Abstract
Differential diagnoses of pigmented lesions of the nipple include melanocytic nevus, melanosis of the nipple, seborrheic keratosis, pigmented basal cell carcinoma, melanoma and Paget disease. The histologic exam with appropriate immunohistochemistry is a fundamental tool to achieve a correct diagnosis. We present a patient with a pigmented lesion of her right nipple revealing mammary Paget disease and elucidate diagnostic obstacles and prognostic importance of early breast cancer detection.

Key-words: Mammary Paget's disease; melanoma; tumor biomarkers; immunohistochemistry

Case synopsis
A 42-year-old woman was referred to our department regarding a nonpruritic pigmented lesion on the right nipple. That lesion had been slowly growing for 2 years. There was no excoriation of the nipple, no retraction, no palpable masses, and no lymphadenopathy.

Physical examination revealed an irregular hyperpigmented macule, 10x8 mm, involving the lateral quadrants of the right nipple (Figure 1).
On dermoscopy, a non-specific brown reticular pigmentation was observed (Figure 2).

The skin biopsy disclosed a junctional proliferation characterized by atypical cells with enlarged nuclei and pale cytoplasm, some of which contained brown melanin granular pigment, with intraepithelial dissemination and no invasion. Also, rare mitosis (1/mm²), a discrete lympho-plasmocytic infiltrate, and melanophages were observed (Figure 3).
Immunohistochemically, tumor cells were positive for cytokeratin-7, HMB-45, and S-100 (Figure 4). These confirmed pigmented mammary Paget disease. Mammary imaging was performed (ultrasound, mammography and magnetic resonance imaging), showing no suspected nodules or calcifications.

Therapeutic excision was decided, including the entire nipple areolar complex and attached subcutaneous tissue. Histologic exam revealed an in situ ductal breast carcinoma.

**Discussion**

Mammary Paget disease (MPD) represents 1-2% of all breast cancers. Most often it results from intraductal spread of ductal carcinoma cells into the skin, but it can also be caused by direct invasion of the epidermis by infiltrating carcinoma cells [1-3].

MPD usually presents as an erythematous patch or plaque, typically eczematous in appearance. An underlying mass is palpable in 45% of cases [1-3].

Infrequently, MPD can present as a pigmented lesion that may clinically, dermoscopically, and histologically simulate malignant melanoma [4, 5].

Different mechanisms can account for the occurrence of pigmented MPD (PMPD): increased number of dendritic melanocytes between carcinomatous cells, phagocytosis of melanin by atypical cells, and the presence of melanophages in the reactive dermal infiltrate [2].
Histological exam, application of a panel of antibodies, and careful analysis of the immunohistochemical findings are recommended to clarify the expression pattern of the malignant cells (epithelial or melanocytic) to achieve a correct diagnosis. MPD typically has positive epithelial markers and negative melanin markers [2, 6, 7].

Anti-cytokeratin 7 has the highest diagnostic accuracy for MPD [2, 8]. It is important to note that S-100 and HMBP-45, melanocytic markers that have been used to differentiate pigmented mammary Paget disease from malignant melanoma, are sometimes not reliable, as in our case [9, 10].

In conclusion, pigmented lesions of the nipple should be carefully examined. It is important to include PMPD in the differential diagnostics, because it can mimic pigmentation after inflammation, seborrheic keratosis, junctional nevus, pigmented basal cell carcinoma, or malignant melanoma. PMPD is an uncommon diagnosis still more usual than melanoma of the nipple. Therefore, it should always be remembered.

Our case confirms the difficulty of establishing a correct diagnosis with hematoxylin-eosin staining alone. Immunohistochemical analysis, including anti-cytokeratin 7, should be considered mandatory in lesions featuring a prominent pagetoid infiltration, to avoid mistaking PMPD for melanocytic or other tumors.

References