Primary Cutaneous Melanomas Seen as Inflamed Pigmented Lesions in Patients Undergoing Adjuvant Interferon Treatment

A Possible Diagnostic Clue for Physicians

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Background: In addition to a complete skin examination every few months, adjuvant interferon treatment is often recommended for patients with high-risk melanomas. Therefore, dermatologists play an important role in detecting multiple primary melanomas and may be required to attempt to identify the primary melanoma in patients with metastatic disease.

Observations: We describe 3 patients with a diagnosis of melanoma who were diagnosed as having a new primary cutaneous melanoma within weeks of initiating interferon treatment. All 3 melanomas were inflamed clinically, prompting excisional biopsy. Histopathologic analysis of the melanomas revealed thin (<1.0 mm Breslow thickness) invasive tumors, as well as the presence of tumor-infiltrating lymphocytes and/or regression.

Conclusions: Inflamed melanocytic lesions in patients undergoing interferon treatment should be further evaluated to investigate the possibility of primary cutaneous melanomas. This observation may enable earlier detection and treatment of melanomas in patients with multiple tumors or metastatic melanoma with an unknown primary site.


DERMATOLOGISTS PLAY AN IMPORTANT role in the long-term care of patients with a history of melanoma and must be aware of clinical subtleties that may aid in early diagnosis of subsequent melanomas. In addition, dermatologists must attempt to identify primary melanomas in patients with metastatic disease of unknown primary origin, which can be clinically challenging. Such cases are estimated to comprise between 3.7% and 6% of all incident melanomas and frequently pose difficult diagnostic and therapeutic problems.

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REPORT OF CASES

CASE 1

A 52-year-old woman sought treatment at Beth Israel Deaconess Medical Center Cutaneous Oncology Program after being diagnosed as having stage IIIA melanoma. The primary melanoma presented as an irregularly pigmented papule on her right ankle that had bled with shaving. The melanoma was at least 1.9 mm thick, extending to Clark level IV without evidence of ulceration, regression, or tumor-infiltrating lymphocytes. An inguinal lymph node dissection revealed that 3 of 11 nodes were positive for microscopic disease. Physical examination at that time revealed fewer than 40 scattered, 1- to 4-mm...
evenly pigmented nevi, none of which were thought to be suspicious for malignancy.

The patient was started on a standard protocol of adjuvant interferon alfa-2b therapy. At a follow-up visit during her 12th week of interferon alfa-2b treatment, a complete dermatologic examination was significant for a 4-mm inflamed erythematous papule with a peripheral focus of brown pigment on her left posterior thigh. Dermoscopic examination revealed a homogeneous red-pink area with some prominent vessels and a peripheral remnant of pigment network. Examination of an excisional biopsy specimen revealed a superficial spreading melanoma, invasive to a Breslow depth of 0.62 mm, Clark level IV, without ulceration. Tumor-infiltrating lymphocytes were present and nonbrisk, and there was focal regression. The patient underwent a wide local excision and restarted interferon alfa-2b therapy, which was discontinued after 39 weeks because of multiple adverse effects. She remained without recurrence 19 months after discontinuing treatment with interferon alfa-2b.

**CASE 2**

A 50-year-old man with a history of atypical nevi sought treatment at the Beth Israel Deaconess Medical Center Cutaneous Oncology Program with a diagnosis of stage III metastatic melanoma of unknown primary site. The patient had a palpable node in his left axilla, and a lymph node dissection demonstrated that 7 of 37 nodes were positive for melanoma with extracapsular extension. On complete skin examination, a densely pigmented macule on the mid-back was biopsied, and examination of the biopsy specimen revealed a nevoid melanoma, which was presumed to be the primary site. The tumor was invasive to a depth of 0.45 mm and Clark level IV without ulceration. The patient had a wide local excision and radiation therapy to the axilla and started receiving adjuvant interferon alfa-2b.

On a complete skin examination during the 12th week of interferon alfa-2b treatment, a 5-mm inflamed erythematous papule with slightly irregular light brown pigmentation was identified on the patient's lower back. Dermoscopic examination revealed a light brown pigment network with some irregular linear vessels (Figure 1A). Examination of a biopsy specimen revealed an invasive superficial spreading melanoma with a depth of 0.4 mm, Clark level III, in association with a dermal nevus (Figure 1B). The melanoma was nonulcerated, and dermal regression as well as a nonbrisk tumor-infiltrating lymphocytic response was present. The patient underwent a wide local excision and completed 1 year of interferon alfa-2b therapy. He did well until 7 months later, when he developed mesenteric and ileal metastases. He completed 4 cycles of biochemotherapy as well as maintenance interleukin-2 therapy and remained in remission 22 months later.

**CASE 3**

A 45-year-old woman sought treatment at the University of Arizona Dermatology Clinic after being diagnosed as having metastatic melanoma of unknown pri-
mary site involving the right axilla. Six weeks earlier, the patient sought treatment for a rapidly growing, painful mass in her right axilla; she underwent a lymph node dissection, which revealed that 4 of 22 nodes were positive for melanoma with extracapsular extension. A comprehensive dermatologic examination revealed a slightly increased prevalence of benign-appearing melanocytic nevi involving the trunk, none of which were consistent with melanoma. The patient underwent adjuvant radiation therapy to her right axilla and started a standard course of treatment with interferon alfa-2b.

As the patient began her sixth week of interferon alfa-2b treatment, a dermatologic examination demonstrated a 4-mm inflamed papule with even light brown pigmentation on her right posterior shoulder. Dermoscopic examination revealed a homogeneous light brown area with a slightly increased number of telangiectasias (Figure 2A). Examination of a biopsy specimen demonstrated a superficial spreading melanoma extending to a Breslow thickness of 1.1 mm, Clark level IV, without evidence of ulceration or regression and with a brisk tumor-infiltrating lymphocytic response (Figure 2B). After a wide local excision, the patient restarted interferon alfa-2b therapy, which was discontinued after 7 months secondary to adverse effects. She remained in remission 13 months after discontinuing treatment with interferon alfa-2b.

In this case series, we describe 3 patients with stage III melanoma who were diagnosed as having primary cutaneous melanoma shortly after the initiation of interferon alfa-2b treatment. Cases 1 and 2 likely represented second primary melanomas that appeared inflamed during interferon treatment, whereas in case 3, the patient’s new diagnosis of cutaneous melanoma could have represented either a second primary melanoma or the “unmasked” primary melanoma of her metastatic disease. All melanomas diagnosed while undergoing interferon treatment had the distinguishing clinical feature of isolated inflammation, which prompted a biopsy. Given that the patients had normal skin examinations several weeks before initiating interferon alfa-2b treatment, it is possible that the direct immunomodulatory effects of interferon targeting melanoma unmasked or “lit up” these subsequent primary melanomas. Histologically, all 3 melanomas had tumor-infiltrating lymphocytes and/or regression associated with inflammatory changes, which could have been induced by interferon alfa-2b.

Inflammation of cutaneous melanoma in the setting of interferon alfa-2b treatment may indicate the induction of a complex network of cytokines involved in the regulation of melanoma cell growth. It has been shown that melanomas with spontaneous regression possess high levels of expression of myxovirus resistance protein A (MxA), an antiviral protein specifically induced by endogenous interferon, along with large numbers of natural interferon-producing plasmacytoid dendritic cells, CXCR3+ lymphocytes, and granzyme B+ lymphocytes. In addition, interferon has been shown to inhibit melanoma cells in vitro and cause apoptosis and lymphohistiocytic infiltration of metastatic melanoma tumors. These data suggest that in...
terferon is involved in melanoma regression, and we postulate that adjuvant interferon alfa-2b administered to patients with melanoma may similarly lead to inflammation and possible regression of additional cutaneous melanomas. As a counterargument, one could postulate that interferon alfa-2b may induce or stimulate the progression of atypical melanocytic neoplasms. However, this hypothesis is not supported by our current understanding of the biological effects of interferon alfa-2b in melanoma, both in vitro and in vivo.

Inflamed melanocytic lesions should be carefully evaluated, especially among patients with melanoma receiving interferon treatment. In this case series, all melanomas identified by inflammation during interferon alfa-2b treatment were clinically small (4-5 mm in diameter) and relatively thin (Breslow depths, 0.4 mm-1.1 mm). All patients remained in remission 13 to 22 months after discontinuing treatment with interferon. It is our hope that this potential diagnostic clue can assist physicians in early detection of second primary cutaneous melanomas and identification of the unmasked primary melanoma in patients with metastatic disease.

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REFERENCES


Archives Web Quiz Winner

Congratulations to the winner of our February quiz, Enver Turan, MD, Department of Dermatology, Istanbul Education and Research Hospital, Istanbul, Turkey. The correct answer to our February challenge was ofr infection. For a complete discussion of this case, see the Off-Center Fold section in the March Archives (Swick BL, DeBates SM. A solitary nodule on the finger. Arch Dermatol. 2009;145[3]:321-326).

Be sure to visit the Archives of Dermatology Web site (http://www.archdermatol.com) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of The Art of JAMA II.