Hypopigmented Mycosis Fungoides: A Report of 7 Cases and Review of the Literature

Melody L. Stone, BS, Kansas City, Missouri
Angela R. Styles, MD, Dallas, Texas
Clay J. Cockerell, MD, Dallas, Texas
Amit G. Pandya, MD, Dallas, Texas

Over the last 2 decades, hypopigmented macules have been reported with increasing frequency as an initial presentation of mycosis fungoides (MF). We retrospectively reviewed 7 patients with hypopigmented MF. The mean age was 35 years at disease onset, with a mean of 5.5 years' duration of illness before presentation. All of our patients were Fitzpatrick skin type IV or V, and most reported pruritus. Histologic findings in all cases were consistent with MF. Treatment with topical nitrogen mustard produced repigmentation in 4 of 6 patients.

Because of its similarity to other hypopigmentation disorders, mycosis fungoides (MF) should be included in the differential diagnosis of hypopigmented macules. Topical nitrogen mustard appears to effectively induce remission in patients with stage I disease.

MF is a malignancy of T cells that presents in the skin, usually in the form of scaly plaques, papules, nodules, tumors, or erythroderma. Cutaneous pigmentary changes associated with MF, occasionally occurring in the form of hypopigmentation, have been described over the last 3 decades.[1,2] In the past, hypopigmentation was not believed to be a true presentation of MF unless accompanied by poikiloderma or following therapy.[2-5] However, more recently, a purely macular hypopigmented form of MF has been reported in the literature with increasing frequency.[3-10] Once thought to occur exclusively in dark-skinned individuals, this unique mode of presentation has now been reported in Caucasians as well.[11-13] We describe 7 patients with hypopigmented MF, one of whom had an unusually aggressive course that resulted in death (Table 1). Most of our patients were treated with topical nitrogen mustard.

Ms. Stone is a medical student at the University of Missouri, Kansas City School of Medicine. Dr. Styles, Dr. Cockerell, and Dr. Pandya are from the Department of Dermatology, University of Texas Southwestern Medical Center, Dallas.
Reprints: Amit G. Pandya, MD, Department of Dermatology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9069.

Case Reports

A summary of our patients is presented in Table 1. Two selected patients are presented.

Patient 1—A 36-year-old black male presented with a more than 10-year history of slightly pruritic, hypopigmented macules on his arms, legs, and trunk, involving approximately 40% of his total body surface area (Figure 1). The lesions were poorly circumscribed, and a few were slightly atrophic. Initial laboratory data included a normal complete blood cell count and liver function tests. The patient had no lymphadenopathy, and the remainder of the physical examination was normal. He was started on topical nitrogen mustard ointment, and at follow-up 6 months later, the patient demonstrated slight repigmentation in affected areas. He was subsequently lost to follow-up.

Histologic examination of a skin biopsy specimen demonstrated a bandlike infiltrate of atypical mononuclear cells in the papillary dermis, with prominent exocytosis. There was minimal pigmentation of the epidermis (Figure 2). These findings were diagnostic of hypopigmented MF.

Patient 2—A 56-year-old black female presented with pruritic, slightly scaly hypo- and hyperpigmented macules, patches, and plaques on her arms, legs, trunk, face, scalp, and buttocks (Figure 3). Approximately 40% of her total body surface area was affected. The patient stated that she first noticed "ringwormlike" skin lesions on her anterior upper chest approximately 34 years previously. The lesions

Table 1.

Summary of Patients*

Case No.	Age, y	Race	Sex	% TBSA Involvement and Distribution	Duration of Symptoms	Treatment	Course
1	36	Black	M	40% arms, legs, trunk	>10 y	NM	Slight repigmentation at 6 mo, subsequently lost to follow-up
2	56	Black	F	40% arms, legs, trunk, face, scalp, buttocks	>30 y	NM	2 y postdiagnosis, patient progressed to plaques, tumors, and death
3	28	Latin-American	M	20% legs, arms, trunk	1 y	PUVA	Lost to follow-up
4	41	Black	F	30% back, buttocks, legs, left thigh	>10 y	NM	Slight repigmentation, stable
5	30	Black	F	5% neck/submental area	3 y	NM	Lost to follow-up
6	51	Black	M	10% arms, legs, thighs, trunk, buttocks	4 y	NM	Slight repigmentation, stable
7	62	Black	F	20% hips, buttocks, trunk	6 mo	NM	Slight repigmentation, stable

*TBSA indicates total body surface area; M, male; F, female; NM, nitrogen mustard (topical ointment); PUVA, psoralen and ultraviolet A phototherapy.

would wax and wane but were not pruritic. Seven years prior to presentation, the lesions began to spread and became pruritic. One year before presentation, she developed flulike symptoms, followed by a rapid growth of the cutaneous lesions.

Histologic examination of 2 punch biopsy specimens from the right thigh and shoulder revealed slight hyperkeratosis, parakeratosis, acanthosis, slight spongiosis, and marked exocytosis of lymphocytes in the epidermis, with a superficial dermal perivascular infiltration of lymphocytes and histiocytes (Figure 4). The lymphocytes appeared atypical, with hyperchromasia and nuclear enlargement. The histologic findings were diagnostic for MF. No lymphadenopathy or organomegaly was present, and laboratory examination revealed anemia but normal liver function tests. Based on a diagnosis of stage I patch and plaque stage MF, she

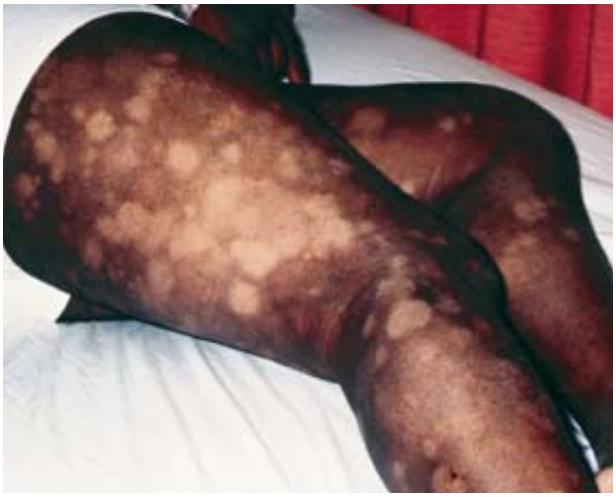

Figure 1. Multiple hypopigmented macules on the legs of patient 1.

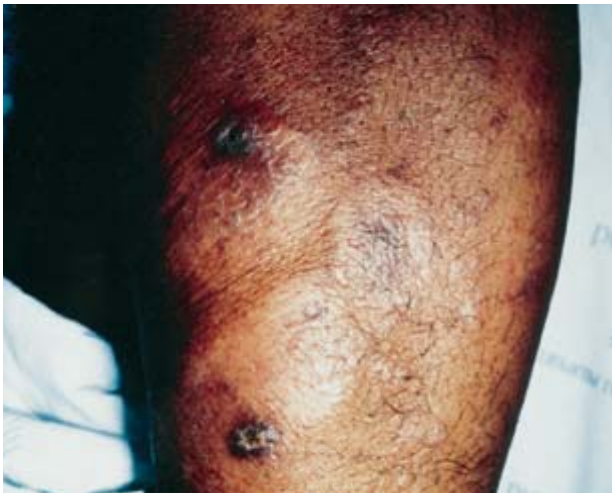

Figure 3. Hypopigmented macules and plaques on the arm of patient 2.

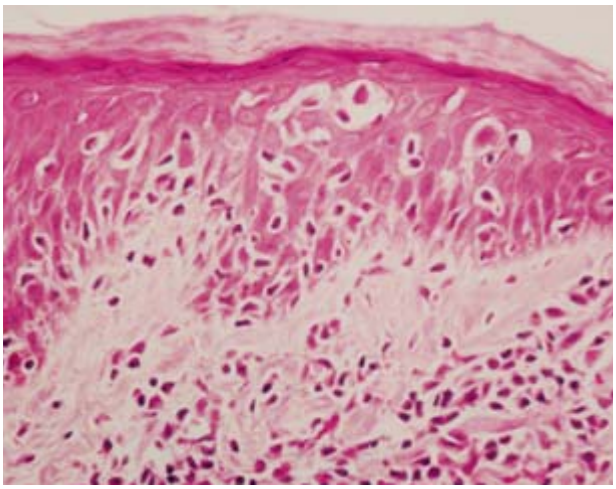

Figure 2. Atypical mononuclear cells in the papillary dermis with prominent exocytosis (patient 1) (H&E, original magnification ×200).

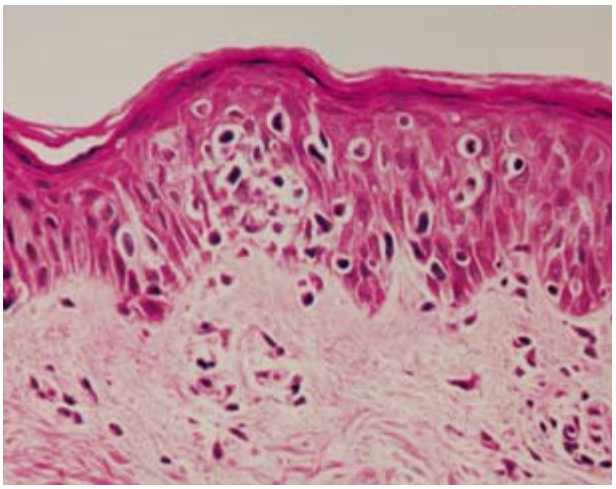

Figure 4. Exocytosis of atypical mononuclear cells, with a Pautrier's microabcess in the epidermis (patient 2) (H&E, original magnification ×100).

was started on topical nitrogen mustard ointment daily for the entire body surface area.

Approximately 2 years later, the patient presented with a 2- to 3-month history of generalized erythematous plaques, nodules, and tumors in the previous areas of hypopigmentation. The patient had developed otitis media, thrush, and severe infection with genital herpes simplex virus. Chest x-rays showed generalized lymphadenopathy and bilateral infiltrates. An assay for human immunodeficiency virus was negative, and bronchoscopy failed to reveal malignant cells or infection with *Pneumocystis carinii*, tuberculosis, or fungus. It was thought that her lung disease was due to lymphomatous spread from her cutaneous T-cell lymphoma. The patient subsequently progressed to acute respiratory distress syndrome and died. Permission to perform an autopsy was denied.

Comment

Hypopigmented MF is a unique clinical entity distinct from poikiloderma or pigmentary changes that may develop in resolving MF lesions. It affects predominantly dark-skinned individuals. However, a few Caucasian patients have been reported.[11-13]

Immunophenotypic analysis of the infiltrating lymphoid cells in hypopigmented MF demonstrates a predominance of $CD4^+$ T cells, similar to what is seen in the usual forms of MF.[4,6,13,14] Other studies on subset populations of T cells in MF lesions report an admixture or predominance of suppressor/cytotoxic T cells, which suggests a benign inflammatory dermatosis.[9,15] It has been suggested by Rustin et al[15] that T-suppressor lymphocytes might play an immunoregulatory and suppressive role in the disease process before the onset of more aggressive disease. Such

Table 2.

Comparison of Hypopigmented Mycosis Fungoides and Patch and Plaque Stage Mycosis Fungoides*

	Hypopigmented MF		Patch and Plaque MF
	Present Report (n=7)	Previous Reports[3-15] (n=20)	
Average age of onset, y	35	28	6th decade
Average duration of illness before presentation, y	5.5	5.7	4.9[17]
Sex (M:F)	0.75:1	1:1	2.2:1[18]
Race			
Black/brown	100%	93%	15%[18]
Caucasian	0%	7%	85%
Pruritus	85%	30%	Frequently reported
Lymphadenopathy	0%	9%	None
Results of treatment			
Nitrogen mustard	6/7 (85%) repigmentation in 4 patients	3/20 (15%) repigmentation in all 3 patients	Complete response in 51%–80%[17,19-21]
PUVA	1/7 (14%) lost to follow-up	13/20 (65%) repigmentation in 12 patients	Complete response in 58%–88%[22-24]
Electron beam radiation	0%	1/20 (5%) repigmentation achieved	Complete response in >90%[25-27]

*PUVA indicates psoralen and ultraviolet A phototherapy.

suppression would help to explain the long history of the disease in some cases before diagnosis.[15]

The actual mechanism of the hypopigmentation in this form of MF is still unknown. Breathnach et al[5] postulated that atypical lymphoid cells infiltrating the epidermis caused melanocytic degeneration. They found no evidence of a block in the transfer of melanosomes from melanocytes to keratinocytes. Using electron microscopy, they found intraepidermal and dermal edema and abnormalities in melanocytes, such as swelling of cytoplasmic organelles, mitochondria with loss of cristae, dilation of rough endoplasmic reticulum, and cytoplasmic vacuolation. Disordered melanogenesis with the production of spherical, incompletely melanized melanosomes was noted, and keratinocytes were found to contain cytoplasmic vacuolation with a normal number of melanosomes. They concluded that these changes appeared to be caused by a nonspecific response to cell injury associated with inflammation.[5] This response may be related to ischemia secondary to disruption of normal epidermal architecture by the accumulation of intraepidermal and dermal edema fluid in MF lesions.

Other researchers have noted some of the same degenerative changes within cells but point out that these changes are not specific for MF and also have been observed in association with leprosy, pityriasis versicolor, idiopathic guttate melanosis and halo nevi.[13,15] Goldberg et al[3] reported a decrease in the number of normal-appearing melanosomes within keratinocytes (1–2 melanosomes/keratinocyte), with abundant and intact melanosomes in adjacent melanocytes. They found no degenerative changes in melanocytes but suggested a defect in the transfer of melanosomes from melanocytes to keratinocytes, in direct contrast to the findings of Breathnach et al.[5] In addition, Goldberg et al[3] studied a biopsy from repigmented normal-appearing skin after treatment with nitrogen mustard and found numerous normal-appearing melanosomes within keratinocytes; this led to the hypothesis that nitrogen mustard, in addition to resolving the lesions of MF, may reverse the defect in the transfer of melanosomes and activate melanocytes to repigment the hypopigmented areas.

Flaxman et al[16] noted an increased number of melanosomes within keratinocytes in the skin of patients with MF after topical therapy with nitrogen mustard. Others have reported an increased number of Langerhans cells in the epidermis in biopsies from hypopigmented MF.[4,15] At present, the relationship between melanocyte dysfunction, T-lymphocyte subsets in the cellular infiltrate, and the increased number of Langerhans cells remains speculative.

Infiltration, scale, atrophy, pruritus, and erythema have all been variably reported in patients with hypopigmented MF, with most patients presenting with lesions on the trunk, hips, and extremities. The average age of onset in our patients was 35 years, which is higher than other reported cases in which the average age was approximately 28 years. The age of onset in patients with hypopigmented MF is younger than typical patch and plaque stage MF in which approximately 81% of patients present at 45 years or older.[6] Table 2 presents a comparison between hypopigmented MF and patch and plaque stage MF. Prognosis in patients with hypopigmented MF is unknown due to the small number of reported cases and short follow-up periods. Overall, these patients tend to have an earlier age of onset, slow progression, and good prognosis compared with MF patients overall.[10,12] However, patient 2 progressed to death from MF after many years of hypopigmented macules, patches, and plaques. Occurrence in childhood and adolescence is rare.[28]

Conclusion

In addition to its many other disguises, MF should be included in the differential diagnosis of pigmentary disorders such as vitiligo, tinea versicolor, pityriasis alba, postinflammatory hypopigmentation, leprosy, syphilis, sarcoidosis, and pityriasis lichenoides chronica, all of which may present as hypopigmented macules. Because hypopigmented MF is being reported with increased frequency, it is important to consider this diagnosis and perform a skin biopsy, if indicated, in patients with hypopigmentation that persists or continues to progress despite therapy. Hypopigmented MF may be more common than described in the literature. The perceived rarity may be secondary to underreporting of the disorder, incorrect diagnosis, or a combination of the two. Further studies are necessary to fully elucidate the clinical and biologic behavior of this seemingly uncommon variant of MF.

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