9 patients (22.2%), 3/9 patient (33.3%) and 2/9 patients (22.2%), respectively, as shown in Table 1. Only atrophy appearance was presented in one patient with hypopigmented MF significantly, compared with patients with other diagnoses.

Most patients had lesions that were smaller than 5 cm (6/9 patients; 75%) and 2/9 patients (25%) had lesions that were <5 cm and ≥5 cm in the same individuals. No patient had lesion ≥5 cm solely. Most patients with hypopigmented MF (7/9 patients, 87.5%) presented lesions ≥10% BSA similar to patients with other diagnoses as shown in Table 1.

The lesions were most commonly noted on the trunk (8/9 patients; 88.9%) and proximal upper extremities (8/9 patients; 88.9%) followed by the proximal lower extremities (6/9 patients; 66.7%), distal upper extremities (5/9 patients; 55.6%), distal lower extremities (3/9 patients; 33.3%) and head and neck (3/9 patients; 33.3%).

All nine patients received skin biopsies which had histologic findings compatible with mycosis fungoides. Histologic findings of patients consisted of epidermotrophism (8/9; 88.9%), monomorphous lymphocytes and haloed lymphocytes (6/9; 66.7%), larger epidermal lymphocytes (6/9; 66.7%) and basilar tagging of lymphocytes (5/9; 55.6%).

Immunohistochemistry (IHC) stains was performed in only one patient (1/9; 11.1%). The IHC showed positive both CD4 and CD8 and loss of CD2, and CD7 expression.

Eight patients (8/9; 88.9%) were investigated for systemic involvements including computer tomography neck/chest/ whole abdomen scan or whole abdomen ultrasonography which were all negative for systemic involvement. All patients received hematologist consultation. Bone marrow aspiration/ biopsy was decided and performed among three patients (3/9; 33.3%) by hematologists showing normal results. Peripheral blood investigation for basic laboratory results (complete blood count, liver function test, renal function test and lactate dehydrogenase) was performed among nine patients and all were normal.

Among nine patients with hypopigmented MF, almost all were in early stage which comprised stage IB among six patients and stage IA among two patients. One patient was lost to follow up after skin biopsy and did not receive any investigation for staging.

Time of follow up ranged from 0.5 to 38 months. Eight patients received phototherapy consisting of narrow band UVB (NBUVB) combined with topical steroid and/or oral acitretin. Three patients were lost to follow-up (3/9, 33.3%) after diagnosis and started treatment in the duration of 0.5 to 4 months. Only five patients obtained complete treatments and follow-up. One patient did not receive any treatment due to being lost to follow-up after receiving skin biopsy.

Five patients, receiving complete treatment and follow-up (5/9, 55.6%), received skin biopsy after complete clinical clearance showing negative for atypical cells. Mean follow-up duration was 4.8 months.

Compared with patients revealing other diagnoses, patients with hypopigmented MF usually had lesions with ill-defined margins (P-value=0.045) and presence of atrophy lesion (P-value=0.023) as shown in Table 1.

Discussion

Hypopigmented MF is a variant of MF which is usually found among dark-skinned and Asian patients.[4,8] Unlike conventional MF, hypopigmented MF usually begins in childhood and has excellent prognosis.[4,8,12]

However, the diagnosis is difficult due to frequent misdiagnoses of other hypopigmented diseases such as vitiligo, leprosy and postinflammatory pigmentary change, etc.[14]

The prevalence of hypopigmented MF among patients with MF is around 10.8% among Chinese, 30% among Indians and 42.6% among Thais.[14-16]

Few studies have reported the prevalence of hypopigmented MF among patients presenting hypopigmented lesions.[16-18]

In our study, the prevalence of patients with hypopigmented MF presenting hypopigmented lesions was 16.07% similar to related studies from Abdel-Halim M, et al for which the presence of 16% of hypopigmented MF was noted among patients presenting hypopigmented lesions.[18]

The mean age of hypopigmented MF among our patients was 39.6 ± 15.6 years. Male to female ratio was 5:2 showing a male predilection.

Our patients possessed a higher age of onset and male predilection differing from a related report from Thailand reporting a younger age of onset (median age 21.5 year) and female predilection.[19]

Nevertheless, worldwide reports included variables regarding mean age of onset and sex ranging from the second to fourth decades of life.[8,12,15,16,20,21] Male predilection was commonly observed in many related studies.[8,12,16,17] Some reports had no sex predilection and few cases had female predilection.[15,18,20,21]

The differentiation can be explained by the differences in patient populations. Our hospital comprises a military hospital which usually has male predilection and our data did not include pediatric populations.

According to clinical manifestations, compared with patients with other hypopigmented disorders, ill-defined margins and atrophy were significantly frequent among patients with hypopigmented MF. Most of the hypopigmented MF cases indicated non-scaly hypopigmented lesions similar to related reports that most cases of hypopigmented MF had non-scaly ill-defined border hypopigmented lesions.[8,15,20,21]

Atrophic change was significantly frequent in hypopigmented MF as reported in our study compare with other diagnoses having less mention in prior reports.[16]

Our study found no significant difference in erythema, mottled hyperpigmentation and telangiectasia in the two groups.

Regarding size, most patients had skin lesions smaller than 5 cm involving ≥10% of body surface area. Our result contrasted that of a related study reporting a significantly higher prevalence of large sized lesions (>5 cm) among patients with hypopigmented MF.[18]

Our study showed that the distribution mostly involved the trunk and proximal upper extremities followed by the proximal lower extremities. Compared with patients in other diagnoses, the distribution of lesions involving the two groups revealed no statistical significance. In contrast to a related study showing the distribution in distal upper and proximal lower limbs, significant findings could be compared with other hypopigmented lesions.[18]

Nevertheless, the distribution of HMF in our study was similar to related reports of HMF which usually affected the trunk and extremities.[4,8,15,16,20,21]

Our study found only one cases having IHC stains revealing positive results for both CD4 and CD8 and loss of CD2 and CD7 expression. The diagnoses were made from classically histopathologic features of MF. The typical immunophenotypes involving classic MF comprised CD2+, CD3+, CD5+ CD4+ and CD8-.[14]

However, in HMF, several authors have shown predominant CD8+ cell epidermotrophism.[4,5,22,23] Nevertheless, some papers presented the typical immunophenotype features of predominance of CD4+ T cells and preservation of a normal ratio of CD4+ and CD8+ T cells in HMF.[4,6,16]

Four patients had recurrent diseases, which can be explained in that they did not present IHC stain results in the second biopsy. One case was lost to follow-up after skin biopsy. The three remaining cases, indicated no explanation in the medical records for reason of not receiving IHC stains.

Eight patients received phototherapy which consisted of NBUVB combined with topical steroid and/or oral acitretin. Five patients were noted as having complete remission after treatment duration three to nine months. All received complete clinical examination and skin biopsy to diagnose complete remission. Compared with complete remission in other reports of early stage mycosis fungoides, our study indicated a shorter duration of remission.[24,25] Four of five patients (4/5 patients, 80%) with complete remission presented recurrence diseases after 7 to 11 months (mean 8.5 months) of follow up period. All the recurring diseases at the same stages (IA to IB) of primary diagnosis without systemic involvement.

The rate of recurrence in our study was higher compare with that of related studies.[2,8,15,17,18,20,21,24-26]

This may be explained from our small number of the patients. Four of the patients received a diagnosis of recurrent hypopigmented MF, involving regular follow-up. This may have resulted in early diagnoses of recurrence and early treatment which may have caused a shorter period of complete remission. Another explanation may have involved a too early diagnosis of remission. We assume that some patients did not have complete remission. They received early skin biopsy without waiting at least three months after clinical remission and received early stop treatment which could explain the shorter complete remission and higher rate of recurrence.

No patients died during the study.

Limitations

Due to the retrospective study design, limitations were encountered to identify causal relationships and to collect the complete clinical symptoms and signs which actually restricted what could be literally described in the medical records.

A lack of complete work up and IHC stains were noted in some of the cases as well as a shorter follow-up time.

The small number of hypopigmented MF cases, compare with other diagnoses might have made the result insignificant and limited beneficial outcomes.

We include all cases of recurrent hypopigmented MF presenting with hypopigmentation in this study.

This will affect some parts of the results, including the received IHC stains.

Conclusion

The prevalence of hypopigmented mycosis fungoides involved 16.1% of patients presenting hypopigmentation. The presence of ill-defined margins and atrophic lesions led to suspected hypopigmented MF in our study. This data could be useful in epidemiologic information and might be adapted when choosing lesions for biopsy to diagnose MF.

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