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Paget's disease of the male breast: case report and a point of view from actual literature

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SUMMARY: **Paget's Disease of the male breast: case report and a point of view from actual literature.**

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Introduction. *Paget disease of the nipple in man is a very rare breast cancer, and there are not standard procedures or guidelines. In any cases, a Paget's disease could hide an invasive ductal breast cancer.*

Case description. *We report the case of a 77-years old man affected by Alzheimer's disease, who presented to our attention because of an ulcerated palpable mass in the right nipple. A biopsy of the lesion showed "intra-epidermic proliferation of epitelioid cells, associated with linfo-plasmacellular infiltration of superficial dermis, compatible with Paget's disease (pTis)".*

We discussed the case in the multidisciplinary meeting and decided to subject the patient to surgery, so a right mastectomy plus sentinel lymph node biopsy (SLNB) were performed. Histo-pathological examination revealed "invasive ductal carcinoma of the breast, associated with a small component of in situ ductal carcinoma and Paget's disease of the nipple with superficial ulceration". Resection margins were free. Sentinel lymph node was negative. Biological features were as follows: ER 95%, PR 60%, Her-2/neu 1+, Ki-67 35%. The patient was discharged in the third post-operative day in good conditions. In the following weeks the patient's healing process was good and free of complications.

Conclusions. *Clinical recognition of Paget's disease is very important also in man, because it can be the alarm bell for an underlying invasive ductal breast cancer, often more aggressive than in woman.*

KEY WORDS: Breast cancer - Male - Paget.

Introduction

Paget's disease (PD) of the breast is a rare disorder of the nipple-areolar complex (NAC) accounting for 0.7-4.3% of all breast carcinoma and it is associated with an underlying in situ or invasive breast cancer in 82-100% of cases (1). It may affects patients aged 20-90 years (2) but it is more common in postmenopausal women with a mean age at diagnosis of 62.6 years (3). Paget's disease of breast is extremely rare in males, accounting for 1.43% of all male breast cancer, with a mean age at diagnosis of 68.1 years (1). It is characterized by erythematous and eczematous changes in the nipple, due to the presence of malignant (Paget's) cells in the NAC's epidermis. Velpeau firstly described it in 1856, but only Sir James Paget highlighted the connection between the NAC's eczema and breast carcinoma, reporting a series of 15 women who developed breast cancer within 1-2 years after the nipple-crusted lesions (4). Some risk factors for PD have been identified, including: genetic factors; environmental exposure to radiations, high temperature and electromagnetic fields; hyperestrogenism; alcohol abuse, African or Ashkenazi Jewish ancestry.

Two theories have been proposed to explain the pathogenesis of PD: the epidermotropic one, according which ductal cancer cells that migrate along the basal membrane of the nipple are the origin of Paget's cells; and the transformation one, suggesting that Paget's cells originate from malignant transformation

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of keratinocytes which would give rise to PD (5-7).

Initial treatment of PD includes surgery; in terms of mastectomy or lumpectomy plus sentinel node biopsy, followed by adjuvant chemotherapy, radiation or hormonal treatment depending on stage of the underlying carcinoma (8-11). Post surgical radiation has been recommended for male breast cancer with positive nodes, tumor size > 5 cm or positive margins (12-13). Prognosis depends on the underlying breast carcinoma. Most PD associated carcinoma are Her2 +, usually suggesting an aggressive behavior. However, because of rarity of the disease neither randomized studies nor evidenced-based guidelines about management of Paget's disease of breast still exist, and most experiences reported in literature come from retrospectives studies. Here we report our experience on a male case of Paget's disease of the breast.

Case report

We report the case of a 77 years old man coming to our attention because of an ulcerated palpable mass in the right nipple. The patient was affected by Alzheimer, without major cardiovascular co-morbidities, he was no-smoker, without a family history for cancer. After clinical evaluation, the patient was subjected to breast US that showed "moderate thickening of dermal layer, appearing irregularly hypoechoic, associated with two deeper small hypoechoic areas compatible with residual focal lesions". Thus a skin biopsy of the mass of right nipple was performed. The histopathologic examination showed "intraepidermic proliferation of epithelioid cells characterized by rounded leptocromatinic nuclei, evident nucleoli and large eosinophilic cytoplasm, ER-positive, PG-positive, Her2/Neu-positive, CK7-positive, S100-negative, associated with linfo-plasmacellular infiltration of superficial dermis, compatible with Paget's disease (pTis) (Figures 1 and 2 A, B)".

The case was discussed in a multidisciplinary meeting and the collegial decision was to subject the patient to surgery, so a right mastectomy and sentinel lymph node biopsy (SLNB) were performed. The sentinel lymph node was found to be negative intra-operatively, thus further axillary dissection was not indicated. The operation lasted 60 minutes and the estimated blood loss was 100cc. The patient was discharged on third post-operative day in good conditions. Definitive histopathological examination revealed "invasive ductal carcinoma of the breast, associated with a small component of in situ ductal carcinoma and Paget's disease of the nipple with superficial ulceration, pT1b pN0 (sn) G2. Resection margins were free. Sentinel lymph node was negative.

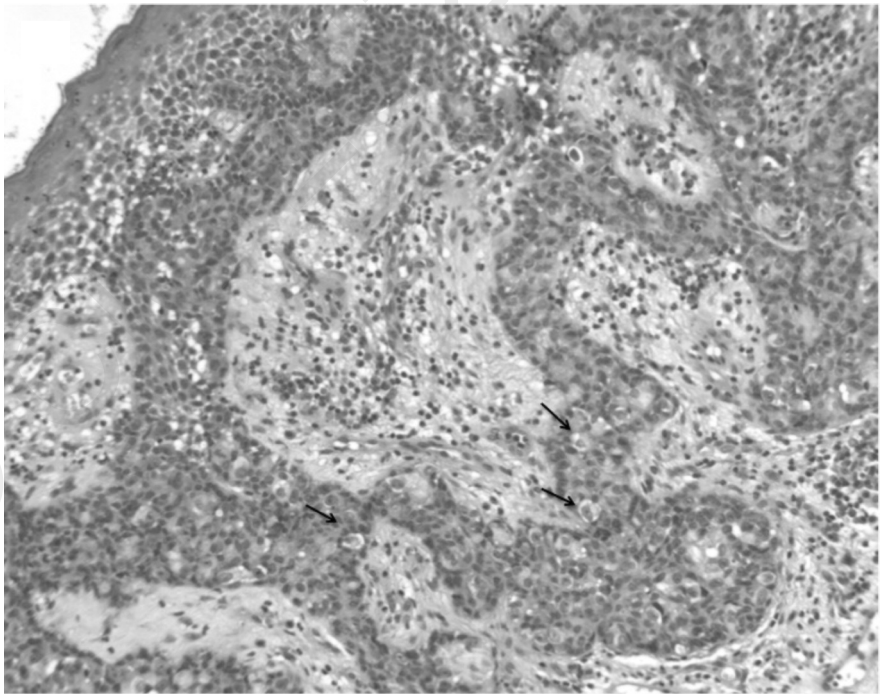

Figure 1 - Paget's carcinoma: the neoplastic cells (black arrows) are individually dispersed among non neoplastic keratinocytes (H&E, original magnification 50x).

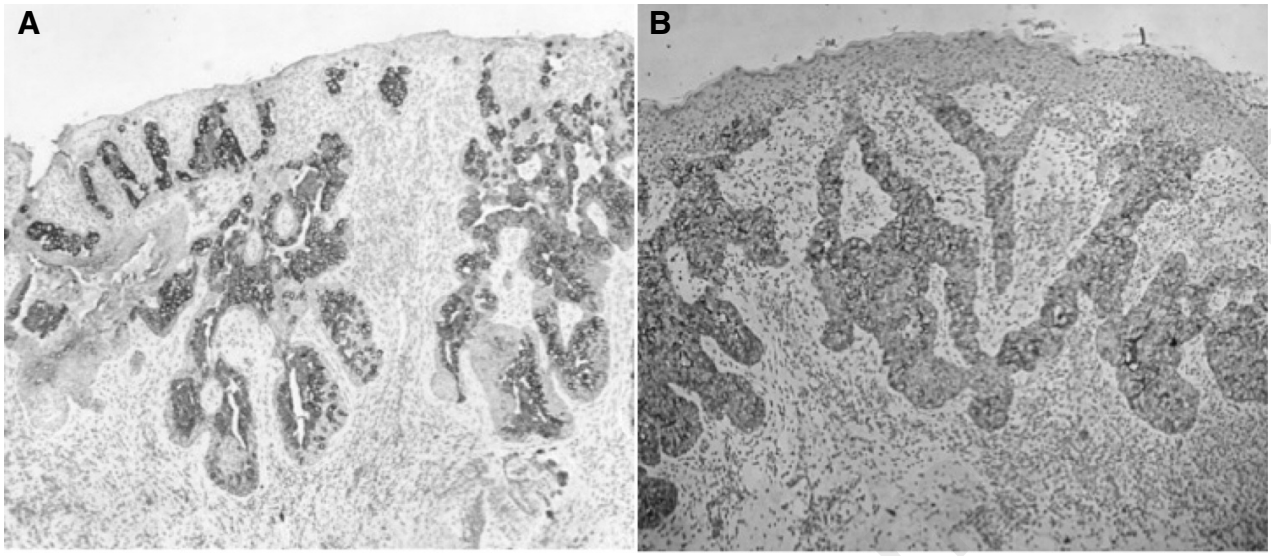

Figure 2 A, B - Neoplastic cells stained intensely for both Cytokeratin 7 (A - Cytokeratin 7 immunostain, original magnification 50x) and c-erb-2 (B - c-erb-2 immunostain, original magnification 50x).

Biological factors were as follows: ER 95%, PR 60%, Her-2/neu 1+, Ki-67 35%". Patient's post-operative course was uneventful and he was followed up without the need of postoperative chemotherapy. Considering the histological features and the hormonal asset of the cancer, we decided to perform the Oncotype DX genetic test; the Recurrence Score was 15 therefore the patient underwent hormonal therapy with Tamoxifen.

Discussion

Paget's disease of the breast in males is a very rare disorder. Few reports have been reported in literature until now. Many theories have been attributed towards the pathogenesis of Paget's disease and several studies have shown that 93% of patients with Paget's disease present with mass lesion of invasive breast cancer, as appeared in our case (14). The clinical features in men look to be similar to those in women and in more advanced stages the lesions may progress to ulceration and cause nipple retraction or bloody discharge from the nipple as in our experience (15).

Our patient showed no obvious risk factors for breast cancer such as testicular abnormalities, infertility, obesity, hyperestrogenism or Klinefelter's syndrome nor was he known to have a family history for breast cancer.

Because of its rarity and the lack of randomized studies and evidence-based guidelines, the management of Paget's disease is still debatable. After a multidisciplinary meeting the decision of our treatment was focused on the size of lesion and the suspicious of pathology of the underlying tumor, thus a right radical mastectomy was performed; in line with most evidences reported in literature. Limited and little information are available regarding the indications for adjuvant radiotherapy and effectiveness of adjuvant chemotherapy in male patients with breast cancer. Most studies (16-21) show similar recommendations and benefit in both men and women but, still now, no randomized studies so far have compared the treatment options for mammary Paget's disease with breast cancer in men due to the relative scarcity of cases in this population.

Adjuvant radiotherapy seems to reduce local recurrence rates in male patients without focal skin involvement (16), while adjuvant chemotherapy lowers the risk of recurrence with prognosis improvement in male patients affected by Stage II breast cancer (17). Considering the role of hormonal therapy in male breast cancer, tamoxifen is still the first and main agent in the adjuvant treatment as well as in advanced disease. In our case we adopted this adjuvant treatment founding on the Recurrence Score of 15 resulted at the Oncotype DX genetic test (22).

Conclusion

Clinical recognition of Paget's disease is very important also in men because, even if it is rare, it is almost always associated with an underlying invasive ductal breast cancer, often more aggressive than in women. Any involvement of nipple–areolar complex should be carefully considered and investigated also through biopsy. If promptly recognized Paget's disease of male breast could be appropriately treated with a favourable prognosis.

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