Reflectance Confocal Microscopy as a First-Line Diagnostic Technique for Mycosis Fungoides

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PRACTICE **POINTS**

- Mycosis fungoides (MF) can be a challenging diagnosis to establish and often requires multiple biopsies.
- Reflectance confocal microscopy (RCM) may be helpful as a bedside noninvasive diagnostic technique.
- In suspected MF cases, RCM may assist in selecting the optimal biopsy site for better yield of histopathologic results.

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma and is a diagnostic challenge in its early stages. It often can be misdiagnosed as chronic contact dermatitis, atopic dermatitis, psoriasis, or other common dermatoses. Histologic diagnosis remains the gold standard for MF; however, in many cases repeat biopsies may be needed over time, especially in early patch stages of MF. Reflectance confocal microscopy (RCM) is a quick and noninvasive diagnostic tool that may be useful to determine an appropriate area to biopsy. We present the case of a 60-year-old man with plaque and tumor lesions clinically suspicious for MF that had originally been misdiagnosed as psoriasis. Reflectance confocal microscopy was used to evaluate for findings specific to MF and to select an appropriate biopsy site. The features noted on RCM were consistent with MF, and subsequent biopsy revealed tumor-stage disease. This article describes a unique case in which RCM was used for initial primary diagnosis of tumor-stage MF in a clinical setting. As in prior studies, our evaluation failed to identify unique RCM features specific to tumor-stage MF when compared to plaque- or patch-stage disease. Nonetheless, RCM may be useful in providing a quick noninvasive diagnosis when the clinical presentation of MF is ambiguous, especially in early lesions.

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Case Report

A 60-year-old man with a history of Hodgkin lymphoma that had been treated with chemotherapy 6 years prior presented to our dermatology clinic with a persistent pruritic rash on the back, abdomen, and bilateral arms and legs. The eruption initially began as localized discrete lesions on the lower back 1 year prior to the current presentation; at that time a diagnosis of psoriasis was made at an outside dermatology clinic, and treatment with mometasone furoate cream was initiated. Despite the patient's compliance with this treatment, the lesions did not resolve and began spreading to the arms, legs, chest, and abdomen. His current medications included lisinopril, escitalopram, aspirin, and omeprazole.

On presentation to our clinic, physical examination revealed round, scaly, pink plaques and tumors of variable sizes (3–10 cm) distributed asymmetrically on the chest, back, abdomen, arms, and legs (Figure 1). The lesions were grouped in well-defined areas encompassing approximately 30% of the body surface area. No lymphadenopathy was appreciated. In vivo reflectance confocal microscopy (RCM) performed on one of the lesions revealed disarray of the epidermis with small, weakly refractile, round to oval cells scattered within the spinous layer and dermoepidermal junction (Figure 2). Additionally, these weakly refractile, round to oval cells also were seen in vesiclelike dark spaces, and hyporefractile basal

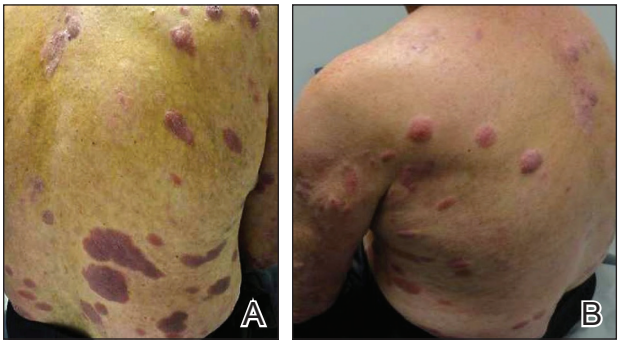

FIGURE 1. Mycosis fungoides with round, scaly, pink plaques of variable sizes ranging from 3 to 10 cm distributed asymmetrically on the back, flank, and arms (A and B).

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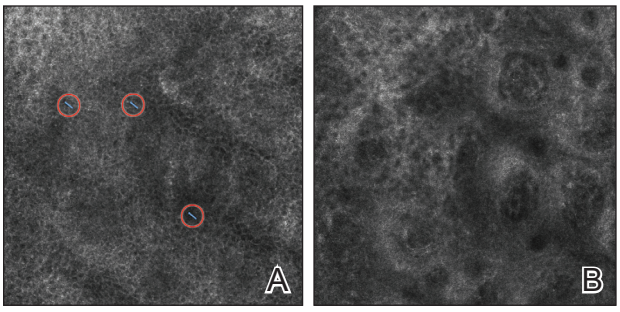

FIGURE 2. Reflectance confocal microscopy of the stratum spinosum revealed epidermal disarray with small, weakly refractile, round to oval cells (blue markings) scattered among keratinocytes in vesiclelike dark spaces (A). At the level of the dermoepidermal junction, there were more weakly refractile, dermal, papillary rings compared to normal skin, as well as more weakly refractile, round to oval cells in the epidermis and dermis (B).

cells were appreciated surrounding the dermal papillae. Mycosis fungoides (MF) was diagnosed following correlation of the RCM findings with the clinical picture.

A biopsy was performed, with pathologic examination confirming the diagnosis of tumor-stage MF. Parakeratosis with epidermotropism of lymphocytes was noted along the basal layer and into the spinous layer of the epidermis (Figure 3). Underlying the epidermis there was a dense mononuclear infiltrate and conspicuous eosinophils extending to the deeper reticular dermis. The infiltrating cells had cerebriform nuclei and large pale cytoplasm. On immunostaining, the lymphocytes were positive for CD3 and CD4, and negative for CD5, CD7, and CD8. The patient was referred to the oncology department for disease management. Staging workup including computed tomography, flow cytometry, and T-cell receptor gene rearrangement were consistent with tumor-stage MF (T3N0M0B0).

Comment

Clinical Presentation of MF—Mycosis fungoides, a non-Hodgkin lymphoma of T-cell origin, is the most commonly diagnosed cutaneous lymphoma worldwide.[1] It has an annual incidence of approximately 0.36 per 100,000 persons, and this number continues to rise.[2,3] The median age of diagnosis is 55 to 60 years, and MF occurs twice as often in men versus women.[4]

The clinical presentation of MF varies and is classified by stages including patches, plaques, tumors, and erythroderma.[5] Classically, MF is slowly progressive and begins as pruritic erythematous patches that have a predilection for non–sun-exposed areas of the skin. Over time, these patches may evolve into plaques and tumors. Early or patch-stage MF often presents as well-demarcated lesions of various sizes and shapes that tend to enlarge.[6] These lesions may resemble eczema or psoriasis if there is scaling, such as in our patient. At the tumor stage, flat or dome-shaped nodules that may vary in color and are deeper than plaques begin to appear. Ulcerations, which were absent in our case, may often be seen.

Because of the diverse clinical manifestations of MF, which can mimic other common dermatoses, diagnosis often is challenging for clinicians. Furthermore, histology can yield nonspecific diagnostic results and may even resemble chronic inflammatory dermatoses.[7] As a result, patients frequently are subjected to multiple skin biopsies to establish the diagnosis,[8] and diagnosis may be delayed, with the median time from onset of skin symptoms to diagnosis being approximately 6 years.[9]

Reflectance Confocal Microscopy—In vivo RCM is a noninvasive technique that allows visualization of the skin at a cellular level and recently has been evaluated as a diagnostic tool for many skin conditions.[10,11] Reflectance confocal microscopy findings have been well established for many cutaneous malignancies as well as inflammatory conditions such as psoriasis and atopic dermatitis.[12,13] Specifically, 2 preliminary descriptive studies utilized RCM to visualize the characteristic features of MF in vivo.[14,15] These studies reported the histopathologic correlation of RCM findings in biopsy-proven MF lesions. Consistent in all stages of MF is the presence of small, weakly refractile, round to oval cells within the spinous layer that correlate with atypical lymphocytes, in addition to hyporefractile basal cells surrounding the dermal papillae.

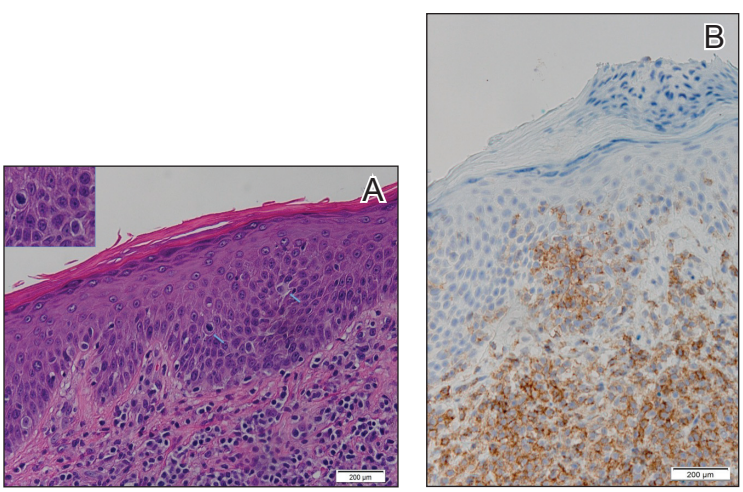

FIGURE 3. Atypical enlarged lymphocytes in the epidermis with hyperchromatic irregular nuclei of cells (inset) as well as a dense infiltrate in the dermis (A)(H&E, original magnifications ×10 and ×50 [inset]). CD4 immunohistochemical staining revealed atypical lymphocytes with dermal and epidermal infiltration (B)(original magnification ×10).

Patch-stage MF lesions have more subtle epidermal findings compared to plaque-stage lesions, which tend to have more prominent vesiclelike dark spaces filled with collections of monomorphous, weakly refractile, round to oval cells corresponding with Pautrier microabscesses and evidence of spongiosis.[14,15] The first descriptive study of RCM in the diagnosis of MF failed to identify features of tumor-stage MF that would distinguish it from patch- or plaque-stage disease. The investigators also stated that deep nodular collections of atypical lymphocytes seen on histopathology in tumor-stage MF were missed on RCM evaluation.[14] Furthermore, the second descriptive study of RCM and MF, which included 2 patients with tumor-stage disease, also failed to differentiate tumor-stage MF from the patch or plaque stages.[15]

Because of these 2 descriptive studies, a pilot study was conducted to determine the applicability and reproducibility of RCM findings for MF diagnosis.[16] Two blinded confocalists were asked to diagnose RCM images as MF when compared to either normal skin or a variety of lymphoproliferative disorders. Of 15 patients, the confocalists correctly diagnosed MF in 84% and 90% of cases, respectively. Additionally, they reported the specificity and sensitivity of the following RCM features in the diagnosis of MF: spongiosis, 88.9% and 94.7%; loss of demarcation, 88.9% and 94.7%; disarray of the epidermis, 77.8% and 89.5%; hyporefractile rings, 88.9% and 78.9%; junctional atypical lymphocytes, 100% and 73.7%; and vesiclelike structures (Pautrier microabscesses), 100% and 73.7%. Importantly, this study did not evaluate the specificity and sensitivity of MF diagnosis compared to other eczematous or inflammatory conditions that may share similar RCM findings; therefore, these results are not generalizable, and many of the RCM findings characteristically seen in MF are not specific to its diagnosis.[16]

One study assessed the diagnostic accuracy of RCM in evaluating erythematosquamous diseases including MF, psoriasis, contact dermatitis, discoid lupus, and subacute cutaneous lupus.[17] In this study, 3 blinded confocalists achieved a 95.41% and 92.89% specificity and 89.13% and 63.33% sensitivity for psoriasis and MF, respectively. Typical features of psoriasis on RCM included parakeratosis, reduction or absence of the granular layer, papillomatosis, acanthosis with normal honeycomb pattern of the epidermis, and dilated vessels in the upper dermis. Features that were more specific to MF included epidermotropic atypical lymphocytes, interface dermatitis, pleomorphic tumor cells, and dendritic cells.[17] However, atypical lymphocytes and interface dermatitis also may be seen in cutaneous lupus; therefore, additional studies are still needed to validate RCM's utility in differentiating between erythematosquamous skin diseases, including psoriasis, cutaneous lupus, and MF. Currently, RCM findings must be interpreted in conjunction with the clinical and histologic picture.

Importantly, RCM also is limited when evaluating MF due to its limited depth of visualization, as it allows imaging only to the superficial papillary dermis. Furthermore, any infiltrative process such as epidermal hyperplasia, spongiosis, or scaling, which can be seen in MF, may further impair the imaging quality of the deeper dermis.

Conclusion

Despite its limitations, RCM has the potential to be advantageous in evaluating skin lesions suspicious for MF in real time and is a promising technology for a quick noninvasive bedside adjunct tool. Its utility in selecting the optimal site for biopsy for better yield of histopathologic results in suspected MF cases has been demonstrated.[16] However, large-scale studies still are needed to evaluate RCM in the diagnosis of the wide diversity of MF lesions as well as its efficacy in selecting optimal biopsy sites.

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