Mycosis fungoides associated with recurrence of malignant melanoma

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INTRODUCTION

Patients with cutaneous T-cell lymphoma (CTCL) have an increased risk of additional malignancy.[1] Eighteen cases of patients with both mycosis fungoides (MF) and melanoma have been reported; only 6 of these cases describe malignant melanoma diagnosed at or before the time of MF diagnosis.[1-3] Immunologic and genetic links have been proposed between the 2 diseases without consensus. We report a case of MF associated with a history of malignant melanoma and later melanoma recurrence.

Abbreviations used:

CTCL:	cutaneous T-cell lymphoma
HLA:	histocompatibility locus antigen
MF:	mycosis fungoides

CASE REPORT

A 65-year-old white man with a history of stage IIb ulcerated malignant melanoma of the forearm presented to clinic in June 2014. The melanoma was diagnosed in June 2012 with a Breslow depth of 3.3 mm and had been treated with wide local excision with negative sentinel lymph node biopsy. The patient presented with scaly erythematous patches of the extremities, buttocks, and abdomen and inguinal lymphadenopathy (Fig 1).

Initial biopsy of the patches favored chronic eczema, with left groin lymph node biopsy read as dermatopathic without evidence of malignancy. On re-evaluation in March 2015 and June 2015, additional biopsies were not diagnostic of MF. The patient was seen in the CTCL clinic in September 2015; flow cytometry was negative for Sézary cells or *TCR* gene rearrangement to suggest CTCL. However, due to continued clinical concern, the patient was started on 10 mg methotrexate weekly without improvement over 5 months. CTCL was definitively diagnosed in February 2016 after repeat biopsy (Fig 2).

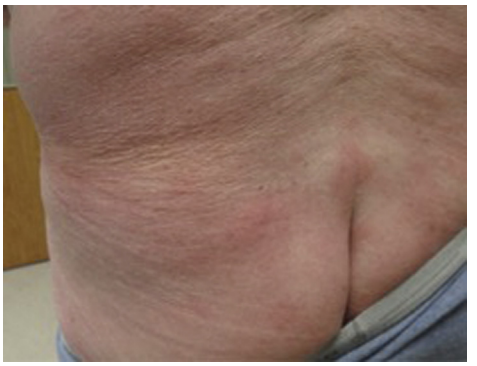

Fig 1. MF: clinical presentation. Scaly erythematous patches of the back and buttocks.

The patient did not respond to multiple therapies, including systemic bexarotene, narrow-band ultraviolet B, and topical nitrogen mustard. However, he improved on topical steroids and was maintained on triamcinolone 0.1% ointment with a body surface area of less than 5%.

In September 2018, the patient began experiencing abdominal pain. Positron emission tomography/computed tomography found bilateral adrenal masses. Pathology after bilateral adrenalectomy and left nephrectomy revealed metastatic melanoma

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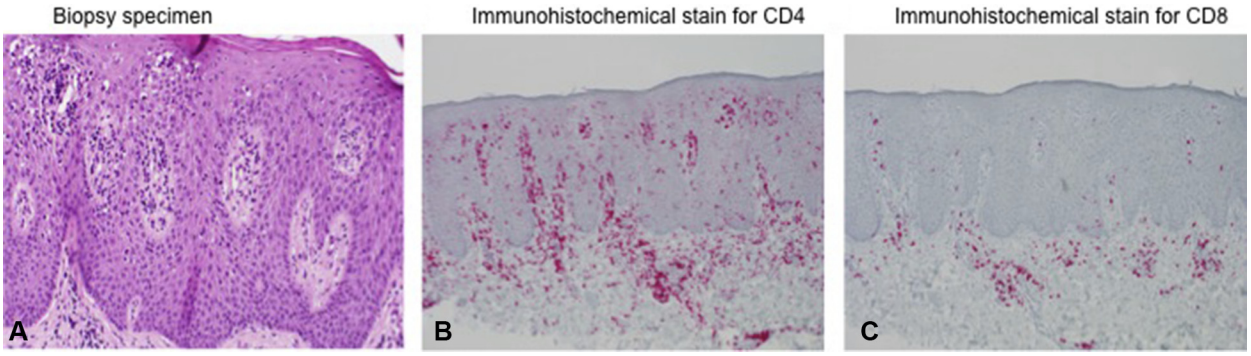

Fig 2. MF: histopathology. **A**, Lichenoid lymphocytic infiltrate with epidermotropism with tagging at the dermoepidermal junction, exocytosis, and Pautrier-type microabscesses. **B** and **C**, Immunohistochemical studies revealing a markedly elevated CD4:CD8 ratio in the epidermis. (**A**, hematoxylin-eosin stain; original magnifications: **A**, ×20; **B** and **C**, ×10.)

(stage IV). He received 16 cycles of adjuvant pembrolizumab, 200 mg beginning in 2018. Most recent positron emission tomography performed in December 2019 found no evidence of residual or recurrent disease.

DISCUSSION

We present a case of melanoma preceding CTCL diagnosis with later melanoma recurrence and metastasis. Impaired cell-mediated immunity associated with CTCL, a malignancy of T lymphocytes, may contribute to malignancy and recurrence of malignancy in these patients. The immunosuppressive and potentially carcinogenic effects of CTCL therapy such as psoralen ultraviolet A, total skin electron beam therapy, and nitrogen mustard may also confer additional susceptibility to melanoma and other malignancies, particularly nonmelanoma skin cancers.[1]

However, reports of malignant melanoma diagnosed before CTCL indicate other pathologic links, including genetic and immunologic alterations predisposing to the development of both diseases. Possible culprits include mutations in the *CDKN2A* gene (encoding tumor suppressor protein p16) or histocompatibility locus antigen (HLA) alleles, including HLA-DR5 and DQB1*03, which are overexpressed in both CTCL and malignant melanoma.[1,4,5] Expression of CTLA-4, a negative regulator of T-cell immune responses, is also seen in malignant T cells in patients with MF, mirroring findings in melanoma.[6-8] CTLA-4 expression may contribute to the pathogenesis of both diseases, with higher tumor expression of CTLA-4 portending worse prognosis and therapeutic targeting of CTLA-4 associated with clinical improvement. Melanoma patients with higher tumor CTLA-4 expression exhibited poorer prognosis before the introduction of immunotherapies such as ipilimumab, a CTLA-4 inhibitor.[8] Therapeutic targeting of CTLA-4 with ipilimumab prolongs survival in advanced melanoma, and complete regression of MF has been observed in a patient with advanced melanoma treated with ipilimumab.[9,10]

The recurrence of melanoma in the patient presented here indicates that neither hypothesis is complete but that both are contributory. Patients' genetic milieu may predispose to the development of both malignant melanoma and CTCL, whereas the altered immunity and immunosuppression conferred by CTCL may increase the risk of recurrence of melanoma. Additional studies are necessary to determine if p16 and HLA allele expression are altered in these patients. Nonetheless, this study confirms the need for increased vigilance for recurrence in CTCL patients with histories of other primary malignancies, particularly melanoma.

REFERENCES

1. Pielop JA, Brownell I, Duvic M. Mycosis fungoides associated with malignant melanoma and dysplastic nevus syndrome. *Int J Dermatol*. 2003;42(2):116-122.
2. Soong V, Lee PC, Kissel RB, Sams WM Jr, Tyring SK. Fatal malignant melanoma associated with a completely regressed primary melanoma in a patient with cutaneous T-cell lymphoma. *Arch Dermatol*. 1987;123(10):1270-1272.
3. Flindt-Hansen H, Brandrup F. Malignant melanoma associated with mycosis fungoides. *Dermatologica*. 1984;169(4):167-168.
4. Jackow CM, McHam JB, Friss A, Alvear J, Reveille JR, Duvic M. HLA-DR5 and DQB1*03 class II alleles are associated with cutaneous T-cell lymphoma. *J Invest Dermatol*. 1996;107(3):373-376.
5. Lee JE, Reveille JD, Ross MI, Platsoucas CD. HLA-DQB1*0301 association with increased cutaneous melanoma risk. *Int J Cancer*. 1994;59(4):510-513.
6. Wong HK, Wilson AJ, Gibson HM, et al. Increased expression of CTLA-4 in malignant T-cells from patients with mycosis fungoides -- cutaneous T cell lymphoma. *J Invest Dermatol*. 2006;126(1):212-219.

7. Mo X, Zhang H, Preston S, et al. Interferon-γ signaling in melanocytes and melanoma cells regulates expression of CTLA-4. *Cancer Res*. 2018;78(2):436-450.
8. Shah KV, Chien AJ, Yee C, Moon RT. CTLA-4 Is a direct target of Wnt/β-catenin signaling and is expressed in human melanoma tumors. *J Invest Dermatol*. 2008;128(12): 2870-2879.
9. Maio M, Grob JJ, Aamdal S, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. *J Clin Oncol*. 2015;33(10):1191-1196.
10. Bar-Sela G, Bergman R. Complete regression of mycosis fungoides after ipilimumab therapy for advanced melanoma. *JAAD Case Rep*. 2015;1(2):99-100.