Quiz

Correct answer to the quiz. check your diagnosis

Pigmented paget's disease of the nipple

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Pigmented Paget's disease of the nipple (PPD) is an uncommon variant of Paget's disease. An accumulation of melanin within the lesion imparts a brown color to the affected area, so the lesion might clinically as well as histologically mimic melanoma. We present a case of PPD in a 60-year-old woman.

Key words: pigmented Paget disease of the nipple.

Introduction

Paget's disease of the nipple is a rare form (1-4%) of breast cancer. Clinically it manifests most commonly as an eczematous or erythematous lesion of the nipple. In Paget's disease of the nipple, Paget cells, which are malignant glandular cells, are seen within the epidermis of the nipple and sometimes extend to the areola or adjacent skin. It is usually associated with an underlying carcinoma, which is in this case a postulated source of Paget cells [1-3]. In rare cases not associated with the underlying carcinoma, the Paget cells might presumably derive from Toker cells [2, 4] or malignant transformation of keratinocytes [5].

Pigmented Paget's disease of the nipple (PPD) is a very rare variant of Paget's disease of the nipple [1, 4, 6]. Available reports describe 24 cases of PPD [1, 4]. It manifests clinically as a pigmented lesion of the nipple, which is caused by accumulation of melanin [1, 4, 6]. Hyperpigmentation is associated with proliferation of dendritic melanocytes or with accumulation of melanin within the cytoplasm of Paget cells, keratinocytes or melanophages [7, 8].

Case report

A 60-year-old woman was admitted to the 1st Chair of General, Oncological, and Gastrointestinal Surgery, Jagiellonian University Medical College because of the diagnosis of an invasive ductal carcinoma of her left breast. At physical examination no palpable tumor in the breast or enlarged regional lymph nodes were revealed, but the nipple was inverted and surrounded by a pigmented area of skin. According to the patient's statements, the nipple had been inverted for the last five years. No contributory family history was revealed. The patient suffered from hypertension, sciatica and chronic pancreatitis. She had experienced a cerebral stroke and had undergone C-section, appendectomy and cholecystectomy.

Mammography showed a tumor of the left breast, sized 15 mm, surrounded by areas of microcalcifications up to 110 mm in the largest dimension. Ultrasonography of the left breast showed an invasive lesion, sized 14 × 11 × 8 mm, surrounded by an area of swelling, spreading towards the skin and nipple. Ultrasonography of the left axilla revealed a lymph node suspicious for metastatic disease, but the cyto-

logical examination was negative for atypical cells. Because of the extent of mammographically detected lesions the patient was qualified for simple mastectomy with sentinel lymph node biopsy.

Macroscopically there was an invasive tumor in the internal upper quadrant, sized 1.4 × 1.2 × 0.9 cm, which was removed with a margin of the surrounding tissues. The nipple was inverted and surrounded by a pigmented area, irregular in contour and pigmentation, diameter 2 cm. There were also two warts, sized 1.2 cm and 0.3 cm, noticeable on the skin's surface.

Histological examination of the macroscopically visible tumor showed an invasive carcinoma of no special type, grade 3, 14 mm in the largest dimension, with vascular invasion adjacent to the tumor. Ductal carcinoma *in situ*, intermediate grade, solid pattern, with central necrosis, identified within the tumor, involved no more than 10% of the area of invasive cancer. It also involved ducts and acini in the vicinity of the tumor (Fig. 1). Two skin warts turned out to be seborrheic warts. Immunohistochemistry revealed that invasive carcinoma cells were positive for estrogen and progesterone receptors (70% and 40% of cells showing strong nuclear expression, respectively) and positive for HER2 (score 3+). According to the 2013 St Gallen consensus, the tumor type was luminal B (HER-2 positive). Two sentinel lymph nodes were free of metastases, so the disease stage was IA.

At all levels of the epidermis of the nipple, both single cells and cells forming nests were visible. These cells showed abundant pale cytoplasm, and some of them contained melanin. Melanin was also seen within the cytoplasm of keratinocytes, melanocytes and in the skin melanophages (Figs. 2, 3). Immunohistochemical studies demonstrated that the tumor cells were positive for keratin 7 (Fig. 4), epithelial membrane antigen, gross cystic disease protein 15, estrogen and progesterone receptors as well as HER2 (Figs. 5, 6). These cells were negative for melanocytic antigens (HMB45 and melanA), but these stains demonstrated numerous dendritic melanocytes accompanying the tumor cells (Figs. 7, 8). Altogether these findings were consistent with a diagnosis of pigmented Paget's disease of the nipple.

After the operation the patient received chemotherapy: 3 cycles of epirubicin, 5-fluorouracil and cyclophosphamide, and then 3 cycles of docetaxel. Currently the patient is receiving trastuzumab and hormonal therapy (an aromatase inhibitor) with fairly good tolerance of treatment.

Discussion

Pigmented Paget's disease of the nipple is an extremely uncommon variant of mammary Paget's disease that can mimic malignant melanoma on clinical, dermatological and even histopathological presentation [1, 4, 6]. It is not uncommon to find melanin in Paget cells' cytoplasm. Culberson and Horn reported presence of pigment within Paget cells' cytoplasm in 10 of 25 cases (40%), but the degree of pigmentation varied, being particularly heavy in only one case [9], which is probably the first reported case of PPD. Neubecker and Bradshaw observed melanin in 8 of 13 cases of Paget's disease. In the majority of these cases pigment granules were few in number and present only in isolated cells. Similarly to the previously mentioned report, in only one case did numerous cells contain abundant pigment [10]. Only in these heavily pigmented cases does clinically visible pigmentation warrant classification as PPD [4].

The mechanism of hyperpigmentation in PPD still remains unknown. There are several hypotheses trying to explain its origin. The first one involves stimulation of melanocytes by growth factors that are produced by cancer cells [1, 7, 11, 12]. The areola, as

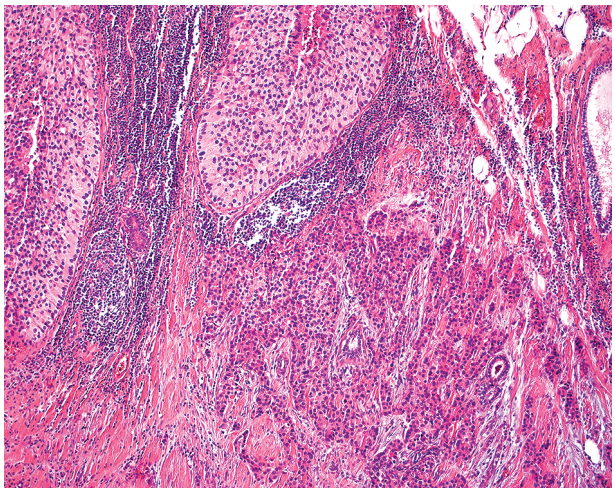

Fig. 1. Invasive carcinoma with accompanying ductal carcinoma *in situ* of the left breast. HE, objective magnification 10×

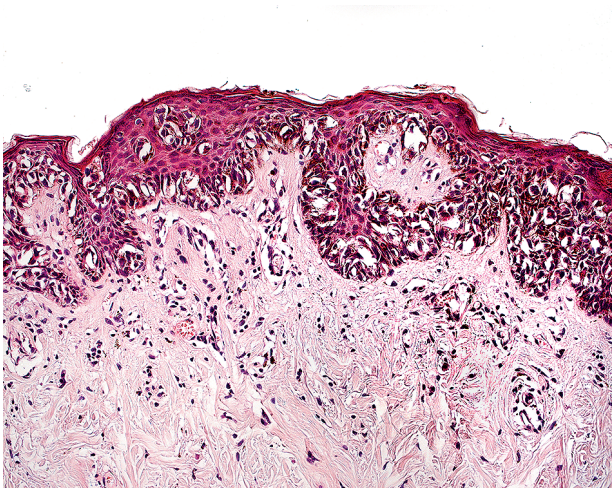

Fig. 2. Paget cells, single and forming nests, are seen at all levels of the epidermis. Within the dermis some melanophages can be seen. HE, objective magnification 20×

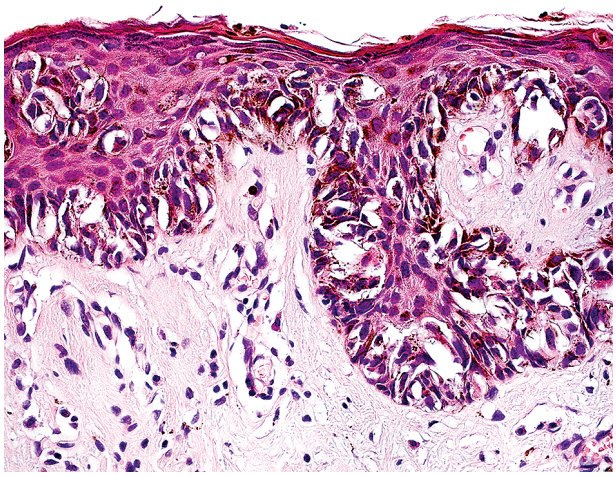

Fig. 3. Melanin is seen within Paget cells' and keratinocytes' cytoplasm. HE, objective magnification 40×

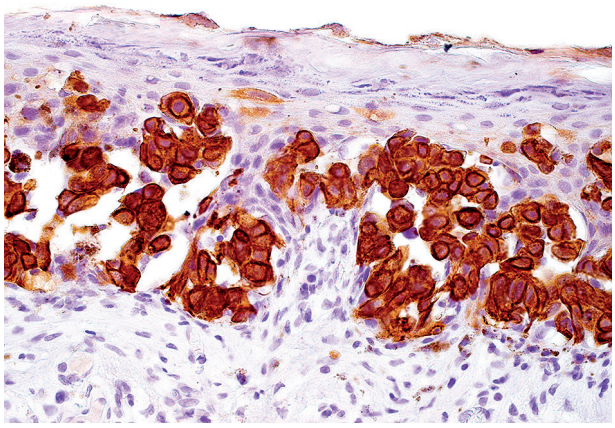

Fig. 4. CK7 demonstrates numerous Paget cells within the epidermis. CK7, objective magnification 40×

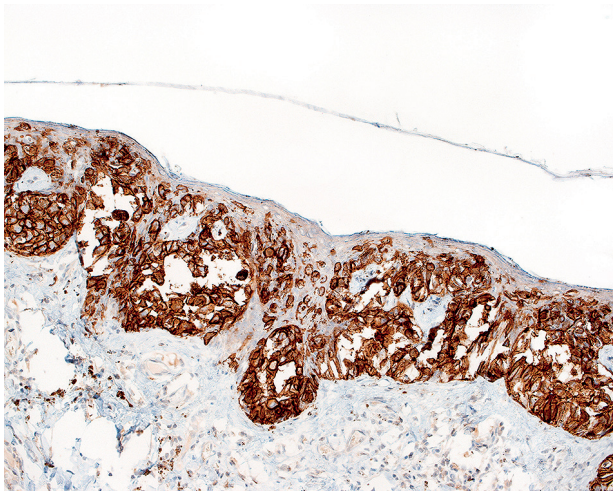

Fig. 5. HER2 expression in Paget cells. HER2, objective magnification 20×

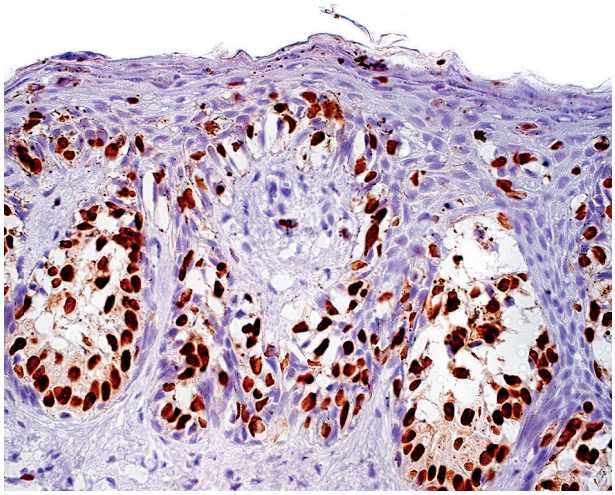

Fig. 6. Estrogen receptor expression in Paget cells. ER, objective magnification 40×

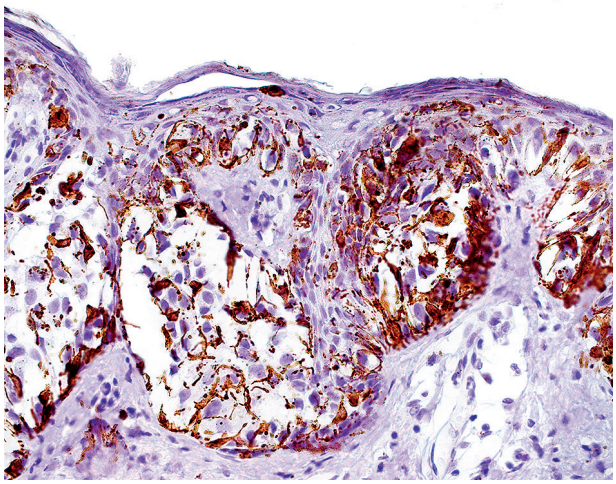

Fig. 7. Numerous dendritic melanocytes accompanying the tumor cells showing expression of HMB45. HMB45, objective magnification 40×

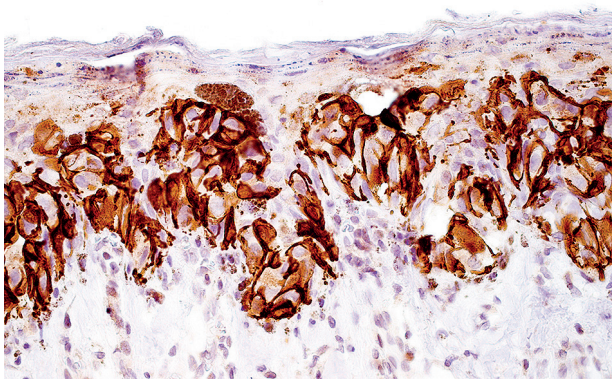

Fig. 8. Numerous dendritic melanocytes accompanying the tumor cells showing expression of melanA. MelanA, objective magnification 40×

a region rich in melanocytes, shows visible effects of that stimulation. However, similar lesions were also observed in extramammary epidermotropic metastases of breast carcinoma [7] and even in other types of carcinomas [7, 13-16]. Some authors suggest that the hyperpigmentation may be caused by pigment blockage of melanocytes that have been stimulated to grow and, after that, chemoattracted by cancer cells. During migration they are blocked and transfer melanin to other epithelial cells [7, 17]. Other authors suggest that the epithelial cells of cancer phagocytose melanin from the melanocytes, which causes hyperpigmentation [1, 7, 11, 18].

Differential diagnosis of this rare entity might be challenging and mainly includes pigmented epidermotropic metastases of breast carcinoma and malignant melanoma [7]. Epidermotropic metastases of breast carcinoma might rarely be pigmented [15]. The differential diagnosis is usually based on clinical history [1, 15]. Epidermotropic metastases of breast carcinoma usually occur on the mammary skin, mastectomy scar or anterior chest wall in a patient with a known history of mammary carcinoma. In contrast, PPD is usually the first manifestation of the disease and affects the nipple [1]. Histological assessment might assist in differential diagnosis, as in epidermotropic metastases of breast carcinoma neoplastic cells involve not only the epidermis but also the dermis [15]. Malignant melanoma only rarely affects the nipple. In melanoma in situ single cells or cells in nests are seen along the dermoepidermal junction and scattered at all levels of the epidermis. In contrast, Paget cells are scattered through suprabasal layers of the epidermis [1, 7, 15]. In our case this feature was not helpful, as we observed Paget cells at all levels of the epidermis, including the dermoepidermal junction. More promising in differential diagnosis seems to be the use of immunohistochemistry. Melanoma cells (in both melanoma in situ and epidermotropic metastatic melanoma) usually demonstrate strong expression of S100 protein and typical melanocytic markers such as HMB45, melanA and MiTF, whilst Paget cells are usually negative for these markers. In contrast, melanoma cells usually do not express cytokeratins, EMA or CEA, which are usually expressed by Paget cells [1, 7]. However, some authors report S100 or HMB45 positivity in Paget cells. Nevertheless, the expression of epithelial markers by the same cells usually resolves the problem and favors the diagnosis of PPD [1, 7, 19]. Additional support in diagnosis of PPD might be the expression by these cells of estrogen and progesterone receptors [1, 3], although reported positivity for estrogen and progesterone receptors in Paget's disease varies and does not exceed 44% of cases [3]. Instead, HER2 positivity is a more consistent finding and might help in differential diagnosis [1, 3]. Nevertheless, caution in interpretation of immunohistochemical stains and use of a panel of markers is recommended due to the numerous melanocytes in PPD showing expression of melanocytic antigens, which might be misleading.

In summary, pigmented mammary Paget's disease is a rare variant of Paget's disease. However, it should not be forgotten and ought to be taken into account in the differential diagnosis of pigmented lesion of the nipple.

The authors declare no conflict of interest.

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