

# Pigmented Paget's disease of the nipple mimicking cutaneous melanoma: importance of the immunohistochemical profile to differentiate between these diseases\*

## *Doença de Paget pigmentada do mamilo simulando melanoma cutâneo: importância da imuno-histoquímica na diferenciação dessas doenças\**

Tatiana Villas Boas Gabbi<sup>1</sup>

Neusa Yuriko Sakai Valente<sup>2</sup>

Luiz Guilherme Martins Castro<sup>3</sup>

**Abstract:** Pigmented mammary Paget's disease is a rare dermatosis, with approximately 12 reported cases in the literature, which can mimic cutaneous melanoma both clinically and histologically. As for classical mammary Paget's disease, the pigmented variant is associated with neoplasia of the breast, originating mainly from intraductal mammary carcinoma that extends to the epidermis of the nipple and areola through a lactiferous duct. Physiopathology of hyperpigmentation remains unknown. We present a 49-year-old female patient who presented with a pigmented lesion of the nipple suspected of melanoma. Histological examination was not sufficient to confirm diagnosis. Immunohistochemical examination confirmed the diagnosis of Paget's disease. Although uncommon, pigmented Paget's disease must be reminded as a differential diagnosis of melanoma in pigmented lesions of the nipple, in both genders.

**Keywords:** Immunohistochemistry; Melanoma; Paget's disease, mammary

**Resumo:** A variante pigmentada da doença de Paget mamária é rara, com cerca de 12 casos relatados, e pode mimetizar clínica e histologicamente o melanoma. Como na forma clássica, em geral associa-se à neoplasia da mama acometida, com origem principalmente no carcinoma intraductal que se estende à epiderme através de ducto lactífero. A fisiopatologia da hiperpigmentação permanece desconhecida. Relata-se o caso de paciente de 49 anos que apresentou lesão pigmentada do mamilo, suspeita de melanoma. O exame histológico não foi suficiente para confirmar o diagnóstico, sendo necessária realização de perfil imuno-histoquímico. Apesar de incomum, o diagnóstico de doença de Paget deve ser lembrado como diferencial de melanoma em lesões pigmentadas dessa região, em ambos os sexos.

**Palavras-chave:** Doença de Paget mamária; Imuno-histoquímica; Melanoma

Received on March 26, 2004.

Approved by the Consultative Council and accepted for publication on June 01, 2005.

\* Work done at Department of Dermatology at Hospital das Clínicas da Universidade de São Paulo (HC-FMUSP) - São Paulo (SP), Brazil.

Conflict of interests: None

<sup>1</sup> Attending Physician of Dermatology at Hospital das Clínicas da Universidade de São Paulo (HC-FMUSP) - São Paulo (SP), Brazil.

<sup>2</sup> Physician, Researcher at the Laboratory of Medical Investigation 53 at Hospital das Clínicas da Universidade de São Paulo (HC-FMUSP) - São Paulo (SP), Brazil.

<sup>3</sup> PhD, Physician, Supervisor of the Department of Dermatology at Hospital das Clínicas da Universidade de São Paulo (HC-FMUSP) - São Paulo (SP), Brazil.

### INTRODUCTION

Mammary Paget's disease (MPD) presents as an eczema-like lesion in nipple and areola skin, usually associated to intraductal mammary carcinoma, which extends to the epidermis through a lactiferous duct, or to invasive carcinoma, which affects the epidermis by continuity through the dermis.<sup>1</sup> Pigmented variant of MPD is rare, having been described in patients of both genders, with little more than 10 described cases in the literature.<sup>1-10</sup> The presence of a pigment makes MPD a likely mimicker of cutaneous melanoma (CM), both clinically and histologically.<sup>1-10</sup> Performance of an immunohistochemical (IH) study is often necessary for establishing the correct diagnosis.<sup>11,12</sup> Below, we present the case of patient who presented a pigmented lesion in the nipple, whose initial diagnostic hypothesis of CM could only be discarded after an IH study, which allowed diagnosing pigmented MPD.

### CASE REPORT

Forty-nine-year old white female patient, born in and coming from São Paulo, was seen in 1994 at the Dermatology Outpatient Clinic at University of São Paulo Medical School Hospital, complaining of a hyperpigmented, non-painful lesion located in the left nipple that had appeared six months before, with gradual growth ever since. Upon dermatological examination, a slight increase in nipple volume could be noted, along with a well-delimited brownish-darkened spot, with irregular borders and erythematic-crustous center, measuring 0.5 x 0.5 cm (Figure 1). On palpation, no breast masses or axillary lymph node enlargements could be noted. Hypothesis of CM was considered, and the patient was submitted to nipple excision, and material was sent for histological studies, which revealed proliferation of large atypical clear cells, isolated or grouped, sometimes with melanin-rich cytoplasm, located between squamous cells, in all levels of the epidermis. In upper dermis, there was a band-like lymphocyte and plasma cell infiltrate (Figures 2 and 3). Since these findings may be present both in Paget-like melanoma and pigmented Paget's disease, and clear differentiation between the two was not possible, we proceed to IH study. Assessed antigens were: AE1 + AE3, CEA, EMA and S100. The first three had positive results in intra-epidermal neoplastic cells, and S100 was negative (Table 1). It was thereby possible to establish diagnosis of Paget's disease and discard the possibility of CM. A later investigation revealed the presence of intraductal mammary carcinoma, and the patient decided to have her oncological treatment elsewhere, where she underwent quadrantectomy and axillary emptying, followed by radiation therapy.



FIGURE 1: Pigmented mammary Paget's disease. Irregular hyperpigmented areola, with erythematic-crustous central area in the left nipple

### DISCUSSION

Numerous melanocytic and non-melanocytic lesions may present with clinical patterns that mimic CM, thus being crucial differential diagnoses for a proper treatment. Among them, are included congenital and acquired nevi, Spitz's nevus, Reed's nevus, basocellular carcinoma, seborrheic keratosis, simple and solar lentigo and tinea nigra.

Pigmented MPD is an uncommon clinicopathological variant of intraductal mammary carcinoma or of invasive mammary carcinoma, which extends up to nipple and areola epidermis. Because of the presence of melanic pigment, such lesions can mimic CM, both clinically and histologically.<sup>13</sup> For this reason, despite its rarity, it should be included in the list of CM diffe-

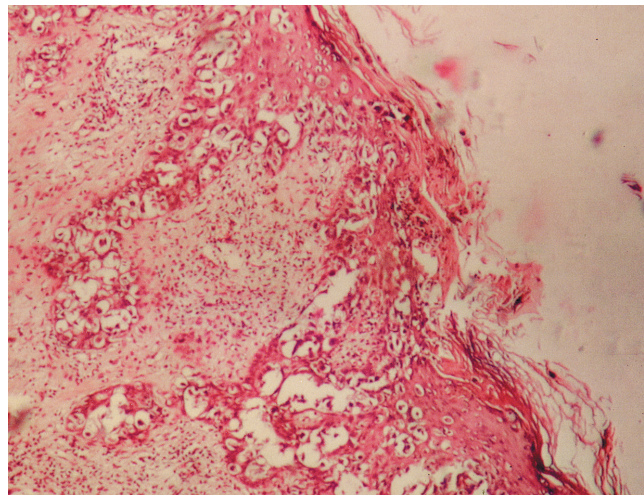


FIGURE 2: Intense proliferation of large cells with clear cytoplasm, isolated and grouped, in all levels of epidermis, affecting the dermoepidermal junction (hematoxylin-eosin. Original magnification: 40X)

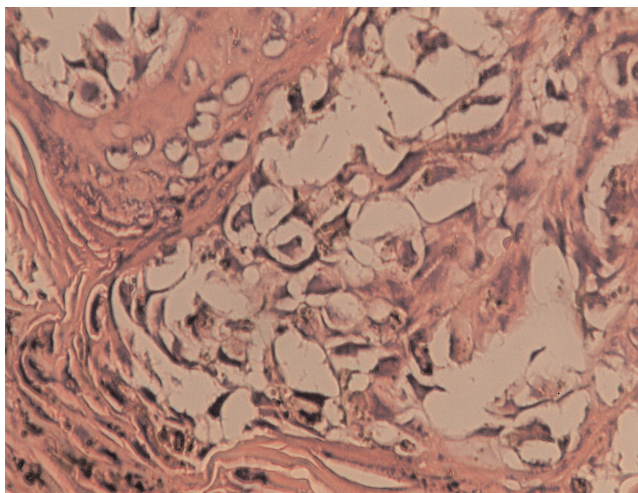


FIGURE 3: Larger magnification. Presence of intra-epidermal Paget cells, some of them containing melanic pigment, with pleomorphic nuclei and sparse mitoses (hematoxylin-eosin. Original magnification: 400X)

rential diagnoses, especially those lesions located in the nipple and mammary areola.

Requena et al.<sup>1</sup> reviewed and reclassified cases of pigmented MPD, describing three others. The also reported six cases of pigmented metastases of epidermotropic carcinoma. Among the 12 reports of MPD found in the literature,<sup>1-10</sup> six occurred in males and six in females. Women age ranged from 42 to 84 years, with an average of 62 years, and men ranged from 47 to 83 years of age, averaging 67 years. IH was performed in order to differentiate from CM in most of these cases, and histological findings were very similar, with the observation of affection of the dermoepidermal junction in all of them. Eight of them presented proliferation of dendritic melanocytes among Paget cells; in two of them melanin was found within neoplastic cells. Two presented both melanocyte proliferation and melanin within Paget cells.

Some theories seek explanations for the origin of the pigment in PD, namely: a) proliferation of dendritic melanocytes containing abundant melanin, sti-

mulated by some chemotactic factor produced by neoplastic cells; b) Paget cells phagocytosed melanin from melanocytes, in association to a blockage of pigment transference from melanocytes to keratinocytes. However, its exact physiopathology remains unknown to the present date.<sup>1</sup>

Differential diagnosis between Paget-like CM and pigmented MPD can be difficult, and demands a correct application of histological and immunohistochemical criteria.<sup>11,12</sup>

There are subtle differences between histological findings from the two lesions.<sup>1,11,13</sup> In *in situ* CM, melanocytes spread through all levels of the epidermis and isolated at the dermoepidermal junction are observed. On the other hand, in pigmented MPD, isolated cells or Paget cell nests are seen in the suprabasal layers, without the junctional component. In *in situ* CM, dermal component is not noted, whereas in pigmented MPD, often an invasive or intraductal mammary carcinoma can be observed in the underlying dermis.<sup>13</sup> Special staining techniques also allow for the differentiation. Paget cells are PAS-positive, diastase-labile, and contain acid mucine, which does not hold for CM. In the present case, upon review of the slides, a ductal carcinoma was noted, which reinforced the diagnosis of pigmented MPD. Nevertheless, since CM may exceptionally exist in the areola,<sup>14</sup> and since a collision between CM and ductal mammary carcinoma has been described,<sup>15</sup> an IH is imperative for establishing a definite diagnosis. When performing IH studies is not possible, special stains for glycogen and acid mucine, as seen previously, may be clarifying.

IH profile will favor either CM or MPD.<sup>12</sup> In the present case, were assessed cytokeratins AE1 + AE3, carcinoembryonary antigen (CEA), epithelial membrane antigen (EMA) and protein S100.

Intra-epidermal Paget-like melanocytes present in CM usually express strong positivity for protein S100, HMB45, melan-A and MITF, unlike for cytokeratins, CEA and EMA. Protein S100 has a high sensitivity

CHART 1: Differences between the immunohistochemical profile usually found in skin melanoma and Paget's disease, and the findings of the present case

Assessed Antigen	<i>In situ</i> Melanoma	Paget's disease	Present case
HMB-45	+	-	NP
Melan-A	+	-	NP
S100	+	-	-
AE1 e AE3	-	+	+
CEA	-	+	+
EMA	-	+	+

+: positive; - : negative; NP: not performed



for CM, albeit with low specificity, thus, when it is negative, there is no need in assessing HMB-45 or melan-A, which are more specific.

Intra-epithelial cells present in mammary carcinoma, on the other hand, are generally negative for protein S100, and, in the rare positive cases, simultaneous expression of cytokeratins, CEA and EMA

would still allow distinction from CM.

In the present IH study, antigens AE1 + AE3 were positive in intra-epidermal neoplastic cells, as well as antigens CEA and EMA, and S100 was negative (Chart 1). This IH profile seals the diagnosis of pigmented MPD. □

### REFERENCES

1. Requena L, Sanguenza M, Sanguenza OP, Kutzner H. Pigmented mammary Paget disease and pigmented epidermotropic metastases from breast carcinoma. *Am J Dermatopathol.* 2002;24:189-98.
2. Peison B, Benisch B. Paget's disease of the nipple simulating malignant melanoma in a black woman. *Am J Dermatopathol.* 1985;7:165-9.
3. Ho TCN, Jacques M, Schopflocher P. Pigmented Paget's disease of the male breast. *J Am Acad Dermatol.* 1990;23:338-41.
4. Kutzner H, Hugel H, Embacher G. Pigmentierter morbus Paget und pigmentierte Mammakarzinometastase. *Hautarzt.* 1992;43:28-31.
5. Stretch JR, Denton KJ, Millard PR, Hodak E. Paget's disease of the male breast clinically and histopathologically mimicking melanoma. *Histopathology.* 1991;19:470-2.
6. Nakamura S, Ishida-Yamamoto A, Takahashi H, Hashimoto Y, Yokoo H, Iizuka H. Pigmented Paget's disease of the male breast: report of a case. *Dermatology.* 2001;202:134-7.
7. Menet E, Vabres P, Brecheteau P, Bonneau-Herve F, Duport G, Levillain P, et al. Maladie de Paget pigmentée du mamelon chez l'homme. *Ann Dermatol Venerol.* 2001;128:649-52.
8. Sau P, Solis J, Lupton G, James WDI. Pigmented breast carcinoma. A clinical and histopathologic simulator of malignant melanoma. *Arch Dermatol.* 1989;125:536-9.
9. Fernandez-Figueras MT, Puig L, Casanova JM, Musulen E, Matias-Guiu X, Navas-Palacios JJ. Pigmented epidermotropic ductal carcinoma of the breast in a male. *J Cutan Pathol.* 1995;22:276-80.
10. Saitoh K, Saga K, Okazaki M, Maeda K. Pigmented primary carcinoma of the breast: a clinical mimic of malignant melanoma. *Br J Dermatol.* 1998;139:287-90.
11. Kohlr S, Rouse RU, Smoller BR. The differential diagnosis of pagetoid cells in the epidermis. *Mod Pathol.* 1998;11:79-92.
12. Gulddhammer B, Norgaard T. The differential diagnosis of intraepidermal malignant lesions using immunohistochemistry. *Am J Dermatopathol.* 1986;8:295-301.
13. Gonzalez SB. Histopathologic diagnosis of pigmented lesions of the skin. *Pathol Res Pract.* 1991;187:387-431.
14. Bernardo MM, Mascarenhas MJ, Lopez DP. Primary malignant melanoma of the breast. *Acta Med Port.* 1980;2:39-43.
15. Padmore RF, Lara JF, Ackerman DJ, Gales T, Sigurdson ER, Ehya H, et al. Primary combined malignant melanoma and ductal carcinoma of the breast: report of two cases. *Cancer.* 1996;78:2515-25.

MAILING ADDRESS:

*Tatiana Villas Boas Gabbi*  
*Divisão de Clínica Dermatológica do Hospital*  
*das Clínicas da FMUSP*  
*Av. Enéias de Carvalho Aguiar, 255 - 3º andar*  
*05403-000 - São Paulo - SP - Brazil*  
*Tel/Fax: +55 11 5044-1008 / 3069-6450*  
*E-mail: gabbi@uol.com.br*