Continuing Medical Education

Hypopigmented Mycosis Fungoides in Younger Patients: A Mimicker of Common Hypopigmented Inflammatory Rashes

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Hypopigmented mycosis fungoides (HMF) is a rare type of cutaneous T-cell lymphoma (CTCL), a non-classic variant among up to 50 variants of mycosis fungoides (MF), that typically affects younger individuals in the second to fourth decades of life of darker skin types. The presenting cutaneous findings of HMF can be mistaken for and mimic other commonly seen hypopigmented skin disorders and misdiagnosed by an untrained eye in the dermatologic and general practice settings. MF has many different variants, and affects both children and adults. For the purpose of this article, the discussion will be limited to HMF specifically presenting in younger patients. With limited literature on HMF commonly affecting the younger generations, knowledge of how to diagnose and treat this cutaneous malignancy is lacking among clinicians. The goal of this CME article is to provide more awareness to clinicians on this rare form of CTCL, thus improving patient care through early detection and treatment in this patient population.

Learning Objectives

1. Discuss the clinical and physical presentations of hypopigmented mycosis fungoides compared to commonly seen hypopigmented rashes.
2. Review current workup and treatment for hypopigmented mycosis fungoides.
3. Discuss delayed diagnosis, long-term clinical prognosis, and recurrence rate with hypopigmented mycosis fungoides.
4. Describe histopathological findings

INTRODUCTION

Hypopigmented mycosis fungoides (HMF), is an extremely rare variant of mycosis fungoides (MF), a cutaneous T-cell lymphoma (CTCL).1–3 Onset typically occurs in younger patients in the second to fourth decade of life, and have predominantly been reported in the pediatric and juvenile patient populations.1,2,4–7 The prevalence of HMF noted among men and women has differed, however recent studies have concluded women tend to be more affected.3,5 HMF occurs more commonly in populations with darker skin phototypes.1,2,4,5,7–9 The presenting hypopigmented achromatic lesions closely resemble commonly seen inflammatory rashes with pigmentation loss, however the distribution and subtle uncommon features can provide clues clinically. Treatment is similar to that of vitiligo and atopic dermatitis. The prognosis tends to be excellent in these younger patients, however close follow up is necessary as recurrence rates are high.1,2

CASE

A 25-year-old woman presented for an evaluation of “white patches” all over her body for the past six years.

HISTORY

The patient reported six years ago she had a red rash develop on her arms that then turned white, followed by additional areas on arms and legs described as having a lighter outer rim and scaly redness on the inner portion. However, she reported all the white patches have remained stable with no new lesions. Additionally, she reported the lesions become more pronounced when out in the sun. She appeared her stated age, well-developed and well-nourished, and her past medical history was noncontributory. The patient reported having been seen by a pediatrician years ago when a biopsy was performed, given the diagnosis of vi-
Figure 1. Ill-defined scattered hypopigmented patches with overlying fine scale and erythema on bilateral anterior lower extremities. Image appears courtesy of Candice E. Macari DMSc, MSPAS, MPH, PA-C
tiligo, and was subsequently told there was no treatment for her condition. She had no additional significant personal past medical or family history.

PHYSICAL EXAMINATION

A total body skin examination (TBSE) was performed and on examination appreciated patient to be of Fitzpatrick skin type III, with ill-defined scattered splotchy hypopigmented patches with some overlying erythema and fine scale of bilateral anterior and posterior lower extremities, upper extremities, buttocks, and abdomen (see Figures 1–3). The patient’s back, neck, face, palms, and soles were clear. A lymph node exam was not performed.

DIAGNOSTIC TESTING

A 2 mm punch biopsy was per-formed on her right posterior calf and sent to an academic medical center dermatopathology lab. A complete blood cell count with differential, liver function tests, and lactate dehydrogenase were completed and found to be unremarkable. Additionally, a Sézary count was ordered to rule out the possibility of Sézary Syndrome, a rare subtype of CTCL; however the patient did not complete due to insurance coverage.

DIAGNOSIS AND OUTCOME

The differential diagnosis included vitiligo, atopic dermatitis, hypopigmented mycosis fungoides, and post-inflammatory hypopigmentation.

Figure 2. Ill-defined hypopigmented patches with overlying fine scale and erythema on chest and bilateral proximal upper extremities. Image appears courtesy of Candice E. Macari DMSc, MSPAS, MPH, PA-C

Formal dermatopathology demonstrated superficial CD8-positive lymphoid infiltrate with slight epidermotropism, CD8 immunostaining avidly labeled the infiltrate, including a tiny focus of epidermotropic cells, and the overall findings were suggestive of hypopigmented mycosis fungoides (HMF). There was no dermatopathologic evidence of vitiligo or atopic dermatitis.

Greater than 10 percent of the patient’s body sur-face area (BSA) was involved, and when coupled with the
Histopathologic findings, her staging fell under the classification of stage IB, T2aN0M0. The patient received narrow band UVB phototherapy (nbUVB) three times per week for approximately two months, then decreased to two times per week for one month. She was initially prescribed clobetasol 0.05% cream to apply to the whole body once daily; however, after 3.5 weeks, the patient reported her insurance would not cover a large quantity greater than 60 grams in a single prescription, and would only fill multiple small 15-gram tubes. Patient was then prescribed betamethasone 0.1% cream to apply once daily, and then decreased to three times per week application.

One month of therapy provided significant improvement with skin repigmentation and almost complete resolution of erythema. She had mild sunburn-like symptoms from her nbUVB phototherapy; otherwise, she had no notable adverse reactions.

Upon receiving the pathology report, she was referred to the closest academic medical center’s cutaneous lymphoma clinic, who favored the biopsy results, and agreed with the treatment plan provided. Providers at the clinic were encouraged by the patient’s significant response exemplified by repigmentation and decreased erythema. Additional treatment recommendations were given, including decreasing the interval of nbUVB phototherapy from three times per week to two times per week for three months after completing another six weeks of treatment of nbUVB at three times per week. She completed approximately 18 weeks and a total 32 sessions of nbUVB phototherapy combined with mid- to high-potency topical corticosteroids. The patient was told to follow up in the specialty clinic after completing the therapeutic plan.

Unfortunately, the patient was lost to follow up in the dermatology clinic after approximately five months from initial and subsequent visits, and final pictures of her repigmentation and clearance were not collected.

**HYPOPIGMENTED MYCOSIS FUNGOIDES**

**DEMOGRAPHICS**

HMF typically affects younger individuals in the second to fourth decades of life; African American, Middle Eastern, Asian, and Hispanic descent; and those of darker skin types higher on the Fitzpatrick scale skin phototypes IV–VI (see Table 1).<sup>1,2,4,5,7</sup> HMF comprises approximately 58–91 percent of pediatric MF cases, with the youngest reported case as young as 6 months old.<sup>5,8</sup> Interestingly, the disease is more prevalent among younger female patients.<sup>5,5</sup> Overall, studies show a higher incidence of HMF among pediatric and juvenile populations.<sup>2,4,6,7</sup>

**HISTOPATHOLOGY**

The pathogenesis behind HMF is not completely understood, and is similar histopathologically to other variants of MF.<sup>4,5</sup> Research has shown HMF is characterized by the uncontrolled expansion of monoclonal malignant T-cells involving the skin, eliciting an antitumor response.<sup>5</sup> HMF is thought to remain in the equilibrium phase of the cancer immunoediting process contributing to HMF not progressing past stage IB.<sup>5</sup> On immunohistochemical findings, epidermotropism and CD8+ T-cells predominate, and their cytotoxic effect are likely the cause for the hypopigmented patches, which differs from other MF variants.<sup>1,4,5,9,11</sup> Additional studies show similar histopathology of skin biopsy specimens upon staining with the predominance of CD8 infiltrates, as well as CD4 infiltrates, mixed CD4/CD8, CD7 loss, atypical lymphocytes within the epidermis forming Pautrier microabscesses, and areas of decreased epidermal melanin.<sup>3–5,11,12</sup> Researchers have suggested patients presenting with a scaly erythema component correlates more with an advanced stage compared to only hypopigmented lesions on histopathology.<sup>12</sup>

**CLINICAL PRESENTATION**

The patient will most commonly present with ill-defined hypopigmented patches or plaques, possible scaly erythema, in areas not typically associated with vitiligo.<sup>4,5,12,13</sup> Typically, patients are asymptomatic, without burning or pruritus of the affected areas; however, pruritus, increased skin sensitivity, skin atrophy, and some cases of peripheral lymphadenopathy have been reported.<sup>4,5,9</sup> The presenting lesion distribution typically occurs on non-sun-exposed areas of the skin located on the extremities, trunk, below the waistline on buttocks, and spares the face, hands, palms and soles, although facial involvement has been reported.<sup>2,4,5,7–9,11,14</sup> Patients rarely progress beyond stage IB, and remain in patch stage.<sup>1,5</sup>

**DIAGNOSTIC WORK-UP**

Studies differ in reported average time frame of disease onset to diagnosis ranging from 3.6 years to 5.3 years.<sup>4,15</sup> Differentiation clinically between similar hypopigmented inflammatory rashes and histopathologically between HMF and inflammatory vitiligo can be challenging.<sup>8</sup> Close attention to the location, more commonly in a bathing suit distribution, the appearance, and symptoms of the rash aid in making the diagnosis, along with skin biopsies to confirm. Pictures should be taken to record initial presentation, and at subsequent visits to document progression, stabilization, or resolution. A thorough check for lymphadenopathy should be performed, although palpable nodes tend to be benign.<sup>5,9</sup> Clinicians may be reluctant to perform a biopsy on younger patients due to resulting undesirable cosmesis. This in turn leads to misdiagnosis and delay in treatment.

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**Table 1. Fitzpatrick Skin Phototype**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Type I</td>
<td>Light, pale white</td>
</tr>
<tr>
<td>Type II</td>
<td>White, fair</td>
</tr>
<tr>
<td>Type III</td>
<td>Medium, white to olive</td>
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<tr>
<td>Type IV</td>
<td>Olive, moderate brown</td>
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<tr>
<td>Type V</td>
<td>Brown, dark brown</td>
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<tr>
<td>Type VI</td>
<td>Very dark brown, black</td>
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</tbody>
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<sup>Journal of Dermatology for Physician Assistants</sup>
resulting in possible disease persistence or stage progression.²

The type of biopsy is crucial for proper diagnostic workup. If a patient presents with different anatomic sites affected, then a biopsy from each of these locations could aid in definitive diagnosis.¹⁶ A shave biopsy is ideal; however, a punch biopsy is sufficient. The shave should be broad and deep enough to include the dermopideral junction as the malignant infiltrate is epidermotropic.¹⁶ The broad shave specimen provides a larger field to extract more DNA for further tests, including perform flow cytometry analysis, T-cell gene rearrangement studies, and immunohistochemical stains to determine the involvement of lymphocytes.¹⁶,¹⁷ Special pathology testing is necessary, and depending upon a clinic's location, access to a dermatopathologist who has more experience with these specific tests may not be readily available. A clinic may need to send off their specimens to a more equipped or specialized pathology department. Further laboratory tests aid in diagnosis and exclusion of other clinical subtypes of CTCL and are at the discretion of the clinician.

Differential Diagnosis

The presenting cutaneous findings of HMF can be mistaken for commonly seen hypopigmented skin disorders in the dermatologic and general practice settings, and therefore the differential diagnosis can be extensive (see Table 2). The most common diagnosis to rule out include vitiligo, atopic dermatitis (AD), pityriasis alba (PA), tinea versicolor (TV), post-inflammatory hypopigmentation (PIH), idiopathic guttate hypomelanosis (IGH), and less common syphilis, sarcoidosis, pityriasis lichenoides chronica, and leprosy.¹²,⁴,⁹

<table>
<thead>
<tr>
<th>Table 2. Hypopigmented mycosis fungoides differential diagnosis</th>
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<tbody>
<tr>
<td>Vitiligo</td>
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<tr>
<td>Atopic dermatitis</td>
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<td>Pityriasis alba</td>
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<tr>
<td>Tinea versicolor</td>
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<tr>
<td>Post-inflammatory hypopigmentation</td>
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<td>Idiopathic guttate hypomelanosis</td>
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<td>Pityriasis lichenoides chronica</td>
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<td>Syphilis</td>
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<td>Sarcoidosis</td>
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<td>Leprosy</td>
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Treatment Considerations

HMF treatment follows early stage classic MF treatment guidelines.⁷ Treatment for these young HMF patients consist of skin-directed therapies including, but not limited to, the use of mid- to high-potency topical corticosteroids, oral psoralen with ultraviolet A phototherapy (PUVA), and nbUVB phototherapy.¹²,⁴,¹³ Previously, PUVA tended to be the treatment of choice.¹¹ PUVA and nbUVB have both shown to provide up to a 90 percent response rate and remission of lesions in less than two months.⁷ Recent literature suggests patients with HMF do not need systemic therapies.⁵

Currently, first-line treatment is nbUVB phototherapy over the course of a few months to a year and/or topical corticosteroids have shown to be the most successful and preferable treatment for disease control of HMF.⁵,⁷,¹¹,¹³ This closely resembles the commonly used treatments for vitiligo and atopic dermatitis. Narrow band ultraviolet B phototherapy (nbUVB) works by suppressing the proliferation of malignant T-cells.⁵

Studies utilizing localized treatment of smaller isolated lesions with 308 nm excimer laser have shown good promise with complete clearance and repigmentation after weekly treatments for one year.¹¹ This treatment option has the potential to be particularly advantageous over nbUVB phototherapy whereby avoiding unnecessary exposure to ultraviolet (UV) radiation of unaffected areas.¹¹

Staging, Prognosis, and Recurrence Prevention

The four evolutionary phases of MF include pre-MF, patch, plaque, and then tumor. MF and the variant HMF are staged using the tumor-node-metastasis (TNM) classification system, and HMF tends to slowly progress and remain in stage I (patch stage) when treated.⁴,¹³ In general, affected children rarely progress past stage IA or IB.¹,⁴,⁵,⁷,⁹

The prognosis for HMF in younger patients is favorable, with an indolent course; however, recurrence rate is high, and long-term follow up is required.⁵,⁷,¹³,¹⁵ The particular presence of hypopigmentation is considered to be a favorable prognostic factor.⁹ Literature suggests hypopigmented lesion repigmentation and complete repigmentation correlates with an effective treatment response, and clinical and histopathologic resolution.⁴ New literature supports the finding of hypopigmentation in HMF, its early onset in those younger in age, and the predominance of CD8+ T-cells, are good prognostic indicators for an active Th1/cytotoxic antitumor immune response, which correlates with HMF rarely advancing beyond stage IB.⁵ The development of new hypopigmented lesions at any given time throughout re-mission suggests relapse.⁴

Regular patient follow up is important in these patients as studies show recurrence is common after treatment withdrawal.¹ Retrospective studies are lacking further investigation into the potential timeline of recurrence onset following treatment discontinuation.⁴ Patients who have remained in follow up for up to 10 years have not shown to have progressed to advanced stages.²

Conclusion

HMF is a rare form of CTCL most commonly occurring in younger patients at an earlier stage, in darker skin types, and presenting cutaneous findings can mimic other common hypopigmented skin disorders in the dermatologic and general practice settings. This can lead to misdiagnosis and
delay in treatment. Therefore, HMF should be on the differential diagnosis of clinicians when a patient presents with hypopigmented patches. Treatment for these young patients with HMF consist of phototherapy and/or topical corticosteroids. Repigmentation of the hypopigmented lesions correlates with successful treatment on a clinical and histopathologic level, and new hypopigmented lesions during remission suggest relapse. The majority of HMF patients remain in stage I, and prognosis is favorable, although recurrence rate is high, and close follow up is recommended.

DISCLOSURE
The author has disclosed no potential conflicts of interest, financial or otherwise, relating to the content of this article.
REFERENCES


