



Pigmented Paget Disease of the Nipple: A Rare Breast Cancer Presentation

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Abstract

Objective: To show the incidence and clinical characteristics of the patients diagnosed with Pigmented Paget Disease in our Institution. In addition, we present the pathological and immunohistochemical criteria for a precise diagnosis.

Materials and methods: Institutional board approval was obtained before commencement of this study. A retrospective study was conducted in all women diagnosed with breast cancer at our institution from January 2005 to December 2013. Standard immunohistochemical breast cancer panel was performed to all patients (ER, PR, Her-2 and Ki-67) and CK-7, P63 and S-100 when the pigmented variety was presented. Patients with pigmented Paget disease were selected and demographic characteristics were established.

Results: Between January 2005 and December 2014, 4148 patients were diagnosed with breast cancer at our institution; Paget disease was found in 69 patients (1.66%), six of them showed the pigmented variety (8.7%). Two of them presented pure Pigmented Paget's disease, while four an invasive component associated. CK-7 was positive in the 6 patients and overexpression of Her-2 in 5 patients, while P63 and PS100 were negative in all patients. The median follow-up was 33.8 months (13-59). No patient developed local or distant recurrence.

Conclusions: Pigmented Paget is a rare entity found in the 8.7% of the patients with Paget disease. Histological with immunohistochemical assessment is essential for diagnosis. Clinical stage should be defined by the invasive component, if it exists. Treatment should be given as in any other mammary Paget disease of the breast, since prognosis is not affected by this kind of presentation.

Keywords

Pigmented paget disease, Breast cancer, Melanoma

Abbreviations

FUCAM: Breast Disease Institute FUCAM, ER: Estrogen Receptors, PR: Progesterone Receptors, HER-2: Human Epidermal Growth Factor 2 Receptor Protein, CK-7: Cytokeratin 7

Introduction

Pigmented Paget Disease is an extremely infrequent form of presentation of mammary Paget disease. It is characterized by a hyperpigmented macula in the nipple or areola with an underlying breast carcinoma [1,2]. Eczema and erythema in the Nipple-areola complex (NAC) could be often associated [3] Through this study we pretend to show the incidence and clinical characteristics of the patients diagnosed with Pigmented Paget Disease in the Instituto de Enfermedades de la Mama, FUCAM. In addition, we present the pathological and immunohistochemical criteria for a precise diagnosis.

Materials and Methods

Institutional board approval was obtained before initiation of this study. A retrospective study was conducted in all women diagnosed with breast cancer at our institution, from January 2005 to December 2014. Patients with Pigmented Paget disease were selected and demographic characteristics were established.

TNM/AJCC stage (Tumor, Node, Metastases / American Joint Committee on Cancer) were all evaluated during the tumor board sessions [4]. Multimodal treatments were administered according to the NCCN Breast Cancer Clinical Practice Guidelines [5]. Pathological and immunohistochemical diagnostic protocols were applied. Immunohistochemical panel was performed according to the American Society of Clinical Oncology and the College of American Pathologists and molecular phenotypes were determined according to the St. Gallen International Breast Cancer Conference [6-8]. Standard immunohistochemical breast cancer panel was routinely performed to all patients with breast cancer in the invasive component, if present (ER, PR, Her-2 and Ki-67). In order to rule out other diseases, when pigmented Paget disease was found, supplementary especial stains were applied directly in the pigmented area. CK-7, Her-2, P63 and S-100 were used in these cases.

Results

Between January 2005 and December 2014, 4148 patients were diagnosed with breast cancer at FUCAM ; 69 patients, with invasive or *in situ* carcinoma, were diagnosed with Paget disease (1.66%). The pigmented variety was shown in six of these patients (8.7%). The

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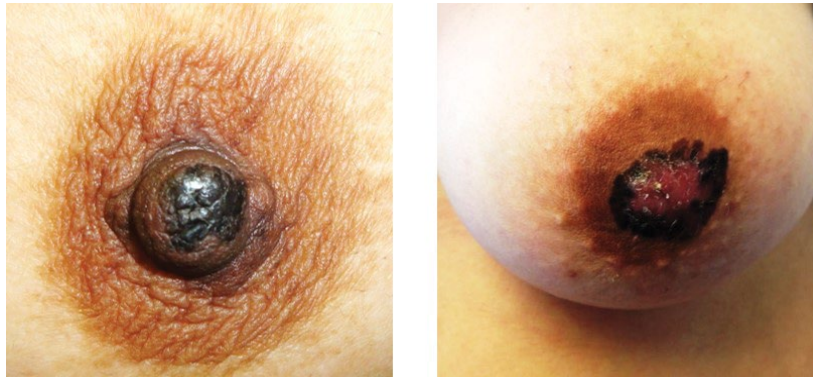


Figure 1: Patients with Pigmented Paget Disease of the NAC.

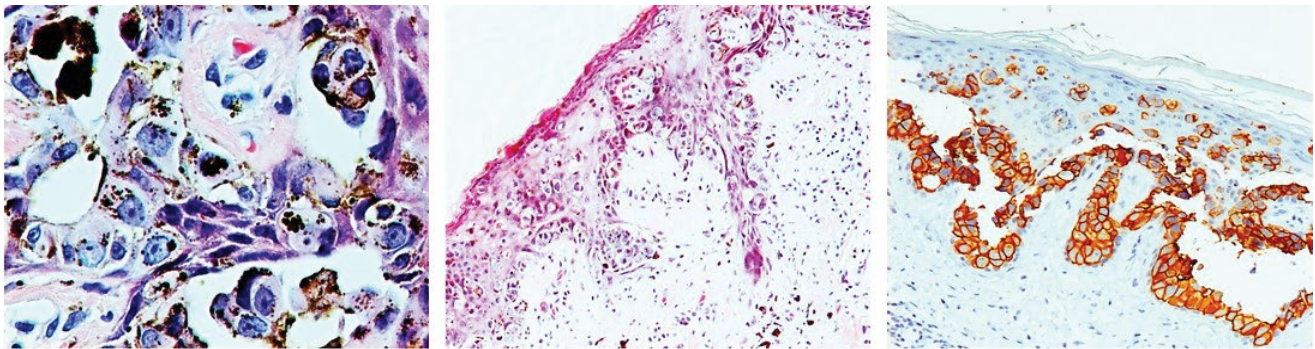


Figure 2: (a) Typical Paget pigmented cells with melanin-like pigment; (b) Pigmented cells in the suprabasal and the presence of carcinoma in the underlying dermis; (c) Positive staining for Her-2.

Table 1: Clinical stages (TNM) in patients with pigmented paget disease.

	n (%)
0	2 (33.3)
I	1 (16.7)
IIA	1 (16.7)
IIB	1 (16.7)

Table 2: Immunohistochemical panel in pigmented cells.

CK-7	HER-2	P63	S-100
+	+	-	-
+	-	-	-
+	+	-	-
+	+	-	-
+	+	-	-
+	+	-	-

mean age of the patients with the pigmented variety was 64.2 years (49 - 79), and 62.5 years in the rest of patients with Paget disease (44 - 78).

Analysing in detail the pigmented category, we found that two patients presented a pure Pigmented Paget disease, without infiltrating component found in the surgical specimen. Both patients were treated with wide excision of the Nipple Areola Complex (NAC). Invasive component was detected in the other four patients. Clinical stages are presented in [table 1](#).

Discussion

Described in 1874, Paget's disease accounts for approximately 1 to 3% of all breast cancers [9,10]. This condition is associated with ductal carcinoma *in situ* and infiltrating ductal carcinoma in 87 to 100% of cases. When it is associated with an invasive component, it is usually more aggressive, with high histological grade, positive axillary nodes and the absence of hormone receptor expression [11].

The usual presentation of Paget's disease is through eczematous changes in the Nipple-Areola Complex (NAC), said itching, scaling and erythema. There is a rare variant of Paget's disease that may mimic melanoma. This form is known as Pigmented Paget disease. It is characterized by the presence of hyperpigmented macules on the NAC ([Figure 1](#)).

When the pagetoid component is only present, just 35 to 50% of cases will have some suggestive mammographic manifestations of malignancy [3]. These changes will be characterized by distortion of architecture and periareolar skin thickening of the NAC.

Pigmented Paget's disease is a rare entity, difficult to distinguish from other conditions such as squamous cell carcinoma of the nipple and melanoma *in situ* of the nipple, which also presents with pagetoid spread.

Paget pigmented cells have a melanin-like pigment which is believed to be transferred by melanocytes. The exact physiopathology remains unknown, but some theories describe a proliferation of melanocytes stimulated by chemotactic factors produced by neoplastic cells; Paget cells phagocyte melanin from melanocytes and finally there is a transference blockage of pigment from melanocytes to keratinocytes ([Figure 2a](#)) [12].

Microscopically, cells with abundant eosinophilic cytoplasm and large nuclei are observed. Such cells will be found grouped in "nests" at the epidermis; infiltration may be attached to the skin. This is a subtle histological difference with pigmented lesions; some authors have described that melanocytes in melanoma spread through all levels of the epidermis while in pigmented Paget disease, isolated cells or nests are seen in the suprabasal layers without the junctional component and an invasive or intraductal mammary carcinoma is often discovered in the underlying dermis ([Figure 2b](#)) [13,14].

The diagnosis might be made by immunohistochemistry, as it will be necessary to make the appropriate treatment. An important

immunohistochemical marker for confirming the breast origin is the cytokeratin 7 (CK-7). It is expected to be positive in all patients. This cytokeratin is expressed in epithelial cells of ovary, lung and breast [15]. Another complimentary immunohistochemistry test that should be done in the pigmented cells is Her-2 staining; 80 to 100% of the cells will express strongly this marker, since Paget disease is commonly associated with High-grade Ductal Carcinoma *In Situ*. The positivity of these two indicators will guide to a mammary origin.

Besides these markers, in order to rule out squamous cell carcinoma or melanoma, it is essential to perform P63 and S-100 respectively, which should be negative in pigmented mammary Paget disease [16].

Currently, there is controversy about the relevance of the expression of Her-2 in carcinomas in situ. Provenzano and Han established that its over-expression was related to a higher incidence of ipsilateral DCIS recurrence, Noh and colleagues in May 2013 stated that although there is no increase in recurrence, it does occur earlier [11,17,18].

As it has been established, treatment should be determined by clinical stage given by the invasive component, if exists. Pigmented variety should be treated as any other mammary Paget disease. Prognosis is not affected by this entity.

Conclusions

Paget's disease represents 1 to 3% of all breast cancers. The pigmented variant is a rare entity, which can mimic cutaneous melanoma; both clinically and histologically with immunohistochemical profile an essential tool to differentiate between these diseases. The positivity to CK-7 and Her-2 in the pigmented cells will lead to confirm pigmented Paget disease. At our institution, incidence of this unusual variation accounts for 8.7% of breast Paget; treatment should be the same as in any other mammary Paget disease of the breast, since prognosis is not affected by this kind of presentation.

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