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An Unusual Pattern of Pseudoepitheliomatous Hyperplasia Associated with Cutaneous Primary Melanoma: Report of Two Cases with Analysis of p53 and bcl-2 Immunoreactivity

Majda Vučić[1], Hrvoje Čupić[1], Karla Tomić[2], Božo Krušlin[1]

[1]Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, Zagreb; [2]Department of Pathology, Dr. Josip Benčević General Hospital, Slavonski Brod, Croatia

Corresponding author:
Majda Vučić, MD, PhD
Ljudevit Jurak University
Department of Pathology
Sestre milosrdnice University Hospital
Vinogradska c. 29
HR-10000 Zagreb
Croatia
mvucic@kbsm.hr

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SUMMARY Pseudoepitheliomatous hyperplasia (PEH) is a benign, reactive epithelial proliferation. PEH is characterized by hyperplasia of the epidermis or adnexal epithelium into irregular squamous strands that extend deep down into the subjacent dermis. PEH occurs in response to underlying infections, inflammatory or neoplastic conditions. The presence of PEH overlying cutaneous melanoma is rare. The clinical and histological features of PEH can closely mimic squamous cell carcinoma and could be misinterpreted. We report two cases of cutaneous primary melanoma associated with PEH and discuss differential diagnoses and potential role of p53 and bcl-2 in the pathogenesis of PEH.

KEY WORDS: pseudoepitheliomatous hyperplasia, primary melanoma, squamous cell carcinoma

INTRODUCTION

Pseudoepitheliomatous hyperplasia (PEH), also known as pseudocarcinomatous hyperplasia, is a benign pathological reaction pattern (1). PEH occurs in response to persistent inflammation of the subjacent dermis due to a chronic wound, retained foreign material or an infection (fungal, bacterial or viral) (2). Reactive, exuberant epithelial proliferation is also seen in coexistence with some dermatological conditions such as prurigo nodularis, granuloma fissuratum, chondrodermatitis nodularis, lichen planus and lichen sclerosus of the vulva (3,4). Tumors with overlying PEH include granular cell tumor, cutaneous T cell lymphomas, and salivary gland pleomorphic adenoma (5-7). The association of PEH with benign melanocytic nevi and Spitz nevi is not uncommon and is well documented in the literature (8,9). However, reports documenting the association of PEH with melanoma are rare. In fact, little is known about the pathogenesis of PEH, regardless of the underlying etiology. We report two cases of cutaneous primary melanoma associated with histological features of PEH mimicking squamous cell carcinoma.

CASE REPORTS

The first patient was a 38-year-old male that presented with a polypoid, grayish-brown skin tumor on the left thigh measuring 1.5 cm in largest diameter. The second patient was a 75-year-old

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Table 1. p53 and bcl-2 immunohistochemical staining in two cases of pseudoepitheliomatous hyperplasia overlying primary cutaneous melanoma

Antibody	Case No.	Overlying hyperplastic epidermis	Horn cysts	Infiltrating epithelial strand
p53	1	++	+	++
p53	2	++	+	++
bcl-2	1	+++	+	+++
bcl-2	2	+++	+	+++

0, negative reaction; +, week staining, similar to adjacent normal basal epithelium; ++, moderate staining, less intense than in atypical melanoma cells; +++, strong staining, equivalent to atypical melanoma cells

female with elevated, brownish tumor on the face, measuring 0.8 cm in largest diameter. Clinically, in both cases hyperkeratotic skin lesions were suspected for squamous cell carcinoma. Histopathologic analysis of excised lesions revealed abnormal architectural and cytological features on hematoxylin and eosin (H&E) stained slides, which were indicative of malignant melanoma, classifed as Breslow III in the first case and Breslow V in the second case.

In each case, prominent hyperkeratosis, epidermal acanthosis with irregular cords of well-differentiated epithelial cells extending into the dermis and infiltrating among and around the melanoma cells, and multiple horn cysts was observed. The hyperplastic foci arose directly from the epidermis without association with adnexal epithelium. In both cases, admixture of the neoplastic melanocytic and hyperplastic keratinocytic components led us to reconsider the diagnosis of malignant melanoma and concurrent invasive squamous cell carcinoma. Serial sectioning using immunohistochemical analysis of HMB-45 and cytokeratin (DAKO, Copenhagen, Denmark) was performed (Fig. 1A, B). On immunohistochemical slides, the neoplastic melanocytic component was easier to identify and distinguish from the hyperplastic epidermal component, and the possibility of squamous cell carcinoma was excluded.

Additionally, in each case immunohistochemical analysis of p53 and bcl-2 (DAKO) was performed. In each patient, 4-µm sections were cut, slides were stained immunohistochemically by the labeled streptavidin biotin method (LSAB) as visualization system on Dako Tech Mate automated immunostainer using microwave streptavidin immunoperoxidase (MSIP) protocol. Staining intensity in the hyperplastic superficial epithelium, strands of proliferative epithelium and epithelium of horn cysts was compared with melanoma cells and adjacent basal epidermal cells (Fig. 2A, B). The intensity of immunostaining was semi-quantitatively scored and defined as: 0 (negative); 1+ (week staining, similar to adjacent normal basal epithelium); 2+ (moderate staining, less intense than in atypical melanoma cells); and 3+ (strong staining, equivalent to atypical melanoma cells). Results are summarized in Table 1.

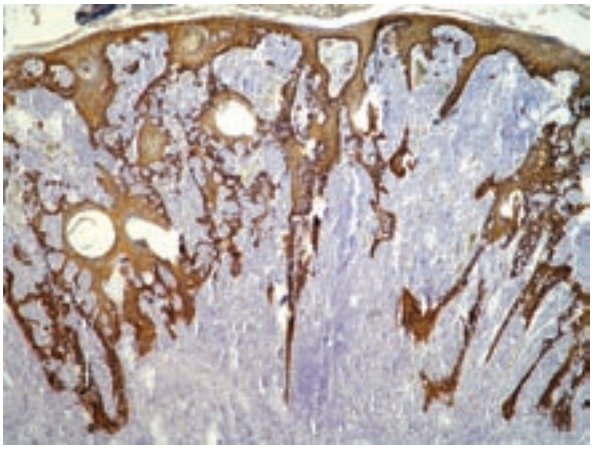

Figure 1A. Epithelial strands with horn cysts originating from the epidermis and infiltrating the dermis among and around melanoma cells. (CK, x100)

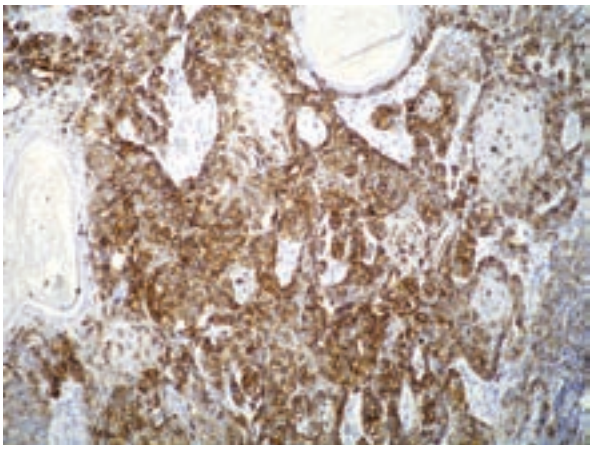

Figure 1B. Admixture of neoplastic melanocytic and hyperplastic keratinocytic cells in the dermis. (HMB-45, x200)

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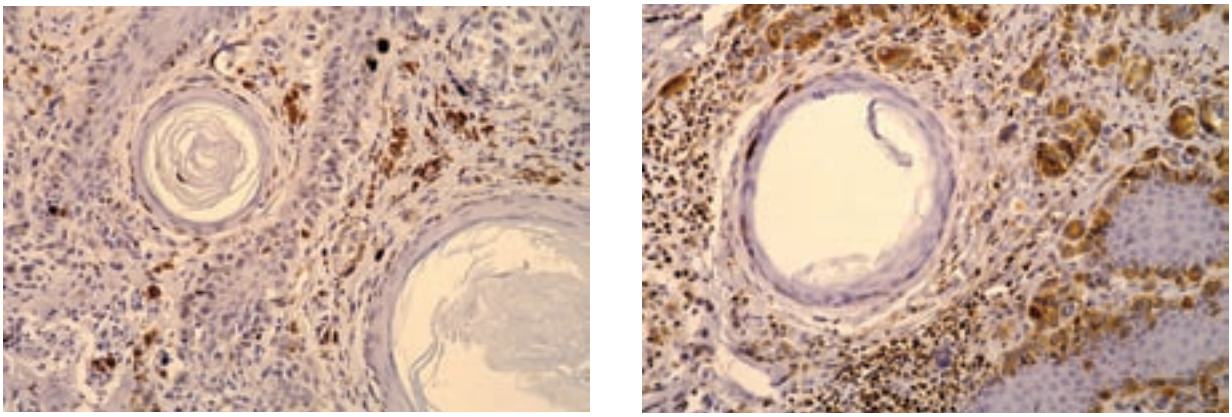

Figure 2. Expression of p53 (A) and bcl-2 (B) in infiltrating keratinocytic cells and horn cysts in the dermis. (A and B, x400)

DISCUSSION

PEH may mimic well differentiated, infiltrating squamous cell carcinoma or complicate the diagnosis of melanoma obscuring the underlying malignant process, thus leading to inappropriate diagnosis and treatment. In the differential diagnosis of atypical pigmented lesion, melanoma associated with PEH can be confused with rare pigmented squamous cell carcinoma of the skin (10). Unlike squamous cell carcinoma, PEH never has atypical mitotic figures, rarely has dyskeratosis or atypical nuclei, and is never involved in vascular, lymphatic or perineural invasion (11).

In the literature, there are some articles that report on PEH overlying cutaneous melanoma. Kamino *et al.* have reported four cases, each case revealing hyperplasia of the epidermis and of upper portion of adnexal epithelium with squamous eddies and horn cysts (12). A case of PEH with thin cords of well differentiated epithelial cells percolating the melanoma cells originating only from the epidermis, without evidence of adnexal origin have been described by Putrino *et al.* (13) and Reis-Filho *et al.* (14). PEH originating from eccrine duct epithelia has been described by Hanly *et al.* (15).

Mott *et al.* collected the largest reported series of 13 cases of PEH in association with melanoma. Seven cases of described PEH overlying melanoma originated from the epidermis, five cases arose directly from follicular epithelium, and one from eccrine epithelium (16). The majority of cases (69%) exhibited acanthosis, hyperkeratosis, papillomatosis, and irregular infiltrating epithelial cords with squamous eddies. The remaining cases (31%) demonstrated basaloid acanthosis, laminated orthokeratosis and horn cysts. Several reports have documented melanoma in conjunction with, or simulating seborrheic keratosis. While most cases represent a collision of the two entities, some authors suggest the possibility that epidermal changes resembling seborrheic keratosis within the confines of the melanoma could be an induced phenomenon (17,18).

The mechanism of PEH is unknown. Some theories speculate that the histogenesis of PEH is due to the proliferative effect of cytokines released by inflammatory or tumor cells within the subjacent dermis. Epidermal proliferation is coordinated by a variety of mediators including epidermal growth factor (EGF), transforming growth factor α (TGF-α) and epidermal growth factor receptor (EGFR), and it is postulated that dysregulation of these growth factors may be important in the development of PEH (19,20). Among the three growth factors mentioned in literature reports, only TGF-α appears to be related to the development of PEH (21,22). Other peptide growth factors such as fibroblastic growth factor and platelet-derived growth factor may be important for exuberant epithelial proliferation in PEH. The reason for PEH development in the absence of growth factors is still unknown.

Expression of p53 in the skin is common and is an early event indicating immaturity and proliferative capacity of the keratinocytic cell. This expression of p53 need not necessarily indicate neoplastic or malignant transformation. Lee and The observed positive staining for p53 in six cases of PEH of the skin (20). The bcl-2 protein suppresses apoptosis and overexpression of the bcl-2 protein has been reported in malignant melanoma of the skin (21). Results of our analyses of p53 and bcl-2 protein expression suggested a difference in the proliferating capacity of infiltrating epithelial strands compared with horn cysts. p53 was expressed mainly in the cells at the base of the

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epidermis. Moderate intensity staining was observed in basal cells of the infiltrating strands and overlying epidermis, and week staining in basal cells of horn cysts. Infiltrating strands of the epithelium, basal and parabasal cells of the hyperplastic epithelium compared with horn cysts also expressed stronger positivity for bcl-2 protein. It is possible that dysregulation of members of the bcl-2 protein family could play a role in the pathogenesis of PEH. Additional studies are necessary to identify the possible cause and prognostic implications for this variant of skin melanomas.

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