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Discohesive malignant melanoma simulating a bullous dermatoses

A variety of clinical and histological presentations can accompany the evolution of malignant melanoma. Unusual cytological variants of malignant melanoma include balloon cell, signet ring cell, myxoid and other metaplastic changes. With the exception of a case of pemphigus-like changes associated with malignant melanoma in paraneoplastic pemphigus, acantholysis is not a common histopathological feature of malignant melanoma. We present two unique cases of malignant melanoma with varying degrees of extensive melanocytic discohesion in an acantholytic pattern mimicking pemphigus vulgaris, further referred to in this article as 'discohesive melanoma'. Routine direct immunofluorescence studies for pemphigus-related antibodies (IgG and C3) were negative. In one case, indirect immunofluorescence for desmoglein autoantibodies characteristic of pemphigus were negative, although positive antibodies to desmoglein 1 was detected using immunosorbent assay. The differential diagnoses and pitfalls in recognition of this unusual presentation of malignant melanoma along with possible pathogenetic mechanisms are discussed.

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Acantholysis is a process where epithelial cells lose desmosomal connections and separate from one another.[1] An acantholytic pattern can result from antibodies targeting cellular connections (desmosomes), a heritable loss of intercellular connections, or from severely increased intercellular edema and shearing of intracellular connections resulting from trauma. The histopathological finding of melanocyte discohesion mimicking acantholysis in a pemphigus vulgaris (PV) pattern with no other cutaneous or mucosal involvement is an exceedingly rare event. A MEDLINE search of the English literature from January 1955 to October 2006 revealed one similar example of a localized variant of paraneoplastic pemphigus (PNP) associated with malignant melanoma.[2]

In our first patient, we observed suprabasal discohesion between melanocytes. In our second patient, we observed a similar pattern of suprabasal melanocytic discohesion as well as discohesion within the melanocytic nests throughout the epidermis. We propose the term 'discohesive melanoma' for these patterns of suprabasal discohesion between melanocytes mimicking acantholysis in a PV pattern. Further investigations in one patient revealed the presence of serological characteristics of PV.

Case reports

Case 1

A 52-year-old Caucasian male presented to our dermatology clinic with a pre-existing 2 cm mole on the upper mid-sternum that had progressively become more painful and grown rapidly in 1 month. The patient denied a history of cutaneous malignancies or skin diseases. On examination, there was a 2 × 2 cm dark brown, rough hypertrophic nodule with punctate bleeding on its surface. No other cutaneous or mucosal blistering was present, and no

lymphadenopathy was noted. The patient underwent an excisional biopsy, which showed a malignant melanoma with positive margins (Fig. 1A). A re-excision of the melanoma with axillary sentinel lymphadenectomy revealed negative margins with a negative axillary lymph node biopsy. He remains disease free 1 year after the surgery.

Case 2

A 34-year-old man presented to his primary care physician with a mole on the right ear that grew rapidly over the previous 6 months and had recently bled. On physical examination, a 1 cm pink-gray nodule on the right ear was noted. The patient underwent excisional biopsy that showed malignant melanoma close to the peripheral margins. No mucocutaneous blistering disease or lymphadenopathy was present. The patient refused a sentinel lymphadenectomy and refused further serological testing. He remains disease free after 1 year.

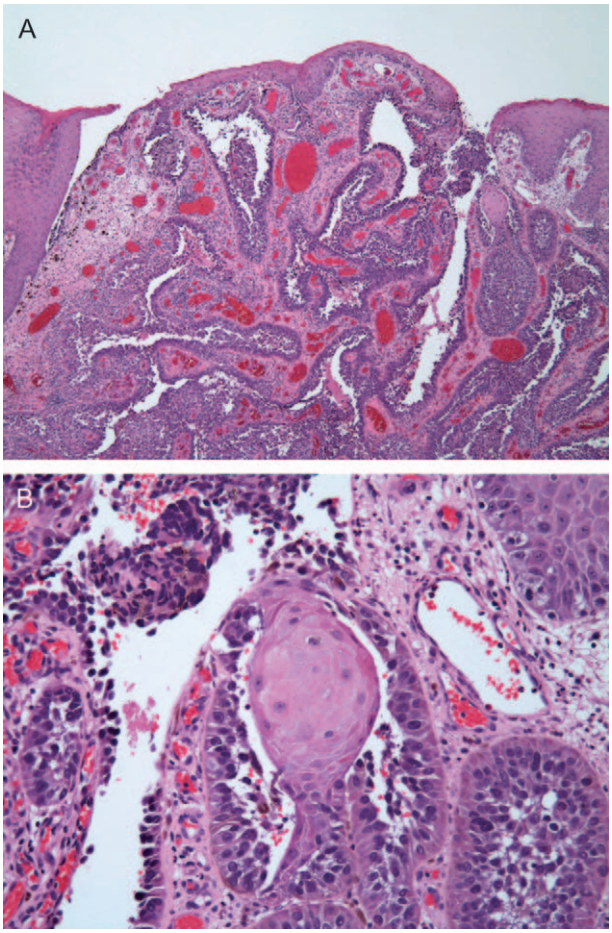

Fig. 1. A) Malignant melanoma in case 1 (Clark level IV, Breslow thickness 6.5 mm) at ×40 magnification. B) Melanocyte discohesion can be seen at suprabasal layers and within melanocytic nests within the melanoma in case 1 at ×200 magnification.

Materials and methods

Hematoxylin and eosin

Four-micrometer thick sections were cut from paraffin blocks and stained with hematoxylin-eosin. Immunohistochemical stains with monoclonal antibodies S-100 (1 : 8000 dilution; DAKO, Carpinteria, CA, USA), Melan-A (1 : 80, Mart-1; DAKO), pan-cytokeratin (AE1/AE3 1 : 400 and LP34 1 : 400; DAKO) and E-cadherin (1 : 100; Zymed, South San Francisco, CA, USA) were performed using a Dako Autostainer and Immunostainer (DakoCytomation, Carpinteria, CA, USA).

Immunofluorescence

Direct immunofluorescence (DIF) studies were only obtained on the first patient's biopsy specimens. DIF was performed on the melanoma biopsy sections and reacted with antibodies directed against human IgG, IgM, IgA, C3 and fibrinogen (Beutner laboratories, Buffalo, NY, USA).[3] Indirect immunofluorescence (IIF) for IgG (IgG1 and IgG4) and complement-fixing antibodies was performed on patient's serum in case 1 using monkey esophagus and rat bladder as substrates.

Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assay (ELISA) on case 1 was performed assaying for anti-desmoglein (Dsg) 1 and anti-Dsg3 antibodies using Dsg1 and Dsg3 recombinant proteins (Beutner laboratories).[4]

Results

Case 1: histological findings

Hematoxylin-eosin-stained sections from the tumor at scanning magnification (Fig. 1A) showed a polypoid nodular melanoma growth arising from the epidermis with infiltration into the reticular dermis (Clark's level IV malignant melanoma, Breslow thickness 6.5 mm). The melanocytes were epithelioid in shape and exhibited large nuclei with prominent nucleoli. The melanoma cells displaced epidermal and dermal components with diffuse sheets and expansile nests. Ten mitotic figures per 10 hpf (magnification ×400) were identified. In multiple foci, the melanoma exhibited a palisading basaloid appearance involving adnexal structures. In these foci, suprabasal and subcorneal melanocytic discohesion was noted (Fig. 1B). No corp ronds or corp grains were identified. An immunohistochemical stain with cytokeratin decorated the epithelial cells but was negative within the melanoma cells (Fig. 2A). The melanoma was strongly immunoreactive with Melan-A and S-100 (Fig. 2B). E-cadherin was strongly positive within the melanoma tumor cells.

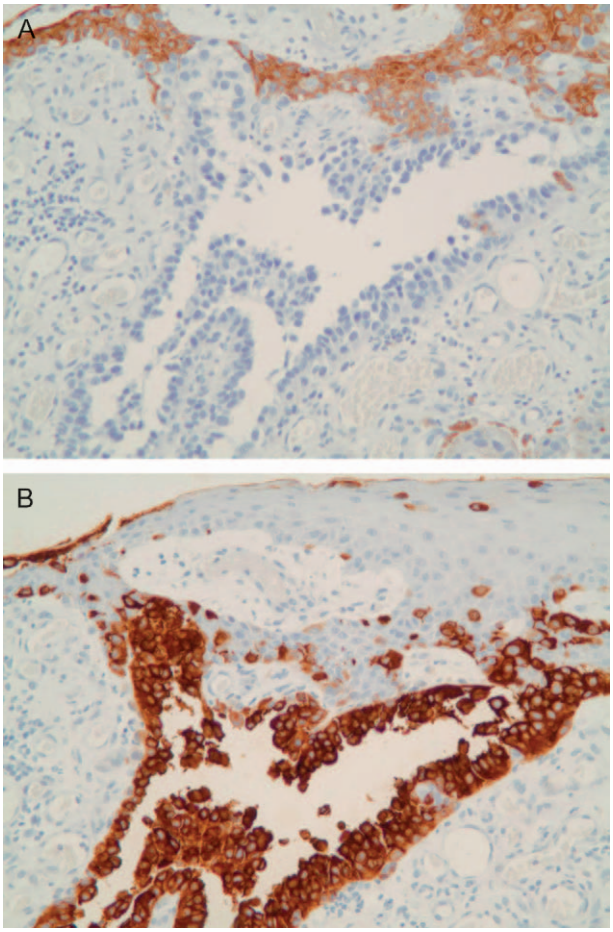

Fig. 2. A) Malignant melanoma in case 1 with immunoperoxidase staining for cytokeratin (magnification ×200). Note the negative staining in the melanoma tumor cells. B) Malignant melanoma in case 1 with positive immunoperoxidase staining for Melan-A (magnification ×200).

Case 2: histological findings

Hematoxylin-eosin-stained sections from the tumor at scanning magnification revealed a nodular melanoma. Sections from this tumor exhibited similar histopathological findings of a nodular melanoma as in case 1 (Clark's level IV, Breslow thickness of 4 mm, extending close to the peripheral margins). Five mitotic figures per 10 hpf were present (magnification ×400). Melanocytic discohesion was seen throughout the melanoma, but predominately localized to the superficial dermal and intra-epithelial component (Fig. 3A). Immunohistochemical stains with cytokeratin, Melan-A, S-100 and E-cadherin revealed an identical staining pattern to the first case (Fig. 3B,C).

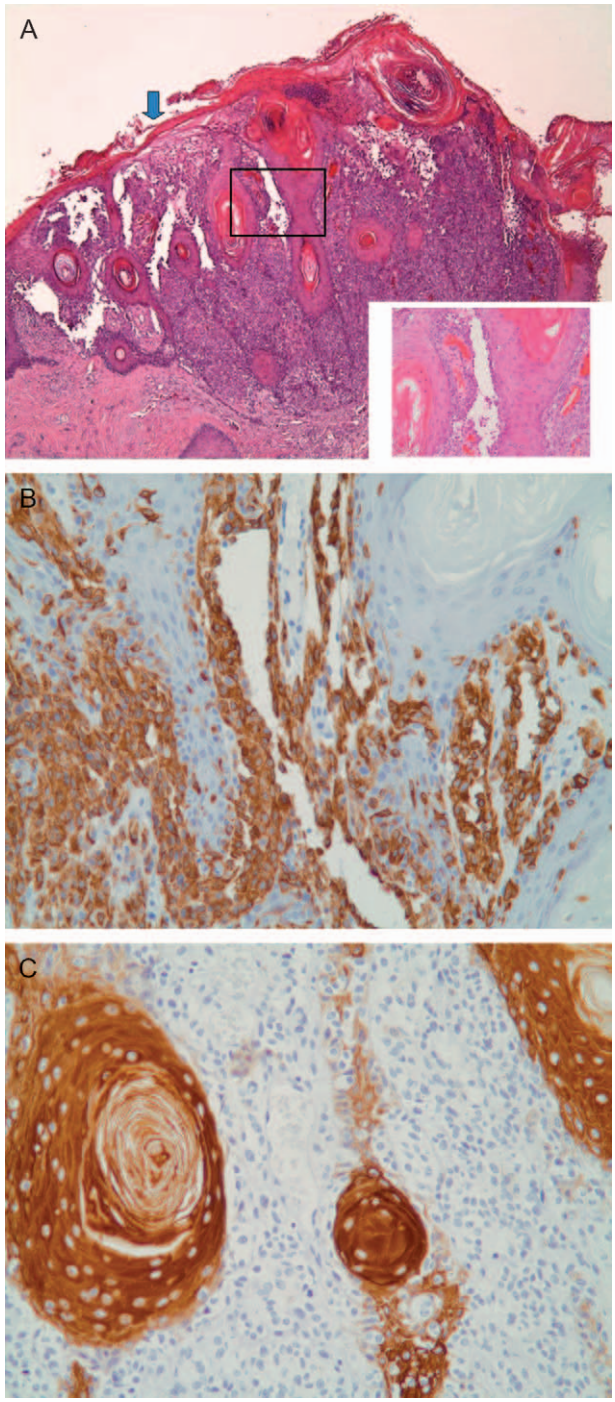

Fig. 3. A) Malignant melanoma in case 2 (Clark level IV, Breslow thickness 4 mm) at ×40 magnification. Consumption of epidermis and epidermal cleft formation is present (arrow). Discohesion between melanocytes is also visible throughout the epidermis (inset at ×200 magnification). B) Malignant melanoma in case 2 with positive immunoperoxidase staining for Melan-A (magnification ×200). C) Malignant melanoma in case 2 with immunoperoxidase staining for cytokeratin (magnification ×200).

Immunofluorescence findings

DIF results for antibody deposition were negative in case 1. IIF for IgG (IgG1 and IgG4) and complement-fixing antibodies on patient's serum in case 1 using monkey esophagus and rat bladder as substrates were negative. However, the antibody profile obtained by ELISA in case 1 showed a positive index of 30.8 for

antibodies to Dsg1, and an indeterminate index of 9.1 was found for antibodies to Dsg3 (an index value greater than 20 is considered positive for both antibodies against Dsg1 and Dsg3).

Discussion

Reports of localized pemphigus-like changes or acantholysis associated with malignant melanoma have been limited to cases of PNP.[2] Acantholytic dyskeratotic patterns have been sporadically reported in melanoma presenting as a bullous lesion, although not in a PV-like pattern as in our patients.[5,6] Our patients are unique with the presentation of a cutaneous melanoma with a spectrum of melanocytic discohesion in a pattern mimicking keratinocyte discohesion in PV and vegetans, but with no obvious clinical stigmata of the autoimmune blistering disorder.

In an attempt to elucidate the pathogenesis of this phenomenon, we assayed for a variety of autoantigens. The first case was negative for direct immunofluorescence studies (IgM, IgG, IgA, C3 and fibrin) within the epidermis, dermis and basement membrane. However, the finding of anti-Dsg1 by ELISA performed on the first patient's serum is intriguing. Immune mechanisms with autoantibodies directed against Dsg1 and Dsg3 have been extensively studied as a crucial factor in autoimmune blistering diseases.[7] The detection of a specific autoantibody profile in a patient's serum can aid in defining the clinical phenotype of pemphigus variants that otherwise share many overlapping clinical findings.[8]

Our patient's serum revealed an anti-Dsg1 titer by ELISA at an index of 30.8, which confirms the presence of Dsg1 antibody (index $>$ 20). This index, however, is relatively low in comparison to prior findings in active PV patients (mean index $=$ 101), but is comparable to index values in PV patients who are in remission (mean index $=$ 22).[9] Based on the ELISA titers, the acantholytic process seen in case 1 would not reflect an active autoimmune response to Dsg1. However, racial differences and genetic factors may also contribute to differences in antigenic profiles.[9] Additionally, unlike in PV, our findings involve melanocyte-keratinocyte and melanocyte-melanocyte discohesion that are not mediated by desmosomal connections. It remains possible that an antigen other than Dsg1 is involved in this process. Our finding may represent a localized autoimmune tissue response that does not involve antibodies directed at pemphigus antigens.

An additional histological feature of melanoma involving cellular discohesion is subepidermal cleft formation (CF), defined as separation between the epidermis and underlying melanocytes at the dermal-epidermal junction. These clefts have been reported in association with consumption of the epidermis (COE) where a thinned epidermis with attenuation of the basal and suprabasal layers and loss of rete ridges overlies a melanoma lesion.[10] Both CF and COE can be seen in Fig. 3A in our melanoma lesion. However, in addition to CF and COE, we also observe distinct discohesion within the melanocytic nests (Fig. 3A, inset).

The etiology of this pattern of discohesive melanoma may be associated with the downregulation of cadherins that occur with the invasive progression of melanoma cells.[11] The loss of regulatory control by surrounding keratinocytes on surrounding melanocytes has been proposed as a facilitating mechanism for the invasion of malignant melanoma cells. The loss of control is reflected in the downregulation of expression of E-cadherin, the major adhesion molecule in the melanocyte-keratinocyte relationship. Hsu et al. showed that transfection of E-cadherin cDNA into melanoma cells leads to cell adhesion to keratinocytes and was able to suppress invasion and to induce apoptosis.[11] Furthermore, melanoma development is also accompanied by the downregulation of Dsg1.[12] The disruption of these adhesion receptors may be responsible for the apparent acantholytic changes seen in our case. A differential expression of E-cadherin receptors has also been reported as a feature associated with different stages in the evolution of melanoma.[13] Similarly, the continuum of discohesive patterns seen in our two cases may reflect different stages in melanoma progression.

A third explanation may be a rare Koebnerization phenomenon at a traumatized site masquerading the initial presentation of pemphigus foliaceus in our patient. Rotunda et al. recently reported a masked pemphigus foliaceus (PF) presentation at postsurgical sites of Mohs procedures.[14] In addition to inducing pre-existing diseases, cutaneous procedures can trigger the onset of new disease. Similarly, the rapid growth of melanoma in our patients was associated with ulceration and may have induced similar traumatic environmental changes in the skin, triggering the onset of a pemphigus foliaceus-like autoimmune profile, contributing to the localized discohesive melanoma changes. This possibility merits further investigation.

The differential diagnosis for our findings also includes a malignant melanoma arising in the setting of a concomitant autoimmune blistering disease. PNP is classically associated with a neoplasia, commonly hematological in origin, with specific inclusion criteria based upon clinical, histological, DIF, IIF and immunoprecipitation tests.[15] The lack of severe mucosal involvement and negative IIF on rat bladder mucosa rules out this diagnosis in our first patient. The DIF and IIF profiles are also not supportive of an underlying PV or vegetans.

The association of contiguous or 'collision' tumors in the same biopsy specimen is often reported in the literature.[6,16–18] We considered the possibility that the discohesive melanoma seen in our case could be the result of a collision tumor between a malignant melanoma with an acantholytic squamous cell carcinoma (ASCC). Histologically, ASCC shows strands and islands of atypical squamous cells extending into the dermis.[19] Connection to the overlying dermis can be seen in most cases, with accompanying hyperkeratosis and parakeratosis and many of the tumor strands exhibiting tubular and alveolar formations, resembling pseudoglandular appendages. The tumor cells in our patient did not express reactivity to cytokeratin but were strongly positive for melanoma markers. In addition, the squamous epithelial cells that were cytokeratin positive were histologically benign.

We also considered the possibility that our case may represent a metastasis to the skin rather than a primary cutaneous melanoma. Metastatic melanoma with epidermotropism of melanoma cells (EMMM) is a histologically rare phenomenon and a challenging diagnosis to make. The classic histopathological criteria of EMMM proposed by Kornberg have been frequently used to diagnose EMMM.[20] Our case lacked many of the classical findings and specifically showed a prominent radial superficial growth and disrupted epidermal architecture but not thinned compared with the surrounding skin. The epidermis was displaced by a dense population of atypical melanocytes in diffuse sheets and expansile nests, extending from the epidermis into the reticular dermis, with a prominent radial epidermal component extending beyond the dermal component. In addition, melanoma cells were not present in endothelial-lined spaces as one would expect in EMMM.

Finally, rare cases of PV may occasionally present with extensive melanin pigment incontinence within the acantholytic cells mimicking the intra-epithelial scatter of a superficial spreading melanoma (personal observation, Paul K. Shitabata). However, none of these cases of PV exhibited the invasive and cytologically malignant cells as evidenced in our current cases.

Conclusion

We report unusual findings of cutaneous malignant melanoma with melanocytic discohesion, illustrating a continuum of histopathological changes. A localized tissue response to melanoma growth results in pemphigus-like discohesion between the suprabasal melanocytes and within melanocytic nests. It is unclear whether undiscovered antigens contributed to this pattern of discohesion between melanocytes in our cases. The presence of antibodies to Dsg1 by ELISA in the first case may be attributed to genetic factors or the patient's predisposition to develop a pemphigus phenotype, but its role in the pathogenesis of our findings remains unclear. This intriguing discohesion between melanocytes and melanocyte-keratinocyte may reflect the progression of malignant melanoma, with loss of control of the keratinocyte-melanocyte relationship. The histopathologist should be aware of this rare and peculiar presentation of a cutaneous malignant melanoma.

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