

PAGET'S DISEASE OF THE BREAST: STUDY OF CASES SERIES

Doença de Paget na mama: estudo de uma série de casos

Walberto Monteiro Neiva Eulálio Filho^{1*}, Flávia Vanessa Carvalho Sousa Esteves¹, Taíla Sousa de Moura Fé², Luan Barbosa Furtado¹, Raimundo Gerônimo da Silva Junior³, Sabas Carlos Vieira¹

ABSTRACT

Objective: To evaluate the survival of a series of patients with Paget's disease of the breast. **Methods:** Observational, retrospective and descriptive study. Data were collected through electronic medical records; the following variables were obtained: age, tumor histology, tumor size, degree of differentiation, lymphatic invasion, vascular invasion, neural invasion, presence or not of potential involvement of axillary lymph nodes, immunohistochemical profile, treatments performed, recurrence, and follow-up. **Results:** Of the 301 cases of assisted breast cancer, six patients were identified with Paget's disease of the breast. The overall survival, with a mean follow-up of 54 months, was 100%. All individuals are free of disease activity. The most common histochemical profile was negative for estrogen and progesterone receptors, and positive for HER-2/neu. Axillary and/or distal metastatic involvement was not identified. **Conclusions:** Overall survival was 100%, with a mean follow-up of 54 months. This high rate is due to the absence of axillary and/or distal metastatic involvement in our series.

KEYWORDS: Paget's disease, mammary; breast; breast diseases; breast neoplasms; eczema.

RESUMO

Objetivos: Avaliar a sobrevida de uma série de pacientes com doença de Paget na mama. **Métodos:** Estudo observacional, retrospectivo, descritivo. Foram coletados os dados através de prontuário eletrônico e obtidas as seguintes variáveis: idade, histologia do tumor, tamanho do tumor, grau de diferenciação, invasão linfática, invasão vascular, invasão neural, presença ou não de comprometimento de linfonodos axilares, perfil imunoistoquímico, tratamentos realizados, recidiva e seguimento. **Resultados:** Dos 301 casos de câncer de mama atendidos, foram identificadas 6 pacientes com doença de Paget na mama. A sobrevida global, com um seguimento médio de 54 meses, foi de 100%. Todas estão sem doença em atividade. O perfil histoquímico mais frequente foi negativo para receptores de estrogênio e de progesterona, e positivo para o HER-2/neu. Não foi identificado comprometimento metastático axilar e/ou a distância. **Conclusões:** A sobrevida global foi de 100%, com um seguimento médio de 54 meses. Essa alta taxa deve-se à ausência de comprometimento metastático axilar e/ou a distância em nossa série.

PALAVRAS-CHAVE: Doença de Paget mamária; mama; doenças mamárias; neoplasias da mama; eczema.

Study carried out at private clinics of Teresina – Teresina (PI), Brazil.

¹Universidade Federal do Piauí – Teresina (PI), Brazil.

²Centro Universitário da Faculdade de Saúde, Ciências Humanas e Tecnológicas do Piauí (UNINOVAFAP) – Teresina (PI), Brazil.

³Laboratório de Patologia e Análises Clínicas (LAPAC) – Teresina (PI), Brazil.

*Corresponding author: walberto@outlook.com

Conflict of interests: nothing to declare.

Received on: 05/12/2017. Accepted on: 06/07/2017

INTRODUCTION

Sir James Paget, a British surgeon and physiologist, was the first person to describe Paget's disease in 1874. Paget's disease of the breast (PDB) is a rare condition occurred exclusively in the papillary-areolar complex, usually associated with an underlying carcinoma and represents only from 0.5 to 5.0% of breast cancer cases¹⁻³. The differential diagnosis includes chronic eczema, intraduct papilloma, basal cell carcinoma, apocrine carcinoma, melanoma, lymphoma, syphilitic cancer, erosive nipple adenomatosis, Bowen's disease of the skin, and ectasia of the breast duct⁴.

The objective of the present study was to evaluate a series of patients with PDB.

METHODS

Observational, retrospective and descriptive study involving all women with PDB who attended a clinic in Teresina, Piauí, between 2001 and 2016. The data were collected by using electronic medical records and obtained the following variables: age, tumor histology, tumor size, degree of differentiation, lymphatic invasion, vascular invasion, neural invasion, presence or not of axillary lymph node involvement, immunohistochemical profile, treatments, recurrence, and follow-up.

The information collected was tabulated and analyzed by using the Microsoft Office Excel®, version 2007 (Microsoft, USA). Clinical staging was performed according to the TNM system of the American Joint Committee of Cancers (AJCC). Values of Ki-67 \geq 13.9% were used as reference.

The study was approved by the Research Ethics Committee of *Universidade Federal do Piauí* (UFPI), No. 0354.0.045.000-11.

RESULTS

Of the 301 cases of breast cancer seen in the period, six patients were identified with PDB (Figure 1), determining a prevalence



Figure 1. Patient with Paget's disease in the right breast.

of 1.9%. The mean age of patients was 59 years old, ranging from 40 to 78.

In situ ductal carcinoma occurred in four cases; infiltrating ductal and lobular carcinomas in situ occurred, each one, in one case — tumors had a mean size of 1.8 cm. Of the six cases of PDB, 66.7% had high differentiation level; 16.7%, moderate differentiation level; and 16.7% were not classified in the histopathological report (Figure 2).

An assessment of the axillary lymph node condition was carried out in five patients. Among them, one underwent radical axillary emptying, in which 16 lymph nodes were evaluated, all of which were negative; four patients underwent research for sentinel lymph nodes, and all results were negative.

Four patients underwent a simple mastectomy and a segmental resection. In one case, the PDB manifested itself eight years after a mastectomy with preservation of skin and papillary-areolar complex (PAC), so that after the diagnosis of PDB, a resection of PAC was performed with free margins and preservation of both the prosthesis and the skin. A patient underwent chemotherapy and one, radiotherapy along with a conservative treatment. As for hormone therapy, a patient who presented positive estrogen receptor received adjuvant tamoxifen. The evolution of patients is shown in Table 1.

Regarding the analyzed molecular markers— HER-2/neu, proliferative index (Ki-67), estrogen receptor (ER), and progesterone receptor (PR) —, Table 2 was obtained (Figure 3).

One patient missed out on the follow-up. There were no deaths related to the disease. All subjects are alive and disease-free, with a mean follow-up of 54 months, ranging from 5 to 104 months since the breast cancer diagnosis.

DISCUSSION

The mean age of patients (from 59 years of age, ranging from 40 to 78) is in agreement with the literature, in which there

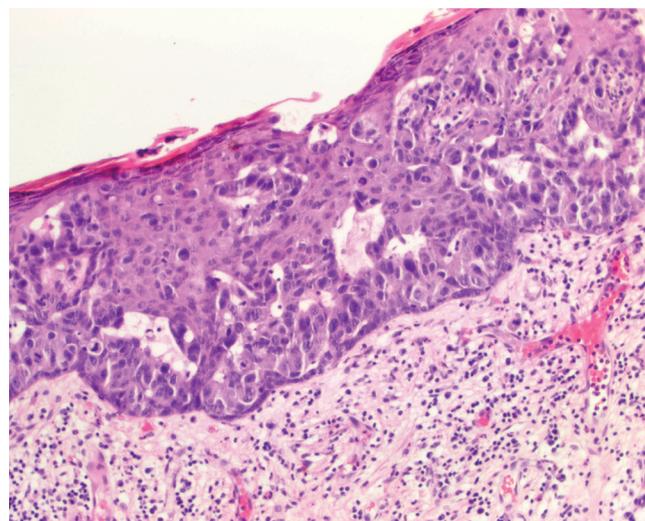


Figure 2. Detail of epidermis with the presence of atypical cells up to the surface (100x).

is a predominance of postmenopausal patients aged between 50 and 60 years. There are reports of PDB in women aged between 24 and 90 years old and, more rarely, in men³. The prevalence of PDB is low: it usually corresponds to less than 5% of breast cancers⁵; in our study, the prevalence was 1.9%.

PDB, histopathologically speaking, is characterized by Paget's epidermal cells, which are malignant glandular epithelial cells with abundant and clear cytoplasm, usually containing mucin, pleomorphic, and hyperchromatic nuclei. The number of cells varies from some to large quantities, and it may even completely replace epidermal cells. The invasion of attachment structures may occur. The dermis presents reactive characteristics, such as telangiectasia, chronic inflammation, and ulceration in advanced cases⁶. In our series, the most common differentiation degree was "moderate or high" (83.33%) and the most frequent histological type was "in situ ductal carcinoma" (66.7%).

Regarding immunohistochemistry, the results diverge from the literature as to the hormone receptors, although they all agree that less than 50% of cases have positive activity of these receptors^{3,7-9}. In our study, only one patient had positive ERs. The HER-2/neu is associated with worse prognostic

in women with breast cancer and, in PDB, it is usually associated with the increased expression of this receptor in nearly all patients (80 to 100%), according to a recent meta-analysis^{3,10}.

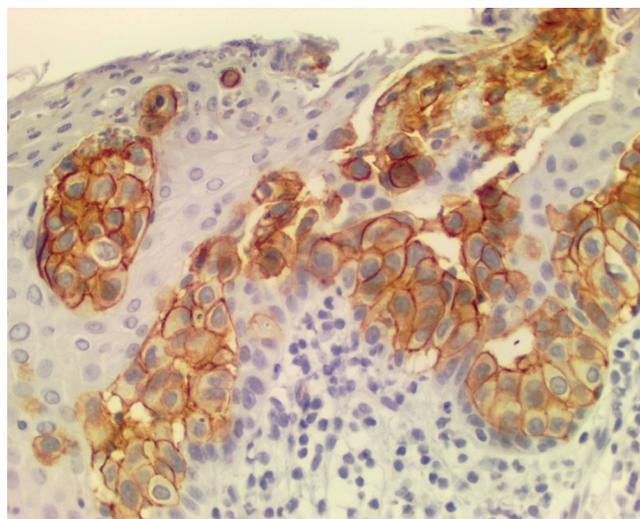


Figure 3. Immunohistochemistry showing positive activity of neoplastic cells to HER-2/neu (200x).

Table 1. Cases series of Paget's disease of the breast.

Case	Age (years)	Skin alteration	Axillary metastasis	CS	Treatment		Lymph nodal condition		Life condition	Follow-up (months)
					Surgery	CT/RT/HT	SL	Lymphadenectomy		
1	78	Yes	No	I	mastectomy	HT	-	16 neg.	Alive and disease-free	74
2	56	Yes	No	II	mastectomy	CT	1 neg.	-	Alive and disease-free	67
3	40	Yes	No	0	mastectomy	-	6 neg.	-	Alive and disease-free	29
4	58	Yes	No	I	Segmental resection	RT	3 neg.	-	L	46
5	57	Yes	No	II	mastectomy	-	1 neg.	-	Alive and disease-free	5
6	67	Yes	No	I	Resection of PAC	-	-	-	Alive and disease-free	104

CS: clinical staging; CT: chemotherapy; RT: radiotherapy; HT: hormone therapy; SL: sentinel lymph node; PAC: papillary-areolar complex; L: lost follow-up contact; neg: negative.

Table 2. Anatomopathological characteristics of cases series of Paget's diseases of the breast.

Case	Type	Degree	ER	PR	HER-2/neu	Ki-67 (%)	Size (cm)
1	ICD	-	Neg.	Neg.	1 +	70	1.5
2	DCis	2	Neg.	Neg.	3 +	90	4.5
3	LCis	3	Neg.	Neg.	1 +	30	0.4
4	DCis	3	Neg.	Neg.	3 +	25	2.0
5	DCis	3	Neg.	Neg.	3 +	-	2.3
6	DCis	3	Pos.	Neg.	1 +	5	0.4

ICD: invasive ductal carcinoma; DCis: ductal carcinoma "in situ"; LCis: lobular carcinoma in situ; Degree: histological degree; ER: estrogen receptor, PR: progesterone receptor; Pos.: positive; Neg.: negative.

In the present study, 50% of the sample had positive activity for the HER-2/neu receptor.

Ki-67 ranged from 5 to 90%, being considerably higher than what was observed in the literature, whose mean is less than 20%; patients with rates higher or equal to 25% have worse overall survival. In the present study, 80% of women with an obtained response had Ki-67 higher than 13.9%⁹.

Due to the low incidence of PDB, there are no randomized studies evaluating the best therapeutic strategy. Historically, mastectomy is the recommended surgical treatment, considering the possibility of extensive, multifocal or breast lesions. However, similar results have been observed between mastectomy and conservative surgical techniques in patients' overall survival, although the rate of local recurrence is significantly higher among women undergoing conservative surgery. Prospective and multicentered studies should be carried out in order to assist the surgeon on the most appropriate surgical approach, considering that the description of new oncoplastic techniques and the evolution of mastectomies may change the currently observed recurrence rates⁵. In the present series, the treatment of choice is consistent with the literature²⁻⁴: all patients underwent surgical treatment;

one of them received radiotherapy, one received chemotherapy and another, hormone therapy with tamoxifen.

A recent meta-analysis evaluating the recurrence rate among patients undergoing mastectomy and conservative surgery associated with radiotherapy observed that 13.2% of those who underwent conservative treatments and 5.2% of the ones who underwent mastectomy relapsed¹¹. In the present study, no metastatic involvement was observed — neither axillary nor distant —, so the overall survival of patient with mean follow-up of 54 months was 100%. Only one patient had cancer recurrence, 103 months after the initial diagnosis.

CONCLUSION

Due to its rarity and the fact it usually occurs in association with an underlying carcinoma, the PDB should be considered a differential diagnosis of any persistent nipple-areolar alteration. There is no consensus regarding the best treatment of choice. The overall survival rate of patients with a mean follow-up of 54 months was 100%. This is probably due to the absence of axillary and/or distant metastatic involvement.

REFERENCES

1. Beltran C, Orlandini V, Stokkermans-Dubois J, Vergier B, Fauchier JM, Doutré MS, et al. Maladie de Paget mammaire pigmentée. *Ann Dermatol Venereol*. 2008;135:211-6.
2. Lee HW, Kim TE, Cho SY, Kim SW, Kil WH, Lee JE, et al. Invasive Paget disease of the breast: 20 years of experience at a single institution. *Hum Pathol*. 2014;45:2480-7.
3. Sandoval-Leon AC, Drews-Elger K, Gomez-Fernandez CR, Yepes MM, Lippman ME. Paget's disease of the nipple. *Breast Cancer Res Treat*. 2013;141:1-12.
4. Albarrán JM, Gadea C, Saldivia F, Prince J, Ramos S, Gutierrez N, et al. Enfermedad de Paget de la mama. Reporte de 13 casos. *Rev Venez Oncol*. 2010;22:194-200.
5. Cirqueira MB, Soares LR, Moreira MAR, Rosa VDL, Freitas-Junior R. Doença de Paget da mama: experiência de um centro universitário. *Rev Bras Mastologia*. 2015;25:90-6.
6. Lopes Filho LL, Lopes IMRS, Lopes LRS, Enokihara MMSS, Michalany AO, Matsunaga N. Mammary and extramammary Paget's disease. *Ann Bras Dermatol*. 2015;90:225-31.
7. Sek P, Zawrocki A, Biernat W, Piekarski JH. HER2 molecular subtype is dominant subtype of mammary Paget's cells. An immunohistochemical study. An immunohistochemical study. *Histopathology*. 2010;57:564-71.
8. Caliskan M, Gatti G, Sosnovskikh I, Rotmensz N, Botteri E, Musmeci S, et al. Paget's disease of the breast: The experience of the European Institute of Oncology and review of the literature. *Breast Cancer Res Treat*. 2008;112:513-21.
9. Marczyk E, Kruczak A, Ambicka A, Mularz K, Harazin-Lechowska A, Moskal J, et al. The routine immunohistochemical evaluation in Paget disease of the nipple. *Pol J Pathol*. 2011;62:229-35.
10. Hanna W, Alowami S, Malik A. The role of HER-2/neu oncogene and vimentin filaments in the production of the Paget's phenotype. *Breast J*. 2003;9:485-90.
11. Li YJ, Huang XE, Zhou XD. Local Breast Cancer Recurrence after Mastectomy and Breast-Conserving Surgery for Paget's Disease: A Meta-Analysis. *Breast Care (Basel)*. 2014;9(6):431-4.