DERMATOLOGY PRACTICAL & CONCEPTUAL
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Melanoma in situ colonizing basal cell carcinoma: a case report and review of the literature

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Key words: basal cell carcinoma, malignant melanoma, colonized tumors

Citation: Mancebo SE, Marchetti MA, Hollmann TJ, Marghoob AA, Busam KJ, Halpern AC. Melanoma in situ colonizing basal cell carcinoma: a case report and review of the literature. Dermatol Pract Concept 2015;5(1):4. doi: 10.5826/dpc.0501a04

Received: September 22, 2014; **Accepted:** October 27, 2014; **Published:** January 30, 2015

Funding: None.

Competing interests: The authors have no conflicts of interest to disclose.

All authors have contributed significantly to this publication.

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ABSTRACT Colonization of basal cell carcinoma (BCC) by melanoma cells is a unique and uncommonly reported cutaneous entity. We describe a bluish nodule on the left forearm found during routine skin cancer surveillance examination with suspicious dermatoscopic findings including central-blue-white veil, sparse atypical dots, and a surrounding pink vascular blush with focal irregular tan-brown pigmentation at the periphery. Histopathology demonstrated a pigmented BCC with an overlying and adjacent melanoma in situ (MIS), as well as colonization of the BCC nodule by melanoma cells. We performed a review of the literature on the topic and discuss other presentations of cutaneous neoplasms composed of both BCC and melanoma, including collision, combined, and biphenotypic tumors. The prognostic and management challenges inherent to this distinctive neoplasm are summarized.

Case presentation

A man in his eighties with a past medical history notable for 4 primary cutaneous melanomas (all AJCC Stage IA or 0), squamous cell skin cancer, and severe actinic damage presented for routine skin cancer surveillance follow-up. On the left dorsal forearm, a new 8 mm bluish nodule was detected during photographically assisted examination using total body photography digital images (Figure 1). The patient was unaware of the lesion and denied the presence of any symptoms, including pain, itching, or bleeding. Non-polarized contact dermatoscopic examination revealed a central blue-white veil, scale, sparse atypical blue and black dots focally at the periphery, and a surrounding pink vascular blush with focal irregular tan-brown pigmentation (Figure 2). No lymphadenopathy was present in the bilateral epitrochlear, axillary, supraclavicular, or cervical nodal basins, and there were no systemic symptoms.

Clinical concern for melanoma prompted an excisional biopsy. Histopathologic examination of the biopsy specimen revealed a nodular basaloid tumor abutting from the epidermis with mucinous stroma, stromal retraction, and small cys-

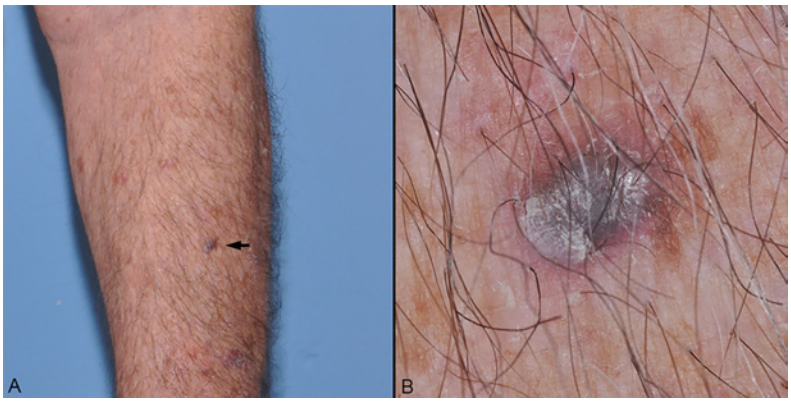

Figure 1. (A) Clinical overview image of a new 8 mm bluish nodule (black arrow). (B) Close-up image reveals a pink halo and peripheral tan pigmentation. (Copyright: ©2015 Mancebo et al.)

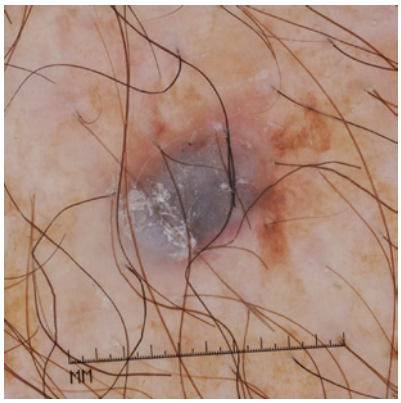

Figure 2. Nonpolarized contact dermoscopic image showing central blue-white veil, scale, sparse atypical blue and black dots focally at the periphery, and a surrounding pink vascular blush with irregular tan-brown pigmentation. (Copyright: ©2015 Mancebo et al.)

tic spaces filled with mucin and melanin pigment (Figure 3). Many atypical melanocytes were identified within the tumor as well as in the adjacent epidermis (Figures 3 and 4). The nodular basaloid tumor stained with BerEp4 (Figure 5). The atypical melanocyte population within the tumor and along the dermal-epidermal junction stained with HMB-45 (Figure 6A and 6B), A103, and Sox10. No invasive melanoma was identified in the dermal stroma outside the basaloid nodule. These findings were interpreted as melanoma in situ (MIS) colonizing a nodular basal cell carcinoma (BCC). Surgical excision with 1 cm margins was performed and revealed residual MIS at a peripheral margin. Two additional excisions, each with 5 mm margins, were required to achieve negative histopathologic margins.

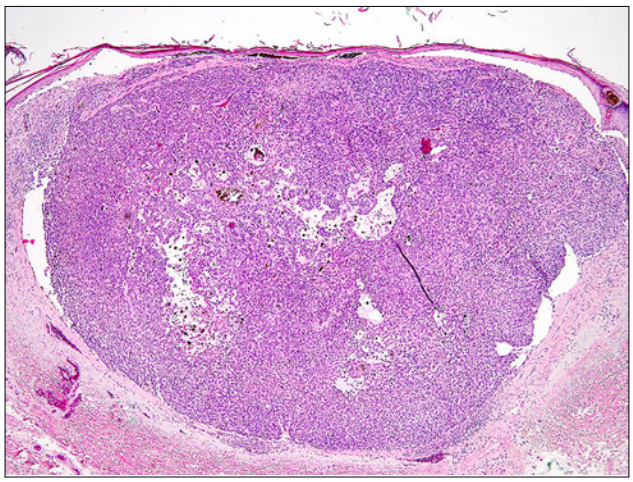

Figure 3. Histopathologic examination revealed a nodular basaloid tumor island budding from the epidermis, stromal retraction, and small cystic spaces filled with mucin and pigment (hematoxylin-eosin, x40). (Copyright: ©2015 Mancebo et al.)

Discussion

Cutaneous neoplasms with two or more distinct cell populations are rare but well documented entities that frequently pose a diagnostic challenge to both clinicians and pathologists. Multiple unique presentations regarding the specific co-existence of BCC with melanoma or melanocytic nevi

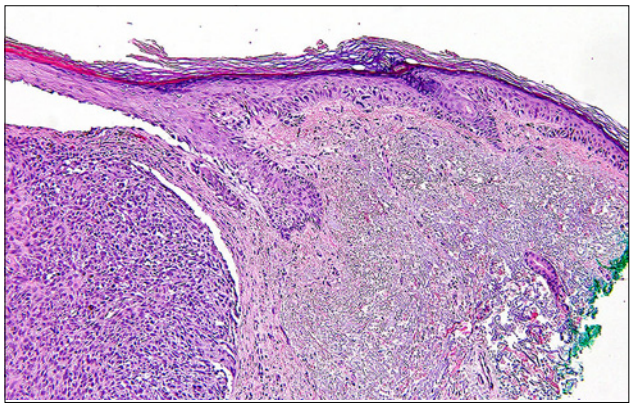

Figure 4. Histopathologic examination also demonstrated atypical melanocytes as single cells and clusters within the basaloid nodule and along the dermal-epidermal junction (hematoxylin-eosin, x400). (Copyright: ©2015 Mancebo et al.)

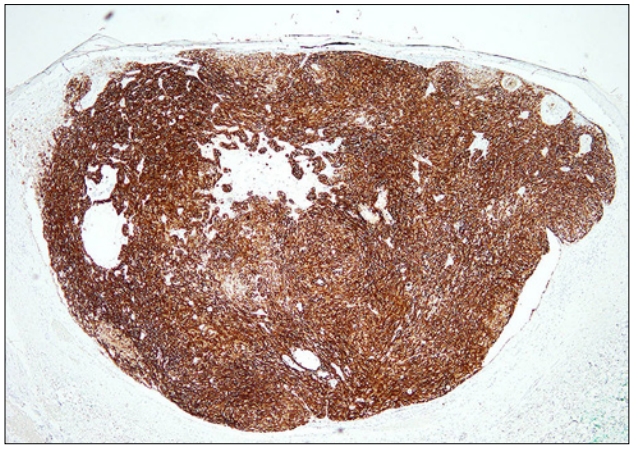

Figure 5. BerEP4 labeled the nodular basaloid tumor, consistent with a diagnosis of basal cell carcinoma (x40). (Copyright: ©2015 Mancebo et al.)

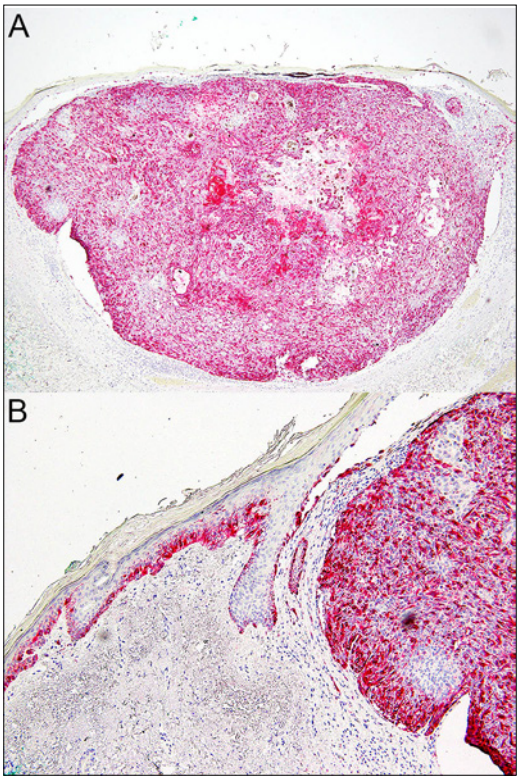

Figure 6. HMB45 highlighted the atypical melanocytes present in the (A) BCC tumor island as well as the (B) dermal-epidermal junctional (A, x40; B, x200). (Copyright: ©2015 Mancebo et al.)

have been reported, often with confusing, overlapping, or imprecise nomenclature. Based on a review of the literature, Satter et al proposed simplifying the terminology used for these lesions and classifying them as collision, combined, colonized, or biphenotypic tumors [1].

Collision tumors are defined as two distinct neoplasms that occur within close proximity of each other but maintain sharp distinct boundaries [1,2]. Pierard et al retrospectively searched a histopathologic case series of 78,000 primary cutaneous cancers and identified 11 collision tumors of melanoma with BCC [3]. Case reports have similarly documented other examples of collisions between BCC and melanoma [4-10], but also with melanocytic nevi [8,11-15] and blue nevi [16,17]. Boyd and Rapini performed a retrospective evaluation of 40,000 cutaneous biopsies and found 69 examples of collision tumors. BCC with melanocytic nevus (n=14) was the most frequently identified collision tumor in their series [11]. The coexistence of BCC and melanoma was not found.

Neoplasms consisting of two phenotypically different, yet imperceptibly intertwined populations of malignant cells are referred to as combined tumors [1,2,18]. Often immunohistochemical stains are required to appreciate the intermingling of two tumor cell populations. Using the above definition, authors have suggested reclassifying some neoplasms previously reported as collision or colonized tumors, as examples of combined BCC and melanoma lesions [1,2,10,19-30].

Biphenotypic tumors are exceptionally rare neoplasms that arise from a common stem cell precursor that undergoes divergent differentiation. The tumor cell populations that arise exhibit overlapping immunohistochemical and molecular properties, such as cytoplasmic organelles normally seen in two different cell lines [1]. Rodriguez et al described two cases of cutaneous neoplasms with combined phenotypical features of BCC and melanoma, employing the term "basomelanocytic" tumor [20]. Nonetheless, the authors could not conclusively demonstrate tumor cells showing combined staining for keratinocytic and melanocytic markers, and these tumors are likely better classified at present as combined neoplasms [1]. In contrast, there is a report of a biphenotypic squamomelanocytic tumor reported by Rosen et al in which dual expression of both S-100 and keratin could be detected, along with expression of both premelanosomes and keratin tonofilaments in the cytoplasm of cells by electron microscopy [31].

A unique situation arises when MIS permeates an adjacent or underlying BCC tumor. In these cases, atypical melanocytes from an adjacent MIS are found interspersed among, but always restricted to basaloid epithelial cell aggregates (i.e., no invasive melanoma component exists). The case presented herein represents an example of such a phenomenon (Table 1) [32-36]. Care must be used with the term "colonization" as this term has also been used to describe the situation where large dendritic non-neoplastic melanocytes populate various neoplasms [2,37-39]. The discovery of colonization of BCC by melanoma cells specifically led Florell et al to analyze nests of BCC using immunohistochemistry. They found that all 10 BCC tumors studied were populated by either dendritic melanocytes at the periphery (5/10) or evenly throughout the tumor (5/10) [37]. The authors further compared the density of melanocytes in BCC tumor islands to a single example of BCC colonized by MIS and found that when BCC is infiltrated by melanoma cells, the melanocyte density is higher and clusters of melanocytes can be observed [37].

Including the case presented herein, the majority of patients who have developed colonization of BCC by MIS have been males (5/6), often with significant risk factors for melanoma including a history of prior invasive melanomas [32-34], severe actinic damage [32,33], CDKN2A gene mutation [32], or xeroderma pigmentosum variant [33]. Anatomic sites with chronic ultraviolet light exposure including the face, ears, forearm, and scalp are most frequently affected. Dermatoscopy or reflectance confocal microscopy (RCM) was rarely used in the evaluation of these neoplasms. Recently, these two diagnostic technologies have emerged as valuable tools for the diagnosis of cutaneous neoplasms with two or more distinct cell populations [8,15,32,40,41]. In one study of 20 benign-malignant collision tumors, dermatoscopy and RCM was successful in identifying the malignant tumor in 14 and 19

TABLE 1. Summary of Reported Cases of Colonization of Basal Cell Carcinoma by Melanoma In Situ (Copyright: ©2015 Mancebo et al.)

Author	Age	Sex	Anatomic Site	Past Medical History	Clinical Description	Dermatoscopic Features	RCM Features	Treatment and/or Outcome
Burkhalter and White [35]	69	M	Ear	No melanoma	Irregular pigmented lesion	—-	—-	Conservative local excision
Wang et al [34]	72	M	Eyelid	Basal cell carcinoma	1 cm scaly reddish-brown nodule	—-	—-	Local excision with negative SLN biopsy
Salerni et al [32]	60	M	Back	*CDKN2A* mutation; 2 prior melanomas; atypical mole syndrome; severe actinic damage	2.6 × 1.6 cm brown to blue plaque	Asymmetric multicomponent lesion with atypical network, irregular globules, multiple colors, and blue color in center	Disarranged epidermal architecture with bright roundish nucleated cells in the spinous layer; non-edged dermal papillae and roundish atypical cell aggregates; dermal nodules with peripheral cleft-like dark spaces	Not provided
Smith and Husain [33]	54	F	Forearm	Xeroderma pigmentosum variant; multiple invasive melanomas; multiple NMSCs	2 cm keratotic nodule	—-	—-	Local excision; Died of metastatic melanoma (unknown primary but history of multiple prior invasive melanomas)
Goeser and Dimaio [34]	83	M	Scalp	Desmoplastic melanoma	Pigmented lesion	—-	—-	Not provided
Current Case	80s	M	Forearm	4 prior melanomas; multiple SCCs; severe actinic damage	8 mm brown to blue nodule with pink halo	Blue-white veil; scale; irregular blue/black dots; peripheral vascular blush and irregular tan-brown pigmentation	—-	No evidence of disease after 3 local excisions

RCM = Reflectance confocal microscopy; CDKN2A = cyclin-dependent kinase inhibitor 2A; NMSC = Non-melanoma skin cancer
SCC = Squamous cell carcinoma

cases, respectively [8]. In our case, the dermatoscopic features observed correlated well with histopathologic findings. The blue-white veil and blue-black dots are due to melanin and aggregates of pigmented neoplastic cells within the dermal nodule. The irregular tan-brown color at the periphery of the lesion corresponds to lentiginous proliferation of in-situ neoplastic melanocytes along the dermal-epidermal junction.

Colonization of BCC by MIS raises important etiologic, prognostic, and therapeutic questions. Currently, the mechanism of colonization is not well elucidated. We suggest an "interaction theory" [2] may be a contributing factor for the colonization of BCC by MIS. We believe that increased secretion of cytokines and growth factors from the BCC may create a favorable environment for the unrestrained proliferation of melanoma cells [2]. Furthermore, it is plausible that a BCC may be populated by melanoma due to poor physical cohesion of BCC cells, allowing melanoma cells to proceed without mechanical resistance. With regards to prognosis, the biologic significance of the Breslow depth of melanoma cells colonizing, but restricted within a BCC tumor island remains unclear. Burkhalter and White originally suggested that the BCC simply acts as a conduit for the extension of neoplastic melanocytes, similar to that seen when MIS extends along adnexa, and therefore does not represent true invasion [35]. We agree with previous authors who have similarly stated that these lesions are unlikely true invasive melanomas with metastatic potential [32-36]. Nonetheless, the following two cases highlight the caution that should be exercised before issuing a diagnosis of BCC colonization by MIS.

Belisle et al report a case of an 82-year old woman where the initial biopsy of a papule on the nose demonstrated lentigo maligna with permeation of BCC nests by melanoma cells [21]. No atypical melanocytes were detected in the dermis outside the BCC epithelium or between collagen bundles. A subsequent re-excision, however, demonstrated true dermal melanoma invasion beyond the limits of the BCC, suggesting invasion of melanoma into the dermis from the overlying epidermis. In a similar case, Taibjee et al report the presentation of a BCC with an overlying lentigo maligna on the nose of a 78-year old man [29]. Atypical melanocytes, both as single cells and clusters, were additionally present in basaloid islands but also throughout the surrounding BCC dermal stroma. It remains unclear in this later case whether melanoma cells entered the dermis through invasion of the epidermis or via the epithelia of the basaloid tumor islands.

In summary, we report a case that may best be interpreted as a melanoma in situ colonizing a BCC. We are of the opinion that these tumors developed independent of each other and the BCC served as a conduit for the extension of melanoma cells. The alternate hypothesis of a biphenotypic tumor with a common precursor diverging towards both epithelial and melanocytic differentiation seems less plausible. Given the absence of adequate prospective data on outcomes, we suggest that these neoplasms should be treated on an individual case-by-case basis, taking into account the adequacy of the original biopsy, the anatomic site of the lesion, and the age and underlying comorbidities of the patient. New technologies, particularly RCM, may be useful in accurately identifying these tumors prior to skin biopsy.

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