

MAMMARY PAGET'S DISEASE – A CASE PRESENTATION

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Summary

Paget's disease is an in situ adenocarcinoma of the nipple-areola complex (mammary Paget's disease) or in other areas of the body with apocrine glands (extramammary Paget's disease). Mammary Paget's disease is associated in 98% of cases with an in situ or invasive intraductal adenocarcinoma. Clinically it appears as a typical erythematous, eczematoid, unilateral plaque, covered with scales or crusts, sometimes ulcerated, accompanied by serous and/or bloody papillary discharge; it may be associated with itching, pain or burning sensation. The nipple may be ulcerated or retracted. Histopathologically it is characterized by Paget cells, round or ovoid, large-sized cells without tonofilaments, PAS-positive, with pale cytoplasm, located in the basal layer. Surgical excision is the best treatment option although recurrences are frequent.

We present the case of a 62-year-old female patient, who requested a dermatological consultation for the appearance of an erythematous-squamous, itchy plaque, located on the right nipple, with scaly surface and regular, polycyclic borders, evolving for several months. The usual laboratory investigations were within normal limits. The highlighting of Paget's cells at histopathological exam confirm the clinical suspicion of Paget's mammary disease. The patient was referred to the oncology department for further investigations and the appropriate therapeutic management.

Key words: mammary Paget's disease, intraductal adenocarcinoma.

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Case presentation

A 62 year-old female patient attended our clinic for the appearance of a pruritic erythematous-squamous plaque, situated on the right nipple, which has been evolving for several months. The patient underwent topical treatment with corticosteroids, but without significant results.

At the clinical examination it was noticed an erythematous plaque with a diameter of approximately 2 cm, located on the right mammary areola, with the surface covered with scales and with regular, polycyclic margins (figure 1); the nipples were bilaterally retracted from adolescence. No palpable underlying tumor was noticed, nor any loco-regional adenopathy was detected.

The usual laboratory investigations were within normal limits. An incisional biopsy was performed. Histopathological examination revealed numerous large cells in the epidermis, with pale, abundant cytoplasm and intensely basophilic nuclei, organized in groups with nests or pseudo-glandular structures (figures 2 and 3), and a dense inflammatory infiltrate in the superficial dermis, arranged in the band, consisting of lymphocytes. These data confirm the clinical suspicion of Paget's mammary disease.

Subsequently, the patient was referred to the oncology department for further investigations and to establish the appropriate therapeutic management.

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Figure 1. Paget' mammary disease - clinical aspect.

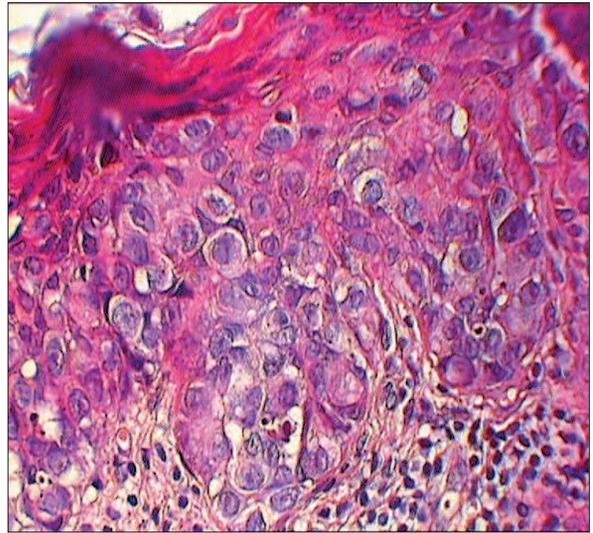


Figure 2. Paget' mammary disease - histopathological findings.

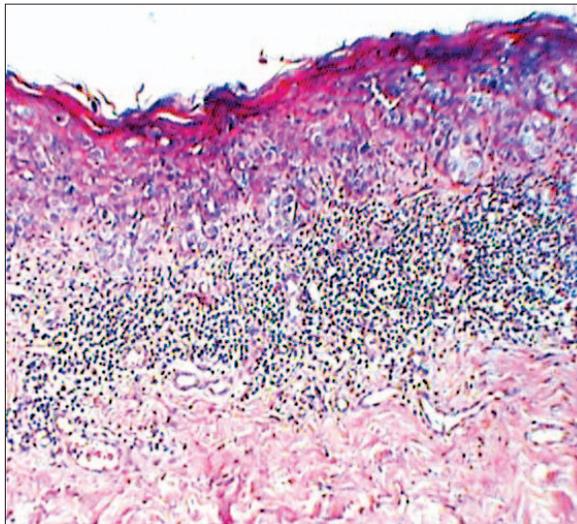


Figure 3. Paget' mammary disease - histopathological findings; detailed depiction.

Discussions

In 1856 Velpeau highlights for the first time the eczematiform lesions characteristic of Paget's disease[1], and in 1874, Sir James Paget, a British surgeon and pathologist, describes Paget's mammary disease as a chronic breast eczema associated with an underlying intraductal carcinoma of the mammary gland.[2] Extra-

mammary Paget's disease was described 15 years later by Henry Radcliffe Crocker[3], who observed both clinically and histopathologically similar lesions in the scrotum and penis area. In 1901 William Dubreuilh reported the first case of vulval extramammary Paget's disease.[4]

Mammary Paget's disease is an intra-epidermal adenocarcinoma located in the nipple-areola complex.[5,6] Extramammary Paget's

disease, although clinically and histopathologically similar to Paget's disease, it is differentiated by involved areas (vulva in women; scrotum and glans in men; perianal, axillary, scalp, auricular, eyelid, etc. in both sexes – regions rich in apocrine or modified apocrine glands); in 10-30% of cases it is associated with apocrine skin carcinoma or visceral neoplasm (bladder, rectum, cervix, prostate, etc.).

Mammary Paget's disease is a rare form of breast cancer, accounting for about 1-4.3% of all breast cancers.[7] It is found especially in women, but it can also rarely occur in men, with a more reserved prognosis.[8,9,10] The maximum incidence is reached between 50 and 60 years, however cases ranging from 26 to 88 years have been reported.[11]

Clinically, mammary Paget's disease presents as a well-demarcated, round, ovoid or polycyclic erythematous or eczema-like plaque, infiltrating, covered with fine scales or crusts, sometimes weeping, bleeding, eroded or ulcerated, which usually starts from the nipple and extends to the areola, with slow centrifugal evolution, for months or even years. In advanced cases it may affect surrounding skin. Paget's disease is usually unilateral, but there have also been cases when both breasts have been affected.[12,13] Sometimes it is accompanied by sero-sanguineous, rarely bloody nipple discharge. Frequent itching, pain or burning sensation may occur, which may precede the occurrence of clinical manifestations. The retraction, ulceration or invagination of the nipple are rare, and may occur especially in advanced stages.[14] There is also described a pigmented variant of mammary Paget's disease that may cause differential diagnosis problems with superficial spreading melanoma or superficial pigmented basal cell carcinoma.[15] The lesions may develop in the ectopic breast tissue, in the accessory nipples and even in patients with congenitally absent nipples.[16] Also, a case of mammary Paget's disease was reported after mastectomy.[17]

In 98% (93-100%) of cases, mammary Paget's disease is associated with an underlying intraductal or invasive adenocarcinoma, usually central or multifocal, located near the areola; there are similarities between the immunohisto-

chemical aspects of intraductal adenocarcinoma and Paget's cells. From here the tumor extends to the nipple or areola along the lactiferous ducts through the basal membrane. It seems that the migration of neoplastic cells occurs under the influence of heregulin- α , a motility factor released by the keratinocytes in the nipple area[18]; the level of HER-2 protein is increased in Paget cells, which is in support of this theory.[18]

In half of the cases, a tumor mass in the breast is palpable, characterized as an invasive carcinoma.[19] In cases where intraductal adenocarcinoma cannot be detected (mammary Paget's disease stage 0) it is assumed that Paget's disease occurs by neoplastic transformation of pluripotent cells located in the basal layer of the epidermis [20] or of Toker cells, benign cells (HER-2 negative) with clear cytoplasm sited predominantly in the basal epidermis of normal nipples around the orifices of lactiferous ducts.

Differential clinical diagnosis is performed with other benign conditions (chronic eczema, contact dermatitis, atopic dermatitis, lichen simplex chronicus, psoriasis, radiodermatitis, erosive adenomatosis of the nipple, intraductal papilloma, , tinea, morphea, *acanthosis nigricans* etc.)[21,22] or malignant (Bowen's disease, superficial basal cell carcinoma, *lentigo maligna*, *lentigo maligna melanoma*, , lymphoma, etc.)[21,22]

Usually the *diagnosis* is based on the clinical aspect and is confirmed by the histopathological examination.

On *histopathological* examination, Paget's cells, malignant glandular epithelial cells, are characteristic. Paget's cells are large cells with abundant basophilic or amphophilic, finely granular cytoplasm and have eccentric, ovoid, hyperchromatic, pleomorphic nucleus, with 1-2 nucleoli. They tend to stand out in contrast to the surrounding epithelial cells and may contain mucin (in this case Paget's cells are PAS positive). Preferentially, Paget's cells are located in the epidermal basal layer, but are able to spread to the stratum corneum.[7,16,23] These cells appear to be organized in groups, with nest-like patterns or gland-like structures, their number may vary, and may eventually replace epidermal cells. Reactive changes are observed in the dermis, with telangiectasia and chronic inflammation. Histopathologically, Paget's disease may mimic

malignant melanoma due to cells that have melanin embedded in the adjacent epidermis. [7,16,23]

Immunohistochemistry plays an important role in difficult cases. Paget's disease differs from malignant melanoma by carcinoembryonic antigen (CEA) positive and S100 protein negative; however, in some cases the S100 protein may be positive and the CEA inconclusive. MART-1 (*Melanoma Antigen Recognized by T cells-1*) or HMB-45 (*Human Melanoma Black-4f*) are more specific for confirming malignant melanoma than S100. Paget's cells are positive for low molecular weight cytokeratins, a feature that can make the difference between Paget's disease and Bowen's disease in which compatibility is expressed for cytokeratins with high molecular weight.[23] In over 80% of cases of Paget's disease, the HER-2 (*Human Epidermal growth factor Receptor-2*) marker is overexpressed, which is associated with a negative prognosis. [22,24]

Presence of CK7 (*cytokeratin 7*), CEA and HER-2 oncoprotein, as well as highlighting mucin by histochemical methods (Alcian blue, colloidal iron, mucicarmin, periodic Schiff acid) are arguments for the histopathological diagnosis of Paget's disease. [24]

Mammography and *mammary ultrasonography* are very important in all cases where Paget's disease diagnosis is suspected; however, in 15-65% of cases they can be negative or not specific. [25,26] Mammography can detect tumoral masses (especially when these lesions are palpable) or calcifications (which may suggest the presence of *in situ* or invasive ductal carcinomas). Ultrasonography examination is particularly useful in cases with negative mammography; however the changes are non-specific, showing hypoechoic areas, discrete masses, skin thickening or ductal dilations. MRI (*magnetic resonance imaging*) is a high sensitivity but not specific investigation; can highlight several changes (thickening of the papillary-areolar complex, enlargement of the nipple, ductal lesions *in situ* or invasive tumors, etc.). However, these non-specific changes can lead to an increase in the number of unnecessary mastectomies instead of choosing a breast conservation therapy. MRI is very useful to assess the extent of underlying tumors. Even if these

investigations are negative, they cannot rule out the presence of a tumor in the breast.[19]

As additional methods, dermatoscopy or *confocal microscopy* may be used. [27] *Dermatoscopically* there can be observed pink structureless areas, with white fine scales and small dotted or linear vessels; in pigmented forms brown structureless areas are present, like as pigmented dots or granules. [27]

The **treatment** of Paget's disease is guided by the stage of the underlying adenocarcinoma (size, radiological appearance, degree of invasion, histological type, etc.), as well as the condition of the loco-regional lymph nodes.

Mastectomy with or without axillary lymph node dissection is the treatment of choice for breast Paget's disease. The risk of breast metastases is higher in women with invasive cancer and palpable mass. The evolution and prognosis depend on the type of breast cancer. In patients with invasive type, the sentinel node biopsy is performed together with the large margin excision mastectomy, and in those with ductal carcinoma *in situ*, sentinel lymph node biopsy is performed only as a preventive measure if an invasive component is identified. [28]

Currently there is a tendency for *conservative treatment* (lumpectomy, partial or segmental mastectomy) which attempts to remove cancerous tissue along with a small area of normal surrounding tissue and excision of the nipple/areola complex, without completely removing the breast. Frequently, after conservative breast surgery, radiation therapy is recommended to destroy the remaining cancer cells. Patients who are not candidates for conservative treatment are those with multiple mammary tumors occupying multiple quadrants; those with a history of lumpectomy with irradiation; those with a history of radiotherapy for other types of tumors; or those who refuse radiotherapy after lumpectomy.[29]

Adjuvant therapy is recommended specifically according to the type of the main tumor. *Radiotherapy* is used in patients who are inoperable or have high postoperative risks; it is also beneficial for local relapses, in patients at high risk of relapse or as a conservative treatment. *Systemic chemotherapy* is indicated in

patients with invasive adenocarcinoma and multiple metastases, when surgery and radiotherapy are contraindicated. [28]

Since there are not yet established therapies, patients should be followed closely, even with regular mammograms.

Poor prognostic factors include the presence and type of invasive ductal carcinoma, axillary metastases, and age below 50 years. Tumor classification is a better prognostic indicator than the presence of Paget's disease. Patients with a palpable tumor mass are at an advanced stage of the disease, having a 5-year survival rate lower (75%) than those without a palpable formation ($\approx 100\%$). [6,9] Also, the survival rate at 10 years is estimated at 47% in those with adenopathy compared to 93% in those without adenopathy. [7]

Conclusions

Mammary Paget's disease is clinically characterized by a persistent erythematous, eczematoid plaque covered by crusts or ulcers that affects the nipple-areola complex and is resistant to treatment.

It is associated with breast cancer (*in situ* or invasive) in 98% of cases; in half of cases the tumor formation may be palpated. Skin biopsy plays an important role in specifying the diagnosis; the defining histopathological marker is the malignant glandular Paget's cell. Para-clinical investigations (mammography, ultrasonography, MRI, etc.) should include careful examination of both breasts and sentinel lymph nodes. The treatment of choice is the surgical one; depending on the type of the basic formation, adjuvant therapy is associated.

Bibliography

1. Velpeau A, editor. On Disease of the Mammary Areola Preceding Cancer of the Mammary Region. London: Sydenham Society; 1856.
2. Paget, J. On disease of the mammary areola preceding cancer of the mammary gland. *St. Bartholomew's Hosp Rep* 1874; 10:87.
3. Crocker HR. Paget's disease affecting the scrotum and penis. *Transactions of the pathological Society of London* 1888-1889;40:187-91.
4. Dubreuilh, W. Paget's disease of the vulva. *Br. J. Dermatol.* 1901 13 (11), 407-13.
5. Ascenso A, Marques M, Capitaomor M. Paget's disease of the nipple. Clinical and pathologic review of 109 female patients. *Dermatologica* 1985; 170: 170-9.
6. Chaudhary M, Millis R, Lane E, Miller N. Paget's disease of the nipple: a ten years review including clinical, pathological and immunohistochemical findings. *Breast Cancer Res Treat* 1986; 8: 139-46.
7. Filho LLL, Lopes IMRS, Lopes LRS, Enokihara MMSS, Michalany AO, Nobuo Matsunaga. Mammary and extramammary Paget's disease. *An Bras Dermatol.* 2015; 90(2):225-31.
8. Ashikari R, Park K, Huvos A *et al.* Paget's disease of the breast. *Cancer* 1970; 26: 680-5.
9. Kawase K, DiMaio D, Tucker S *et al.* Paget's disease of the breast: there is a role for breastconserving therapy. *Ann Surg Oncol* 2005; 12: 1-7.
10. Desai D, Brennan E, Carp N. Paget's disease of the male breast. *Am Surg* 1996; 62: 1068-72.
11. Salvadori B, Fariselli G, Saccozzi R. Analysis of 100 cases of Paget's disease of the breast. *Tumori* 1976; 62: 529-55.
12. Franceschini G, Masetti R, D'Ugo D, Palumbo F, D'Alba P, Mulè A, *et al.* Synchronous bilateral Paget's disease of the nipple associated with bilateral breast carcinoma. *Breast J.* 2005;11:355-6.
13. Babu D, Mohanapriya T, Sai Shalini CN. Bilateral mammary Paget disease in a young adult female. *Radiology Case Reports.* 2018; 135:86-91.
14. Caliskan M, Gatti G, Sosnovskikh I, *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(3):513-21.
15. Ho TC, St Jacques M, Schopflocher P. Pigmented Paget's disease of the male breast. *J Am Acad Dermatol* 1990;23:338-41.
16. Kanitakis J. Mammary and extramammary Paget's disease. *JEADV.*2007; 21: 581-90.
17. Giovannini M, D'Atri C, Piubello Q, Molino A. Mammary Paget's disease occurring after mastectomy. *World Journal of Surgical Oncology.* 2006; 4:51 doi:10.1186/1477-7819-4-51.
18. Schelfhout VR, Coene ED, Delaey B, Thys S, Page DL, De Potter CR. Pathogenesis of Paget's disease: epidermal heregulin-alpha, motility factor and the HER receptor family. *J Natl Cancer Inst.* 2000;92:622-8.

19. Kollmorgen DR, Varanasi JS, Edge SB, et al. Paget's disease of the breast: a 33-year experience. *J Am Coll Surg*.1998;187(2):171-7.
20. Sripathi S, Ayachit A, Kadavigere R, Kumar S, Eleti A, Sraj A. Spectrum of imaging findings in Paget's disease of the breast – a pictorial review. *Insights Imaging* 2015; 6(4):419-29.
21. Cinotti E, Galluccio D, Ardig o M *et al.* Nipple and areola lesions: dermoscopy and reflectance confocal microscopy features. *J Am Acad Dermatol* 2018.
22. Adams SJ, Kanthan R. Paget's disease of the male breast in the 21st century: a systematic review. *Breast* 2016; 29:14-23.
23. Lioyd J, Flanagan AM. Mammary and Extramammary Paget's disease. *J Clin Pathol.* 2000; 53:742-9. [PMCID: PMC1731095] [PubMed: 11064666]
24. Keatings L, Sinclair J, Wright C, Corbett IP, Watchorn C, Hennessy C, *et al.* C-erbB-2 oncoprotein expression in mammary and extramammary Paget's disease: an immunohistochemical study. *Histopathology.* 1990;17:243-7.
25. Günhan-Bilgen I, Oktay A. Paget's disease of the breast: clinical, mammographic, sonographic and pathologic findings in 52 cases. *Eur J Radiol.* 2006;60:256-63.
26. Gaspari E, Ricci A, Liberto V, Scarano AL, Fornari M, Simonetti G. An unusual case of mammary Paget's disease diagnosed using dynamic contrast-enhanced MRI. *Case Rep Radiol.* 2013; 2013:20635. doi:10.1155/2013/206235.
27. Apalla Z, Errichetti E, Kyrgidis A, Stolz W, Puig S, Malveyh J, Zalaudek I, Moscarella E, Longo C, Blum A, Lanssens S, Savoia F, Tschandl P, Kittler H, Sinz C, Stinco G, Argenziano G, Lazaridou E, Lallas A. Dermoscopic features of mammary Paget's disease: a retrospective case control study by the International Dermoscopy Society. *JEADV.* 2019, 33:1892-8.
28. Trebska-McGowan K, Terracina KP, Takabe K. Update on the surgical management of Paget's disease. *Gland Surg.* 2013;2(3):137-42. doi: 10.3978/j.issn.2227-684X.2013.08.03.
29. Paone JF, Baker RR. Pathogenesis and treatment of Paget's disease of the breast. *Cancer.*1981;48:825-9. [PubMed: 6265059].

Conflict of interest
NONE DECLARED

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