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CASE REPORT

A Rare Case Of Pigmented Mammary Paget Disease

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Abstract: Pigmented mammary Paget disease is a rare clinicopathologic variant of mammary Paget disease, which can mimic melanoma. We report a patient who visited the dermatology department complaining of asymptomatic brown-black plaque localized on the left nipple that had been present for 1 year. Histopathology showed large neoplastic epithelial cells with enlarged nuclei and pale cytoplasm, some harboring granular brown melanin pigment. Immunohistochemical studies showed that the intraepidermal pagetoid cells were positive for CK7, ER, and Her2, while mostly lacking immunoreactivity for CK5, SOX10, and HMB45, supporting a diagnosis of MPD. Therefore, physicians should be aware of this rare entity when diagnosing patients with pigmented lesions on the breast area.

Keywords: Mammary Paget Disease, malignant melanoma, hyperpigmentation, breast adenocarcinoma

Introduction

Mammary Paget Disease (MPD) presents as a chronic, erythematous lesion resembling eczema, initially localized to the nipple and areola, with gradual extension to surrounding regions. MPD occurs in approximately 1–3% of primary malignant breast tumors and is almost universally associated with an underlying breast cancer in patients exhibiting characteristic nipple abnormalities.[1] Pigmented MPD, a rare clinicopathologic subtype of MPD, was identified by Azzopardi and Eusebi in 1977, as a pigmentation of breast carcinoma.[2] The pigmentation in pigmented MPD primarily results from melanophages in the stroma and dispersed melanocytes in the tumor.[3] Its clinical and histological characteristics closely resemble those of malignant melanoma, making differentiation and accurate diagnosis particularly challenging.

Case Presentation

A 52-year-old female with a previous history of ovarian cancer presented with an asymptomatic brown-black plaque localized on the left nipple that had been present for 1 year (Figure 1). On physical examination other than mild nipple retraction, there were no lymphadenopathy or palpable breast masses. A punch biopsy was taken from the darkest area of the lesion. Hematoxylin and eosin staining revealed large neoplastic epithelial cells with pigmentation. The neoplasm consisted of cells with enlarged nuclei and pale cytoplasm, some harboring granular brown melanin pigment (Figure 2A). These cells exhibited a pagetoid arrangement, involving all epidermal layers. The dermis showed infiltration by cells forming nests and cords interspersed with melanophages accompanied by mild inflammatory cell infiltration (Figure 2B). Melanin and melanophages were distributed throughout the papillary dermis and keratinocytes. The immunohistochemical study was positive for cytokeratin (CK) 7 (Figure 2C) and negative for CK5. The lesion was estrogen receptor-positive (Figure 2D), progesterone receptor-negative (50% and 0% of strong nuclear staining, respectively), and HER2-positive (score 3+) (Figure 2E), and focally positive for SOX10 and HMB45 (Figure 2F). SOX10 and HMB45 predominantly highlights innate melanocytes with dendritic processes, while the majority of lesional Paget

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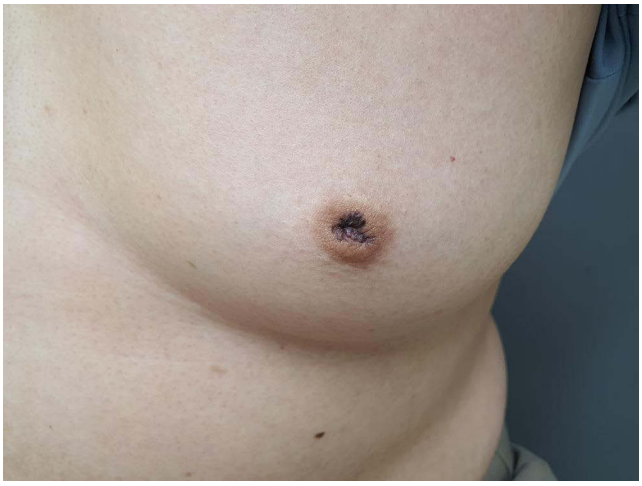

Figure 1 Clinical appearance of the lesion shows a brown-black plaque localized on the left nipple.

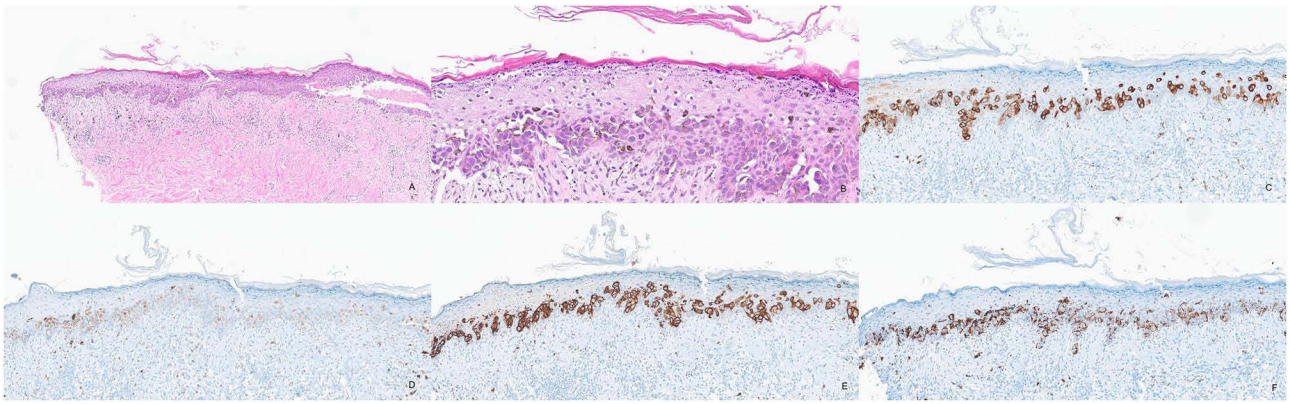

Figure 2 Histologic and immunohistochemical features of pigmented mammary Paget disease. (**A**) Intraepidermal pagetoid proliferation of large neoplastic cells forming nests and cords interspersed with melanophages in the dermis (H&E, ×100). (**B**) Higher magnification showing tumor cells with with enlarged nuclei and pale cytoplasm, some harboring granular brown melanin pigment (H&E, ×400). The immunohistochemical staining of the tumor cells were positive for (**C**) cytokeratin 7 (CK7, x200), (**D**) estrogen receptor (ER, x200), (**E**) HER-2 (x200), and focally positive for (**F**) HMB45 (x200).

cells appear to be negative for SOX10 and HMB45. The diagnosis of pigmented MPD was confirmed based on the histological features and the immunohistochemical profile of the intraepidermal neoplastic cells. The patient was referred to the department of surgery and received breast conserving surgery with sentinel lymph node biopsy. Histologically, ductal carcinoma in situ was identified. The sentinel lymph node was negative for metastasis. The patient received adjuvant breast radiotherapy and chemotherapy. Written informed consent was obtained from the patient for publication.

Discussion

MPD typically arises from intraductal mammary carcinoma that extends to the nipple epidermis via a lactiferous duct or from invasive breast carcinoma that directly invades the epidermis without destruction of epidermal basement membrane. Approximately 98% of patients with MPD have an underlying breast adenocarcinoma.[4] Typically, MPD presents as an erythematous patch resembling nipple eczema, however, pigmented subtypes have been reported. Pigmented MPD is characterized by Paget cells within the epidermis containing dusty melanin pigment, accompanied by intervening dendritic melanocytes.[5] One proposed mechanism for hyperpigmentation is that Paget cells may stimulate melanin production in normal melanocytes.[6] Also, the pigmentation of Paget cells may be caused by transfer of melanin pigment from surrounding melanocytes. The inflammatory process induced by Paget cells promotes the proliferation of melanocytic and dendritic spines, while proliferating melanocytes produced specific GP-100 melanosomes, which transferred into Paget cells' cytoplasm.[7] Additionally, Paget cells may release melanocytic chemoattractants, increasing the number of dendritic melanocytes and melanophages. This cascade of

events promotes melanocyte proliferation, contributing to the development of pigmentation. It has been demonstrated that basic fibroblastic growth factor (bFGF) and other chemotactic factors may facilitate the transfer of pigment from surrounding dendritic melanocytes to pigmented epidermotropic breast carcinoma cells.[6,8] These factors can also contribute to the pathogenesis of pigmented MPD.

The endocytosis of melanin pigment by Paget cells makes it challenging to distinguish it from melanoma in situ without the use of immunohistochemistry. Since the prognosis and treatment of pigmented MPD differ from those of melanoma, careful differentiation of pigmented breast lesions is essential. In this case, immunohistochemical study was crucial for confirming the diagnosis of pigmented MPD. Differential diagnosis includes melanoma and epidermotropic metastasis of breast carcinoma. Epidermotropic metastatic breast carcinoma can typically be excluded based on clinical history, as it often presents as pigmented papules, nodules, or plaques on the mammary skin, mastectomy scar, or anterior chest wall in patients with a known history of breast carcinoma.[9] In contrast, Paget disease is usually the first manifestation of the disease, presenting in the areola/nipple area. Differentiating Paget cells from melanoma cells based solely on histologic features can be challenging. Paget cells are typically located above the basal keratinocytes, and may show ductal formation, whereas melanoma cells are found throughout all epidermal layers, including the basal layer, often with intraepidermal pagetoid spread. However, these differences are not always apparent, making immunohistochemical study essential for accurate diagnosis. Most Paget cells stain positive for CK7, EMA, CEA, Cam 5.2, HER2/neu, mammoglobin, BCA-225, while positivity for carcinoembryonic antigen and epithelial membrane antigen vary across different studies.[10,11] Melanoma cells usually stain positive for melanocytic markers such as S100, HMB45, MART1, SOX10.[12] TRPS1 helps distinguish MPDs from melanomas, as MPDs are almost always positive for TRPS1, while melanomas invariably lack TRPS1 expression.[13,14] It is also useful for diagnosing EMPDs, particularly when the lesions arise in non-perianal regions of the skin and when used as part of a panel including CK7, p63, and SOX10.[13] However triple-negative breast carcinomas can be positive for both TRPS1 and SOX10, complicating the differential diagnosis. Since our case was not a triple-negative breast carcinoma (ER+/HER2+), TRPS1 expression could have contributed to clarifying the diagnosis.

Intraductal or infiltrating ductal carcinoma of the breast is often associated with MPD. The patient in our study was diagnosed with ductal carcinoma in situ. Some previous case studies suggest that PET/CT scans offer advantages for detecting extra-mammary Paget disease, however no reports have addressed its usefulness in MPD. Therefore, skin biopsy should be performed on suspicious lesions.[15] Since the prognosis and treatment of pigmented MPD differ from those of melanoma, careful differentiation of pigmented breast lesions is essential. The treatment of MPD aligns with standard breast cancer management.[16] Involvement of the nipple–areola complex typically requires en bloc excision of the nipple and areola, accompanied by sentinel lymph node evaluation.

Conclusion

Pigmented MPD is quite rare and lacks distinct clinical features differentiating it from melanoma. Accurate diagnosis relies solely on immunohistochemical analysis. As pigmented lesions occurring on the breast area are quite common, physicians should be aware of this rare entity. Proper diagnosis is needed to refrain from overtreating pigmented MPD, which can clinically mimic more aggressive tumors such as melanoma.

Ethics Statement

The publications of images were included in the patient's consent for publication of the case. Institutional approval has been obtained to publish the case details.

Consent Statement

The authors certify that they have obtained all appropriate patient consent forms. The patient signed a consent form for the publication of the case details and images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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