Pigmented Extramammary Paget's Disease

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Extramammary Paget's disease (EMPD) usually presents as an erythematous, scaly patch with crusts, or superficial erosions. Pigmented EMPD is a rare variant of EMPD that may mimic malignant melanoma clinically and histopathologically. We report a case of pigmented EMPD on the genital region. The 58-year-old man had an erythematous, scaly patch with a pigmented macule on the scrotum for 5 years. Histopathological and immunohistochemical examinations of the pigmented region confirmed EMPD with melanocytes colonization and melanin accumulation within Paget cells. Plump tumour cells with a large nucleus and pale cytoplasm proliferated singly or in nests in the epidermis. They are positive for CK-7, carcinoembryonic antigen, and mucicarmine stains. Abundant melanin within the cytoplasm was also noted. Scattering among the tumor cells were many S-100 and HMB-45 positive dendritic cells with a large amount of melanin. Immunohistochemical studies of non-pigmented sites showed that S-100 and HMB-45 positive cells were sparse and only detected on the basal layer of the epidermis. Pigmented EMPD may result from the proliferation of melanocytes accompanying the intraepidermal neoplastic cells or/and from accumulation of melanin within the cytoplasm of Paget cells and melanocytes. The interaction between melanocytes and tumor cells are still incompletely understood.(Dermatol Sinica 22 : 321-326, 2004)

Key words: Extramammary Paget's disease, Pigmented, Melanocyte colonization.

色索性乳房外Paget氏病

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INTRODUCTION
Extramammary Paget's disease (EMPD) represents either an intraepidermal adenocarcinoma in situ, or pagetoid spread of an underlying adnexal tumor or of a regional internal malignancy. It commonly affects areas with a high density of apocrine glands, including the vulva, perianal region, male genitalia, and axillae. Its clinical picture usually presents as moisture superficial eroded or erythematous scaly patches. Pigmented EMPD is a rare variant of EMPD that must be distinguished from malignant melanoma clinically and histopathologically. To the best of our knowledge, there is no previous report of pigmented EMPD in Taiwan. We herein report a case of pigmented EMPD on the genital region.

CASE REPORT
This 58-year-old man was healthy before. He had a scaly, erythematous plaque on the left side of scrotum for 5 years. The skin lesion had gradually enlarged in size and had been ever treated as eczema or tinea cruris with topical agents. He presented to us with a well-defined, palm-sized, erythematous, oozing plaque with a hyperpigmented macule measuring 0.7 X 0.3 cm in part (Fig. 1). Skin biopsy of the erythematous area showed many plump tumor cells with pale and abundant cytoplasm proliferated in nests or in single cells within the epidermis (Fig. 2). These tumour cells that were positive for CK-7, carcinoembryonic antigen (CEA), and mucicarmine stains were present from the basal cell layer through the horny cell layer and also in some hair follicles (Fig. 3). There was no evidence of dermal invasion of the tumour cells. The diagnosis of extramammary Paget's disease was established. There was no regional lymphadenopathy or internal malignancy as revealed by pelvic computer tomography, intravenous pyelography, and sigmoid fibroscopy. The tumor was widely excised and the wound...
was repaired with advancement flap.

The central pigmented macule seemed peculiar and attracted our attention. We suspected it as a different lesion, such as seborrheic keratosis, Bowenoid papulosis, basal cell carcinoma, Bowen's disease, malignant melanoma, or pigmented EMPD. It was examined histopathologically and immunohistochemically. On haematoxylin-eosin staining, many dendritic cells filled with brown pigment were scattered around epidermal tumor cells and also in the papillary dermis. Many Paget cells, which were CK-7 and CEA positive, also contained abundant granular or dusty melanin within their cytoplasm. Fontana-Masson staining revealed increased melanin in the epidermis and upper dermis (Fig. 4). Immunostaining for S-100 protein and HMB-45 confirmed that the melanin-containing dendritic cells in the lesional epidermis were melanocytes (Fig. 5). They were localized not only in the basal cell layer but also in the upper cell layer of the pigmented epidermis. In contrast to non-pigmented area, the number of melanocytes and their melanin content were remarkably increased in the epidermis. The dendritic processes of melanocytes were also well developed. These findings suggest that melanocytes not only increased in number but were activated in these lesions. There were melanophages rather than melanocytes in the upper dermis in S-100 immunostaining preparation. After wide excision, there is no evidence of recurrence of tumor in the following 10 months.

**DISCUSSION**

Extramammary Paget's disease (EMPD) usually presents as an erythematous, scaly patch. Lesions show hyperpigmentation or hypopigmentation rarely. Pigmented EMPD is a rare variant of EMPD. Rare cases have been reported in the English literature. The pigmentation, which is unevenly distributed clinically, can be present in the entire lesion or only in focal region. In our patient, the pigmented area was present in part and the pigmented and non-pigmented areas were within a single lesion. Compared to the non-pigmented part, the pigmented area revealed melanocytes colonization on the basal layer and among Paget's cells. Accumulation of melanin in the cytoplasm of
Paget’s cells, melanocytes and melanophages in the dermis also contributed to the dark-brown discoloration. In pigmented mammary Paget’s disease, either melanocyte colonization, melanin accumulation or both result in pigmentation. Similar to our patient, melanocytes colonization and melanin accumulation both existed in the previous reported cases.

When the pigmented EMPD is located on the genital area, it must be differentiated from seborrheic keratosis, bowenoid papulosis, malignant melanoma, basal cell carcinoma, squamous cell carcinoma clinically and histopathologically.

The most important differential diagnosis of pigmented EMPD is malignant melanoma. These two diseases have many features in common. Clinically, melanoma in situ tends to be smaller and not-scaly. Histopathologically, both lesions are comprised of neoplastic cells that possess large round nuclei and abundant pale-staining cytoplasm, and that are scattered throughout all layers of the epidermis. Nests of neoplastic cells are not equidistant from one another, vary in size and shape, and become confluent focally. Mitotic figures and necrotic cells may be found in both diseases. Since melanin may be seen in the cytoplasm of tumor cells of both diseases, this is not a sound discriminatory diagnostic feature. In a particular section stained by hematoxylin and eosin, the two diseases may not be distinguishable from one another.

Despite of many common characteristics in these two diseases, they usually can be differentiated histopathologically. In melanoma in situ, there are always single melanocytes and nest of them at the dermo-epidermal junction. In extramammary Paget’s disease, neoplastic cells are situated in the basal layer or above it, not at the junction itself. Neoplastic cells in basal layer of the epidermis are not protruding into the dermis or in contact with bundles of collagen. Basal keratinocytes sometimes compressed by nests of neoplastic cells of pigmented EMPD. In addition, there is no mucin in the cytoplasm of neoplastic cells in melanoma. But mucin is found in the cytoplasm of neoplastic cells in pigmented EMPD. Multinucleated cells can occasionally be seen in melanoma, but not in pigmented EMPD.

Immunohistochemical studies also help us to differentiate between these two diseases. The tumor cells in EMPD stain positively for carcinoembryonic antigen, mucin stain and cytokeratin, and are negative for HMB-45 and S-100 reactivity. However, the tumor cells in melanoma stain positively for HMB-45 and S-100 and are negative for carcinoembryonic antigen and cytokeratin reactivity. It must be emphasized that the melanocytes scattered on the basal layer and intermingled with the tumor cells in pigmented EMPD remained HMB-45 and S-100 positive. These melanocytes, which are HMB-45 and S-100 positive, must be distinguished from neoplastic cells of malignant melanoma. There is no previous report of malignant melanoma and EMPD arising in the same lesion. The melanocytes in our patient remain dendritic with small and regular nuclei in contrast to rounded or spindle-shaped cytoplasm with large, irregular, and hyperchromatic nuclei.

Fig. 5
Stellate and spindle melanocytes with dendritic processes among Paget’s cells. arrows: dendritic processes. (HMB-45, X200, AEC)
in melanoma cells. The possibility of melanoma in situ is therefore ruled out.

Melanocyte colonization was coined with the reference to adenocarcinoma of the breast in 1977 by Azzopardi and Eusebi. These authors studied 14 cases of breast carcinoma that extended to the dermis and reached the dermo-epidermal interface. They demonstrated colonization of mammary cancer by melanocytes with attendant pigmentation of cancer cells by melanin, resulting in clinical hyperpigmentation of the lesions. Since then, melanocyte colonization has been reported in a few non-melanoma tumours, such as in basal cell carcinoma, actinic keratosis, Bowen's disease, eccrine porocarcinoma, mammary carcinoma and Paget's disease of the nipple, dermatofibrosarcoma protuberans, and squamous cell carcinoma. The mechanism for the melanocytic proliferation and transfer of melanin from melanocytes to carcinoma cells is unknown. The genital area normally contains more melanocytes along the dermo-epidermal junction compared with other areas of the skin, and it is possible that intraepidermal cancer cells of extramammary Paget's disease stimulate melanocyte activity. Several hypotheses have been proposed to explain its mechanism, including migration and proliferation of melanocytes mediated by tumor-producing factors, such as melanocyte-stimulating hormone, basic fibroblast growth factor (bFGF), epidermal growth factor, insulin and stem cell factor. In the case of pigmented primary mammary carcinoma, it has been suggested that bFGF released from tumor cells might induce proliferation of normal melanocytes in tumor nests. Local production of melanocytic chemotactic factor by breast cancer cells have also been postulated as the cause in some examples of mammary Paget's disease. Dusty melanin has also been described within the cytoplasm of neoplastic cells of mammary Paget disease and cutaneous metastases from breast cancer without an increased number of melanocytes. Phagocytosis of the melanin pigment from the melanocytes by the epithelial cells of the carcinoma would be another possibility. In our patient and the other two patients of pigmented EMPD reported all revealed increasing number and activity of melanocytes. Compared to melanocytes located at the dermis with tumor cells in the pigmented mammary carcinoma, the melanocytes of pigmented EMPD colonized intermingled with tumor cells at the epidermis. It implies that chemotactic factors may play a role in interaction between melanocytes and tumor cells. There may be heterogeneity in the biological characteristics of tumor cells between pigmented and non-pigmented EMPD. Further studies of intratumoral melanocyte symbiosis are required to elucidate the mechanisms.

REFERENCE

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