Melanoma coexisting with solar elastosis: a potential pitfall in the differential diagnosis between nevus and melanoma


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Melanoma Coexisting with Solar Elastosis: A Potential Pitfall in the Differential Diagnosis between Nevus and Melanoma

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This study was approved by the Institutional Review Board at MD Anderson Cancer Center.

Informed consent was obtained from every patient upon arrival for treatment at MD Anderson Cancer Center.

Running title: Melanoma Coexisting with Solar Elastosis

Key words: melanoma, nevus, solar elastosis

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Abstract

Melanomas, like non-melanoma skin cancers, are known to be causally related to sun exposure. It is therefore not surprising to see benign nevi and melanomas in a background of solar damage, which at times may complicate their distinction. Due to their long-standing nature, nevi often occur before the development of solar elastosis, and as such, are intimately associated with the solar elastosis. In contrast, visible solar elastosis often occurs prior to the development of melanoma, in which case the band of solar elastosis is displaced downwards from the overlying invasive melanoma and/or its host response. We describe 4 cases in which invasive melanoma cells were intimately admixed with actinically damaged elastin fibers in the absence of a prominent host response. In each case, melanoma cells were admixed with prominent solar elastosis and lacked a significant host response, suggesting that they were either histiocytes or an associated melanocytic nevus. Recognition of this potential pitfall may be helpful in the diagnosis of primary/in-transit/satellite/metastatic melanoma as well as when evaluating marginal status and determining Breslow thickness.

Highlights

- Melanoma and its host response are known to downwardly displace solar elastosis
- Nevus development predates solar elastosis and melanocytes are seen admixed with it
- Our unusual melanoma cases show tumor cells intimately admixed with solar elastosis
- Recognizing this pitfall is crucial in evaluating margin status and Breslow depth
Introduction

The distinction between nevus and melanoma is a common challenge in dermatopathology, often necessitating the careful integration of numerous individual histologic criteria to discriminate benign from malignant. Because some melanocytic lesions are causally related to sun exposure, they may be accompanied by histologic evidence of actinic damage in the form of solar elastosis. For melanocytic lesions occurring on sun-damaged skin, analysis of the relationship of the lesion to the solar elastotic band (SEB) has been suggested to aid in the differential diagnosis. Horenstein et al. described downward displacement and superficial attenuation of the SEB as an attribute of melanoma and its accompanying host response\(^1\). In contrast, in long-standing benign lesions, the position and thickness of the SEB matches that of perilesional dermis; additionally; nevus cells are seen intercalating amongst individual degenerated elastic fibers. Herein, we describe 4 cases of melanoma in which melanoma cells permeate the SEB and lack a prominent host response, challenging the convention that melanoma cells typically do not infiltrate, but rather displace the SEB deeper into the dermis. These cases illustrate a potential diagnostic pitfall in the initial diagnosis of melanoma. Furthermore, they highlight potential challenges for margin evaluation and determination of Breslow thickness in such cases.
Case Series

Case 1

A 74 year-old white man underwent a wide local re-excision for a melanoma of the right forearm (Figure 1A). Both of the two sentinel lymph nodes biopsied were positive for metastatic melanoma. All margins of resection were negative, with the exception of the lateral en face margin (Figure 1B). Upon initial examination of this margin, there were epithelioid cells intimately associated with solar elastosis that resembled histiocytes, with no prominent overlying melanoma in situ (Figure 1B). However, these cells were large with irregular nuclear contours and prominent nucleoli (Figure 1C), similar to the patient’s melanoma (Figure 1A). An immunohistochemical study with MART1/Ki67 cocktail revealed these atypical cells to be diffusely positive for MART1 with a high Ki67 proliferative index, consistent with melanoma, and thus diagnostic of a microsatellite lesion (Figure 1C inset). The patient underwent a completion lymphadenectomy of the left axillary and epitrochlear basins, showing metastatic melanoma in an additional 8 of 27 lymph nodes. The patient subsequently received local radiation without systemic therapy due to his comorbidities, including end-stage renal disease and Crohn’s disease. Approximately three months after surgery, the patient developed metastases to the lungs and liver (pT4bN3bM1) and died due to pulmonary complications. The clinicohistologic features are summarized in table 1.

Case 2

A skin shave biopsy from the right upper arm of a 63 year-old man revealed a contiguous intraepidermal proliferation of large spindled and epithelioid melanocytes arranged singly and
in large nests along the dermal-epidermal junction with pagetoid spread. Similar appearing cells were seen in the dermis in association with actinically damaged elastin fibers and minimal host response. Additionally, one dermal mitotic figure per square millimeter was noted. The findings were diagnostic of malignant melanoma, superficial spreading type (pT1b, per the AJCC 8th edition). The patient underwent a wide local excision and biopsy of two sentinel lymph nodes, which were negative for residual and metastatic melanoma, respectively. The patient is currently alive with no evidence of disease, 40 months after diagnosis. The clinicohistologic features are summarized in table 1.

Case 3

A 68 year-old man underwent a wide local excision and sentinel lymph node biopsy of a left cheek melanoma (lentigo maligna type, Breslow thickness at least 0.7 mm). The excision revealed healing biopsy site changes, scar formation, and associated melanoma in situ (Figure 2A). The SEB underlying the scar contained a variably dense mononuclear infiltrate resembling histiocytes (Figure 2B). At that time, the primary melanoma from the previous biopsy specimen was not available to review for comparison. A pan-melanocytic immunohistochemical cocktail (MART1, HMB45 and tyrosinase) stained the aforementioned bland mononuclear cells within the SEB (Figure 2C). Perineural invasion of small nerve fibers and two dermal mitotic figures per square millimeter were identified. The overall findings were diagnostic of residual melanoma (pT2aN2bMx). The patient is alive with disease and currently exploring personalized treatment options. The clinicohistologic features are summarized in table 1.

Case 4
Skin shave biopsies from two pigmented papules on the right lower leg of a 75 year-old woman revealed similar histologic features. Each biopsy showed a dermal proliferation of cytologically atypical epithelioid and nevoid cells in a single cell growth pattern without epidermal involvement. These atypical cells were found in association with the actinically damaged elastin fibers with only minimal host response. MART1/Ki67 Immunohistochemical cocktail highlighted the epithelioid/nevoid cells and showed a high proliferative index. The patient had a history of melanoma approximately 20 years ago; however, prior pathology materials were not available for review. Based on the reported history of melanoma, presence of two papules with similar clinico-pathological features and high Ki67-proliferative index, a final diagnosis of metastatic melanoma was rendered. She is currently alive with disease, and exploring available therapeutic options. The clinicohistologic features are summarized in table 1.

Discussion

Ultraviolet radiation is a major causative factor for many cutaneous malignancies and, when received in a sufficient cumulative dosage, is demonstrated histologically by peri-lesional solar elastosis and actinic keratosis. A case-control study of 100 difficult-to-diagnose melanocytic neoplasms deemed the presence of solar elastosis to be an important contributor to a melanoma diagnosis, with a sensitivity of 35% and a specificity of 93% when considered in isolation\(^2\). Additionally, a cross-sectional study of pathologists’ clinical practices found that for 57%, the presence of solar elastosis would influence them towards a more severe diagnosis,
with that number rising to 73% among dermatopathologists\(^3\). However, chronic sun exposure is not required in the pathogenesis of all melanomas, as evidenced by those which lack evidence of solar elastosis or those that arise in sites without sun exposure. Several studies have found that melanomas adjacent to marked solar elastosis are strongly associated with increased age, locations on the head and neck, and self-reported sun exposure\(^4\)-\(^7\). While melanomas occurring in a background of solar elastosis are associated with increased copy numbers of \textit{CCND1} and predominately wild-type \textit{BRAF} and \textit{NRAS} genes, those melanomas occurring in skin without chronic sun-induced damage are associated with frequent \textit{BRAF} or \textit{NRAS} mutations\(^8\).

Despite the above associations of melanoma with solar elastosis, nevi may also occur in association with solar elastosis and thus pose a diagnostic challenge. It is believed that most nevi, due to their long-standing nature, predate the development of solar elastosis. Consequently, the nevus cells may be seen either dispersed amongst the basophilic fibers of the SEB, without fibrosis or inflammation, or are visible below the SEB. Melanoma associated with solar elastosis causes downward displacement and attenuation of the SEB. In melanoma \textit{in situ}, this alteration is produced by the host inflammatory response whereas both the host inflammatory response and melanocytes are responsible for the alterations in invasive melanoma.

All cases in our series were comprised of predominantly male patients (M:F=3:1) with advanced age. Despite their various pathologic stages, all cases demonstrated at least focally atypical cells admixed with actinically damaged elastin fibers, without a significant host inflammatory response, which are typical in benign nevi arising in sun-exposed skin. In Case #1, this finding
was focal and limited to the lateral en face margin (Figure 1B, C), which showed extensive solar elastosis and appeared hypercellular on low power, without an overlying in situ melanoma. High power examination revealed cytologic atypia with morphologic semblance to the main melanoma mass. This case illustrates the point that careful analysis of the SEB should be performed even at locations far from the main lesion so as to not miss microsatellites and/or positive margins. Additionally, the finding of such cytologically atypical melanocytes amongst the solar elastosis fibers should not be assumed to represent an incidental nevus. Cases #2 and #3 showed somewhat bland melanocytes in the dermis intimately associated with solar elastosis and a minimal host inflammatory response with an overlying melanoma in situ component. In case #4, there were similar findings but no melanoma in situ component. Additionally, there is no deeper displacement of the SEB. For these reasons, the cells may be mistaken for nevus cells, potentially resulting in an underestimation of the Breslow thickness or misdiagnosis as benign melanocytic lesions. The exact mechanism causing the peculiar relationship of invasive melanoma to solar elastosis described herein remains unknown. The lack of a significant inflammatory host response may be related, but further studies are needed to explain our findings.

In conclusion, contrary to prior understanding, melanoma does not always cause downward displacement of solar elastosis. Furthermore, the relationship of melanocytic nevi and melanoma to solar elastosis cannot be used reliably to distinguish between the two. In a patient with a history of melanoma, special attention should be paid to the solar elastosis, especially when it appears more cellular than usual; in these cases, evaluation for atypia, mitotic figures, a high proliferation index by immunohistochemistry, perineural invasion and
other indicators of malignancy would be prudent. Our cases show the importance of this pitfall not only in initial diagnosis of a primary or metastatic melanocytic neoplasm but also in evaluation of excision specimens, where dermal melanocytes dispersed amongst solar elastosis may represent the only evidence of residual melanoma. Knowledge of this rare pitfall may also avoid potential discrepancies in measuring the Breslow thickness.

References


Figure legends

Figures 1A-C: A. Melanoma cells intimately associated with solar elastosis with only occasional scattered lymphocytes (x200, H&E), B. Lateral en face margin (x40, H&E), C. Lateral en face margin (x100) showing
atypical epithelioid cells. A pan-melanocytic cocktail (inset) is positive in these cells, consistent with melanoma.

Figures 2A-C: A, B. Melanoma cells intimately associated with prominent solar elastosis with underlying previous biopsy site changes and melanoma in situ (A. x20, H&E) (B. x200, H&E), C. A pan-melanocytic cocktail highlights overlying in situ melanoma and epithelioid cells underlying scar, consistent with invasive melanoma (C. x100 and B. inset x200, pan-melanocytic immunohistochemical cocktail).
Table-1 Summary of demographic and clinicohistologic features of melanoma cases intimately associated with solar elastosis

<table>
<thead>
<tr>
<th>Cases</th>
<th>1</th>
<th>2</th>
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<tr>
<td><strong>Presenting history</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>74</td>
<td>63</td>
<td>68</td>
<td>75</td>
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<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
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<td>F</td>
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<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Anatomic location</td>
<td>Right forearm</td>
<td>Right upper arm</td>
<td>Left cheek</td>
<td>Right lower leg</td>
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<tr>
<td>Family history of malignancy</td>
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<td>Breast Cancer</td>
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<td>NA</td>
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<td>Personal history of malignancy</td>
<td>SCC of skin</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td><strong>Histopathology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Type</td>
<td>Nodular</td>
<td>Superficial spreading</td>
<td>Lentigo maligna</td>
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<tr>
<td>Breslow thickness, mm</td>
<td>6.8</td>
<td>0.9</td>
<td>1.7</td>
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<tr>
<td>Mitotic rate, /mm²</td>
<td>21</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Characteristic</td>
<td>Present</td>
<td>Not identified</td>
<td>Not identified</td>
<td>Not identified</td>
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<td>--------------------------------------</td>
<td>---------</td>
<td>----------------</td>
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</tr>
<tr>
<td>Ulceration</td>
<td>Present (10mm in width)</td>
<td>Not identified</td>
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<tr>
<td>Perineural invasion</td>
<td>Present</td>
<td>Not identified</td>
<td>Present</td>
<td>Present</td>
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<tr>
<td>Lymphovascular invasion</td>
<td>Present</td>
<td>Not identified</td>
<td>Not identified</td>
<td>Not identified</td>
</tr>
<tr>
<td>Clark level</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>NA</td>
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<tr>
<td>Associated nevus</td>
<td>Not identified</td>
<td>Not identified</td>
<td>Not identified</td>
<td>Not identified</td>
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<td>In situ component</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
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<td>Molecular alterations (mutation)</td>
<td>EGFR, RET, CDKN2A</td>
<td>NA</td>
<td>CCND3, RET, ALK, TERT</td>
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**Management and follow-up**

<table>
<thead>
<tr>
<th>Margin status after wide local excision</th>
<th>Positive, lateral en face</th>
<th>Negative</th>
<th>Negative</th>
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<tr>
<td>Lymph node status</td>
<td>2/2 SLNs positive; 0/2 SLNs</td>
<td>1/2 SLNs</td>
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<td></td>
<td>8/27 RLN positive</td>
<td>positive</td>
<td>positive, 1 additional</td>
<td></td>
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<tr>
<td>Clinically positive node</td>
<td>Distant metastasis</td>
<td>Yes (lungs and liver)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------</td>
<td>-----------------------</td>
<td>----</td>
<td>----</td>
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<tr>
<td>Follow-up</td>
<td>Died 13 months</td>
<td>Alive 40 months after diagnosis</td>
<td>Alive and exploring treatment options</td>
<td>Alive and exploring treatment options</td>
</tr>
</tbody>
</table>

NA, not available; RLN, regional lymph node; SLN, sentinel lymph node; SCC, squamous cell carcinoma.