Melanocytic Matrical Carcinoma in a Solid-Organ Transplant Recipient

David R. Pearson, MD; Joshua Wisell, MD; Theresa Pacheco, MD

To the Editor:
A 68-year-old white man presented with a firm, gradually enlarging, mildly tender, grayish black papule with central ulceration on the left dorsal wrist of 4 months' duration (Figure 1). His relevant medical history included multiple basal cell carcinomas (BCCs) and squamous cell carcinomas, as well as a single-lung transplant 2 years prior, for which he was on chronic immunosuppressive therapy with azathioprine, everolimus, tacrolimus, and prednisone. The clinical differential diagnosis included pigmented BCC, malignant melanoma, and ulcerated squamous cell carcinoma.

Histologic examination of the lesion (Figure 2) demonstrated irregular nodules of basaloid tumor cells with rounded nuclei, visible nucleoli, and scant cytoplasm involving the dermis. The tumor produced abrupt matrical-type keratinization, forming ghost cells. The lesion also contained frequent mitotic figures, apoptotic cells, focal areas of necrosis, and abundant melanin pigment. Admixed throughout the lesion were pigmented and dendritic melanocytic cells. The overlying epidermis was focally ulcerated with an adjacent localized connection between the tumor and the epidermis. Keratinocyte atypia was found in the surrounding epidermis, which contained melanophages, solar elastosis, and scattered chronic inflammatory cells. An immunohistochemical study (Figure 3) for tyrosinase demonstrated abundant admixed melanocytic cells. β-Catenin expression was shown in both nuclear and cytoplasmic distributions, and there was focal labeling on BerEP4 staining. Based on these findings, a diagnosis of melanocytic matrical carcinoma (MMC) was made.

The lesion was subsequently treated with wide local excision. Melanocytic matricoma (MM), a rare adnexal tumor, was first described in 1999 by Carlson et al. A PubMed search revealed that MM is an extremely rare adnexal malignancy that can present as a hyperpigmented papule with or without ulceration. Histologically, the lesion resembles a matrical carcinoma with admixed, banal-appearing dendritic melanocytes. Solid-organ transplant recipients are at an increased risk of cutaneous malignancies, including rare cancers such as MMC, and these neoplasms should remain in the clinician's differential diagnosis.

Dr. Pearson is from the Department of Dermatology, University of Minnesota School of Medicine, Minneapolis. Drs. Wisell and Pacheco are from the University of Colorado School of Medicine, Aurora. Dr. Wisell is from the Department of Pathology, and Dr. Pacheco is from the Department of Dermatology.

The authors report no conflict of interest.
Correspondence: David R. Pearson, MD, 516 Delaware St SE, Minneapolis, MN 55455 (pearsond@umn.edu).
search of articles indexed for MEDLINE using the terms melanocytic and matricoma yielded 24 reported cases in the English-language literature.1-17 It consists of an admixed population of basaloid matrical and supramatrical cells, ghost cells, and dendritic melanocytes in a well-circumscribed dermal nodule, typically without epidermal or adnexal connection. In comparison to the more commonly described pilomatrixoma, which can be uncommonly pigmented, MM typically has only focal areas of ghost cells and lacks cystic architecture.1,9,10 A granulomatous reaction to keratinaceous debris is variably present.1,9,10 Histologically, the scattered dendritic melanocytes are classically benign, but cases demonstrating melanocyte atypia have been reported.10,13 Melanocytic matricoma appears most commonly as a black or gray papule on sun-damaged skin in older men and tends not to recur following complete excision; thus, MM is considered to be a clinically benign neoplasm. Given the demographics and distribution of the lesions, exposure to UV radiation is thought to play a contributory role in the pathogenesis.2,10,19 Evidence demonstrating highly conserved β-catenin and downstream lymphoid enhancer binding factor 1 (LEF1) expression, as well as pleckstrin homology-like domain, family A, member 1 (PHLDA1) expression (as a marker for follicular stem cells), points to constitutive activity in the Wnt signaling pathway in follicular stem cells of the bulge area as a major agent of tumorigenesis.12

FIGURE 2. A, Histologic section of a shave biopsy demonstrated an infiltrative basaloid neoplasm with focal epidermal connections (H&E, original magnification ×2). B, Focal necrosis was found within 1 of the small nests (H&E, original magnification ×200). C, Basaloid tumor cells elaborating matrical-type keratin with abundant melanin pigment and dendritic melanocytes (H&E, original magnification ×400).
### Reported Cases of Melanocytic Matrical Carcinoma

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Patient Age, y/ Sex</th>
<th>Lesion Site</th>
<th>Immune Status</th>
<th>Clinical Appearance</th>
<th>Histologic Appearance</th>
<th>Immunohistochemistry</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sloan et al23 (1992)</td>
<td>74/M</td>
<td>Left thigh</td>
<td>Immunocompetent</td>
<td>Rapidly enlarging, brownish red papule</td>
<td>Nested basaloid cells in fibrotic stroma with nuclear atypia, mitoses, focal necrosis, ghost cells, and admixed dendritic melanocytes</td>
<td>Not performed on tumor cells; melanocytes positive for S-100</td>
<td>Standard excision</td>
</tr>
<tr>
<td>Hardisson et al24 (2001)</td>
<td>77/M</td>
<td>Left cheek</td>
<td>Not disclosed</td>
<td>Ulcerated nodule</td>
<td>Atypical basaloid cells with mitoses and ghost cells; numerous tumor cells contained coarse cytoplasmic melanin granules</td>
<td>Not performed</td>
<td>Wide local excision</td>
</tr>
<tr>
<td>Monteagudo et al22 (2003)</td>
<td>48/M</td>
<td>Posterior neck</td>
<td>Not disclosed</td>
<td>Gray-white ulcerated nodule</td>
<td>Matrical and supramatrical cells with nuclear atypia, focal ghost cells, and dendritic melanocytes</td>
<td>Tumor cells positive for AE1/AE3 and CAM 5.2; melanocytes positive for S-100 and HMB-45</td>
<td>3 standard excisions over 3 years</td>
</tr>
<tr>
<td>Jani et al19 (2008)</td>
<td>77/M</td>
<td>Nose</td>
<td>Not disclosed</td>
<td>Ulcerated hemorrhagic nodule</td>
<td>Sheets of basaloid tumor cells with focal ghost cells and dendritic melanocytes</td>
<td>Tumor cells positive for BerEP4, p63 (diffuse nuclear), CK5/6 (weak), BCL-2, HMWK, CK14 (squamous component); melanocytes positive for S-100, HMB-45, and MART-1</td>
<td>Wide local excision</td>
</tr>
<tr>
<td>Soler et al25 (2010)</td>
<td>84/M</td>
<td>Postauricular area</td>
<td>Not disclosed</td>
<td>Dark nodule</td>
<td>Peripheral basaloid cells with central squamous differentiation, focal ghost cells, and dendritic melanocytes</td>
<td>Tumor cells positive for nuclear and cytoplasmic β-catenin with plasma membrane E- and P-cadherin; melanocytes positive for S-100, HMB-45, and Melan-A</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>Ardakani et al26 (2016)</td>
<td>72/F</td>
<td>Right elbow</td>
<td>Not disclosed; history of metastatic breast adenoid cystic carcinoma</td>
<td>Ill-defined gray nodule</td>
<td>Atypical basaloid, matrical, and ghost cells with admixed dendritic melanocytes</td>
<td>Tumor cells positive for diffuse β-catenin, p63, MNF-116, local weak EMA, and patchy CK5/6 and CK7, and negative for BerEP4; melanocytes positive for Melan-A, SOX10, and MITF</td>
<td>Standard excision</td>
</tr>
<tr>
<td>78/M</td>
<td>Right face</td>
<td>Immunocompetent</td>
<td>Crusted, dark-brown papule</td>
<td></td>
<td></td>
<td>Not disclosed</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Patient Age, y/ Sex</td>
<td>Lesion Site</td>
<td>Immune Status</td>
<td>Clinical Appearance</td>
<td>Histologic Appearance</td>
<td>Immunohistochemistry</td>
<td>Treatment</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Villada et al²⁷ (2016)</td>
<td>79/F</td>
<td>Right posterior leg</td>
<td>Not disclosed</td>
<td>Slowly enlarging ulcerated nodule</td>
<td>Atypical basal cells with numerous mitoses, focal necrosis, ghost cells, and dendritic melanocytes</td>
<td>Tumor cells positive for nuclear and cytoplasmic β-catenin and negative for BerEP4 and AE1/AE3; melanocytes positive for S-100, HMB-45, and Melan-A</td>
<td>Excisional biopsy</td>
</tr>
<tr>
<td>Ji et al²⁸ (2017)</td>
<td>80/M</td>
<td>Left preauricular cheek</td>
<td>Not disclosed</td>
<td>Ulcerated dark brown nodule</td>
<td>Atypical basaloid cells with numerous mitoses, necrosis, ghost cells, and dendritic melanocytes</td>
<td>Tumor cells positive for β-catenin, EMA, and p63, and negative for BerEP4; melanocytes positive for SOX10</td>
<td>Standard excision</td>
</tr>
<tr>
<td>Nielson and Vincek²⁹ (2018)</td>
<td>81/M</td>
<td>Left posterior forearm</td>
<td>Not disclosed</td>
<td>Firm nodule</td>
<td>Atypical basaloid matrical cells with ghost cells, focal necrosis, multiple mitoses, and scattered clusters of melanocytes</td>
<td>Tumor cells positive for AE1/AE3, CK5/6, and increased Ki67; melanocytes positive for S-100, HMB-45, and Melan-A</td>
<td>2 standard excisions; patient died of heart failure</td>
</tr>
<tr>
<td>Lehmer et al³⁰ (2019)</td>
<td>85/M</td>
<td>Right preauricular cheek</td>
<td>Immunocompetent</td>
<td>Black firm nodule</td>
<td>Atypical basaloid cells with ghost cells, focal necrosis, and admixed pigmented dendritic melanocytes</td>
<td>Tumor cells positive for BerEP4, AE1/AE3, and β-catenin, and negative for Melan-A, NSE, and CK20; melanocytes positive for Melan-A</td>
<td>Mohs micrographic surgery</td>
</tr>
<tr>
<td>Current case</td>
<td>68/M</td>
<td>Dorsal wrist</td>
<td>Immunocompromised (azathioprine, everolimus, prednisone, tacrolimus)</td>
<td>Grayish black ulcerated papule</td>
<td>Basaloid tumor cells with focal ghost cells and admixed dendritic melanocytes</td>
<td>Tumor cells positive for nuclear and cytoplasmic β-catenin with focal BerEP4; melanocytes positive for tyrosinase</td>
<td>Wide local excision</td>
</tr>
</tbody>
</table>

Abbreviations: M, male; HMB-45, human melanoma black 45; CK, cytokeratin; BCL-2, B-cell lymphoma 2; HMWK, high-molecular-weight keratin; MART-1, melanoma-associated antigen recognized by T cells 1; F, female; EMA, epithelial membrane antigen; SOX10, SRY-box 10; MITF, melanocyte inducing transcription factor; NSE, neuron-specific enolase.
Melanocytic matrical carcinoma, also known as malignant MM or matrical carcinoma with melanocytic hyperplasia, may be considered the malignant counterpart to MM. A PubMed search of articles indexed for MEDLINE using the terms melanocytic matrical carcinoma, malignant melanocytic matricoma, and matrical carcinoma with melanocytic hyperplasia, with review of references to identify additional citations, yielded 13 reported cases of MMC in the English-language literature (Table). As with MM, MMC is a biphasic tumor with basoloid matrical and supramatrical cells; focal areas of ghost cells; and admixed, banal-appearing dendritic melanocytes. However, the basoloid component also demonstrates nuclear atypia, mitoses, occasional ulceration, and variably poor circumscription. Clinically these lesions can mimic pigmented BCC, malignant melanoma, or other malignant adnexal tumors. Their natural history is unknown due to few reported cases, but they can be correlated with matrical carcinomas, which were first described by Weedon et al in 1980. A summary of more than 130 cases of matrical carcinomas in the English-language literature found that MMCs have high rates of local recurrence and metastasis in approximately 13% of cases. Wide local excision demonstrated lower rates of recurrence than simple excision (23% vs 83%), but there were insufficient cases to determine the incidence following Mohs micrographic surgery. Melanocytic matrical carcinomas also demonstrate mutations in the β-catenin pathway, pointing to a similar pathogenesis as their benign counterparts or perhaps direct malignant transformation.

A subset of MMCs are combined cutaneous tumors (CCTs) consisting of epithelial neoplasms in close association with malignant melanocytes. Two of the more common variants include dermal squamomelanocytic tumors, a term first used by Pool et al, and malignant melanocytic tumors, as named by Erickson et al, but trichoblastomelanomas and other types have been documented. Although CCTs typically occur in the same patient populations as MMCs, namely elderly white men with chronically sun-damaged skin, they exhibit several important distinctions. By definition, CCTs have a malignant melanocytic component, whereas melanocytes are nonneoplastic in MMCs. The pathogenesis may differ as well. Various mechanisms for the close association of epithelial tumors and melanoma have been proposed, including field cancerization, tumor collision, tumor-tumor metastases, tumor colonization, and others, though CCTs likely arise through combinations of these processes depending upon their subtype. Paracrine signaling may play an important role in the pathogenesis of both tumors. As with MMCs, the prognosis of CCTs is limited by relatively few reported cases. Despite advanced Breslow depths in many cases, these tumors display more indolent behavior suggestive of melanoma in situ rather than invasive melanoma, perhaps due to dependence upon epithelial paracrine factors.

Solid-organ transplant recipients have higher rates of more aggressive malignancies, of which skin cancer is the most common. Squamous cell carcinoma of the skin accounts for 95% of cutaneous malignancies in this population and occurs at approximately 65 times the rate of the general population. The risk of other skin cancers also is increased, though less dramatically, including BCC (10-fold increased risk) and melanoma (2- to 8-fold increased risk). The cause likely is multifactorial, including older age, history of skin cancer pretransplant, more than 5 years posttransplant, male sex, and incrementally as Fitzpatrick skin type decreases from VI to I. Immunosuppressive therapy also plays a role in tumorigenesis. Azathioprine metabolites have specifically been implicated in UVA radiation–induced promutagenic oxidative damage to DNA. Other studies have found no significant differences in the type of immunosuppressant used but instead have correlated rates of skin cancer to overall immunosuppression. Lung transplant recipients in particular demonstrate high rates of cutaneous malignancy, likely due in part to the necessity of more potent immunosuppressive regimens. Nearly one-third of patients develop a cutaneous malignancy by 5 years and nearly half by 10 years posttransplant.

We report a rare case of MMC in a solid-organ transplant recipient. We hypothesize that the combination of UV radiation exposure–induced photodamage acquired pretransplant in addition to an aggressive immunosuppressive regimen with azathioprine and other agents posttransplant contributed to the development of this patient’s rare malignancy. Although rare, these tumors should remain in the differential diagnosis of clinicians and pathologists caring for this unique patient population.

REFERENCES

MELANOCYTIC MATRICAL CARCINOMA