

Mammary Paget's disease - case presentation and a brief review of the literature

Abstract

Mammary Paget's disease is a rare form of cancer, which involves the nipple-areola complex. In most cases it is associated with an underlying tumor of the breast. Diagnosis is based on clinical appearance and is confirmed by histopathological examination. Imaging tests play an important role in detecting the associated ductal carcinoma. We present the case of a 90-year-old woman, who presented to our clinic for an erythematous-squamous lesion that covers her entire left nipple. The lesion was previously treated as eczema. Histopathological examination revealed features characteristic of Paget's disease.

Keywords: Paget's disease, breast carcinoma, diagnosis, treatment

Introduction

Paget's disease is classified as mammary and extramammary. Mammary Paget's disease (MPD) is a rare condition, with an incidence ranging between 1 and 4.3%. It was first described by Sir James Paget in 1874⁽¹⁾. However the first notes about the disease belong to Velpeau, in 1856⁽²⁾. MPD is an intraepidermal adenocarcinoma affecting the nipple-areola complex. It is most commonly diagnosed in postmenopausal women, in the sixth decade of life⁽³⁾.

Extramammary Paget's disease was originally described by Crocker in 1889. He described lesions similar to those of MPD on the scrotum and penis. In 1901, Dubreuilh has described the first case of Paget's disease located on the vulvar region⁽⁴⁾.

Paget's disease of the breast affects not only women but also men, however much less frequently. In the medical literature 57 cases of Paget's disease of the breast in men have been reported so far. The prognosis is worse than in women. One reason might be the early invasion of the lymph nodes due to the smaller size of the male breast⁽⁵⁾.

Case Report

A 90-year-old woman was admitted to our clinic for the occurrence of erythematous-squamous lesion located on her left nipple. The lesion had appeared about five months earlier and had gradually increased in size. She stated that the lesion was slightly pruritic and not painful. Previously, the patient had been diagnosed with eczema and had received a treatment based on topical corticosteroids without improvement. Her medical history included arterial hypertension and ischemic heart disease. Currently she was in treatment with beta-blockers, nitroglycerin and diuretics.

A physical examination revealed a healthy looking patient with vital parameters within normal range (blood pressure - 130/80 mmHg, heart rate - 68 bpm). Laboratory

tests showed mild anemia (hemoglobin-11g/dl) and a blood glucose level of 110 mg/dl. The dermatological examination revealed a well-defined erythematous-squamous plaque, with irregular margins, covering the entire left nipple (Figure 1). The plaque was slightly exudative. The palpation of the breast did not identify any tumor mass and the axillary lymph nodes were not enlarged. Based on the anamnesis and clinical examination, MPD was suspected. A skin biopsy was performed from the nipple. The patient denied any family history of Paget's disease or other breast carcinomas.

The histopathological examination revealed a fragment of skin with a serofibrinous crust and a marked epidermal atrophy. In the epidermis, numerous large cells with clear abundant cytoplasm and big pyknotic nuclei (Paget cells) were observed. In the dermis many blood vessels, some with distended lumen and dense lymphohistiocytic infiltrate were found. These histopathological findings supported the clinical diagnosis of MPD. The patient was referred to an oncology clinic. The patient was lost to follow up.

Discussion

MPD is a rare form of breast cancer that accounts for 1% to 3% of all primary breast cancers⁽⁶⁾. The study conducted by Chen et al. which included 1738 women diagnosed with MPD revealed that the incidence of the disease between 1988 and 2000 declined. By contrast the number of cases of breast cancer has increased over the same period⁽⁷⁾. MPD can occur in association with breast cancer or a ductal carcinoma *in situ* or may be isolated with no other manifestations⁽⁸⁾. In the above-mentioned study the mean age of disease onset was 62 years and it was highlighted that MPD associated with invasive carcinoma was more frequently detected in younger women⁽⁷⁾. In our case the disease was diagnosed at a very old age.

Cristina Iulia Mitran¹,
Madalina Irina Mitran¹,
Mircea Tampa^{1,2},
Maria Isabela Sarbu²,
Daniela Mihaila³,
Tony L. Hangan⁴,
Dan Navolan⁵,
Simona Roxana Georgescu^{1,2}

1. "Victor Babes" Hospital for Infectious and Tropical Diseases, Romania

2. "Carol Davila" University of Medicine and Pharmacy, Romania

3. "Carol Davila", Nursing School, Bucharest, Romania

4. Faculty of Medicine, "Ovidius" University of Constanta, Romania

5. Department of Obstetrics-Gynecology and Neonatology,

"Victor Babes" University of Medicine and Pharmacy, Romania

Correspondence:
Dr. Mircea Tampa
e-mail: tampa_mircea@yahoo.com

Received:
May 19, 2016

Revised:
June 09, 2016

Accepted:
July 26, 2016



Figure 1. A well defined erythematous-squamous plaque, with irregular margins, encompassing the entire left nipple

Most commonly MPD occurs unilaterally, but some cases of bilateral disease have been reported. MPD evolves slowly over a period of months or years, initially affecting only the nipple and may remain located at this level (Paget's disease of the nipple) or can progress to the areola and the surrounding tissues⁽⁹⁾. Clinically MPD appears as a well-marked erythematous-squamous plaque with irregular margins. In advanced stages it becomes infiltrated and ulcerated⁽¹⁰⁾. In many cases, although an underlying tumor mass is present it cannot be detected during breast examination⁽¹¹⁾. Most studies report the presence of an associated cancer in over 90% of cases⁽²⁾. In our case the tumor mass was not palpable. We decided to send the patient to an oncology clinic for further investigations.

MPD pathogenesis is still not fully understood. Two theories have been postulated. The epidermotropic theory ascertains that Paget cells originate in the apocrine duct, where they undergo malignant transformation resulting in a malignant ductal carcinoma and subsequently they migrate and invade the skin. The arguments for this theory are the association of MPD with an underlying ductal carcinoma in most cases and the resemblance of Paget cells with malignant cells of the associated breast carcinoma. The second theory, called the transformation theory, suggests that in fact Paget cells are transformed malignant keratinocytes and there is no association with an underlying breast carcinoma^(12,13). The study conducted by Schelfhout revealed that heregulin-a, which is released by the epidermal cells, acts as a chemotactic factor for Paget cells, resulting in the migration of these cells to the epidermis. Paget cells express HER2/NEU, HER3 and HER4 receptors, which associate with heregulin-a⁽¹⁴⁾.

Evaluation of patients with MPD includes imaging tests. Mammography may show a tumor mass or detect the presence of calcifications, nipple retraction and skin thickening. Bilateral mammography is recommended to exclude contralateral MPD^(1,15). We must keep in mind that sometimes mammography cannot detect a ductal carcinoma *in situ*⁽¹⁾. Data from medical literature show that in the absence of a palpable mass the mammography is normal in up to 70% cases⁽¹⁶⁾. Ultrasound may bring additional information, being useful, especially in the case of a negative mammography^(1,17). Studies have shown that magnetic resonance imaging has a higher sensitivity than mammography and ultrasound and it is useful in the preoperative assessment of the patient⁽¹⁶⁾.

Dermoscopy can be used in pigmented lesions. However we must take into account that characteristic features of Paget's disease were not clearly defined. Irregular pigmentation, regression and structureless zones have been described. Crignis used dermoscopy in a classic lesion of MPD and revealed the presence of chrysalis-like structures⁽³⁾.

Histopathological examination show glandular malignant cells, with deposits of mucin, invading the epidermis. In hematoxylin and eosin stain the cytoplasm appears pale and the nucleus hyperchromatic with prominent nucleoli. As the disease progresses, atypical cells may be observed⁽¹³⁾. Hyperkeratosis and papillomatosis may be found and sometimes atrophic epidermis may also be detected⁽¹²⁾. Dermal invasion of Paget cells is unusual. In the study of Lee et al. among the 205 cases analyzed, 16 showed dermal invasion. Dermal invasion of Paget cells is sometimes misdiagnosed as an extension of invasive breast carcinoma in the dermis⁽⁶⁾.

Immunohistochemical tests are positive for the following markers, AE1, AE3, carcinoembryonic antigen and epithelial membrane antigen⁽¹²⁾ and reveal the overexpression of cytokeratins 7 (low molecular weight cytokeratins) and lack of expression of cytokeratins 10, 14, 20 (high molecular weight cytokines). We should consider that Paget cells show the same immunohistochemical characteristics as the underlying breast carcinoma cells⁽⁹⁾.

The main differential diagnosis of MPD is eczema. Nonspecific clinical manifestations may lead to a late diagnosis, sometimes the lesions being initially diagnosed as eczema. Unresponsiveness to usual treatment of eczema and persistence over 3 weeks should represent reasons to reconsider the diagnosis. Usually eczema of the nipple occurs bilaterally. Other differential diagnoses are psoriasis, Bowen disease and superficial basal cell carcinoma (BCC)^(10,12). Superficial BCC appears as an erythematous plaque with fine scales on its surface and pearls-like structures in its periphery⁽¹⁸⁾. In advanced stages when the lesion becomes ulcerated it can be confused with BCC. With respect to pigmented lesions the differential diagnosis includes melanoma⁽¹³⁾. In our case the lesion was misdiagnosed as eczema and treated with topical corticosteroids, without a favorable outcome.

Therapeutic approach depends on the underlying breast carcinoma, invasion of lymph nodes and the presence of metastases. Mastectomy with or without lymph nodes dissection is considered the standard treatment by some authors. However mastectomy is not always curative.

Recurrences after surgery were reported. Other authors propose conservative treatment when there is no underlying tumor mass and they recommend tumor

ablation when a tumor mass is detected. Conservative treatment consists of local tumor excision with the excision of the nipple-areola complex and radiotherapy. Studies show that excision without radiotherapy is associated with recurrences in 40% of cases^(1,9,19). Conservative therapy should be used in selected cases⁽⁴⁾. Several studies were performed to define those cases. A study on patients which underwent conservative treatment plus radiotherapy show good results at 15 years follow up. They concluded that this approach is suitable for patients with no palpable mass on clinical examination and mammography without suggestive changes⁽¹⁹⁾. Sentinel lymph node evaluation is recommended in the case of an invasive carcinoma or when a mastectomy is performed⁽²⁰⁾.

Rzaca et al. reported encouraging results regarding the use of cryosurgery in Paget's disease of the nipple. Their results have shown that cryosurgery is useful in the cases of localized disease, in patients with contraindications to surgery or in patients who refuse to undergo a surgical intervention⁽²¹⁾.

The prognosis for patients with Paget's disease with no underlying tumor mass is good, with a 10-year survival rate of 85%. In patients who have a tumor mass the prognosis is poor, the 10-year survival rate being 30-40%, and the rate decreases if lymph nodes are involved^(2,22).

Conclusions

MPD is rarely encountered in current practice and sometimes the diagnosis is delayed. Early diagnosis is important given the association with breast cancer. Identification of clinical features of MPD is essential to a correct and rapid diagnosis. We presented the case of a woman with MPD misdiagnosed as eczema. ■

References

- Karaka C. Paget's disease of the breast. *J Carcinom* 2011, 10, 31.
- Ling H, Hu X, Xu XL. et al. Patients with nipple-areola Paget's disease and underlying invasive breast carcinoma have very poor survival: a matched cohort study. *PLoS One*. 2013, 8(4), e61455.
- Crignis GS, Abreu Ld, Buçard AM. et al. Polarized dermoscopy of mammary Paget disease. *An Bras Dermatol* 2013, 88(2), 290-2.
- Burke ET, Braeuning MP, McLelland R. et al. Paget disease of the breast: a pictorial essay. *Radiographics* 1998, 18(6), 1459-64.
- Adams SJ, Kanthan R. Paget's disease of the male breast in the 21st century: A systematic review. *Breast* 2016, 29, 14-23. doi: 10.1016/j.breast.2016.06.015
- Lee HW, Kim TE, Cho SY. et al. Invasive Paget disease of the breast: 20 years of experience at a single institution. *Hum Pathol* 2014, 45(12), 2480-7.
- Chen CY, Sun LM, Anderson BO. Paget disease of the breast: changing patterns of incidence, clinical presentation, and treatment in the U.S. *Cancer* 2006, 107(7), 1448-58.
- Yim JH, Wick MR, Philpott GW, Norton JA, Doherty GM. Underlying pathology in mammary Paget's disease. *Ann Surg Oncol* 1997, 4, 287-92.
- Lopes Filho LL, Lopes IM, Lopes LR. et al. Mammary and extramammary Paget's disease. *An Bras Dermatol* 2015, 90(2), 225-31.
- Wolff K, Goldsmith LA, Katz SI. et al. Fitzpatrick's Dermatology in General Medicine. Mc. Graw-Hill Professional; Seventh edition 2007.
- Sterry W, Paus R, Burgdorf W. Dermatology. Georg Thieme Verlag KG. 2006, ISBN 3-13-135911-0, 754.
- Lage D, Volpini Cde A, Sasserone Mda G. et al. Paget's disease: the importance of the specialist. *An Bras Dermatol* 2010, 85(3), 365-9.
- Trebska-McGowan K, Terracina KP, Takabe K. et al. Update on the surgical management of Paget's disease. *Gland Surg* 2013, 2(3), 137-42.
- Schelfhout VRI, Coene ED, Delaey B, et al. Pathogenesis of Paget's disease: epidermal heregulin-alpha, motility factor, and the HER receptor family. *J Natl Cancer Inst* 2000, 92(8), 622-8.
- Sawyer RH, Asbury DL. Mammographic appearances in Paget's disease of the breast. *Clin Radiol* 1994, 49, 185-8.
- Helme S, Harvey K, Agrawal A. Breast-conserving surgery in patients with Paget's disease. *Br J Surg* 2015, 102(10), 1167-74.
- 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(2), 256-63.
- Forsea D, Popescu R, Popescu CM. Compendiu de dermatologiesivenerologie. Editura Tehnica, 1996.
- Marshall JK, Griffith KA, Haffty BG. et al. Conservative management of Paget disease of the breast with radiotherapy: 10- and 15-year results. *Cancer* 2003, 97(9), 2142-9.
- Laronga C, Hasson D, Hoover S. et al. Paget's disease in the era of sentinel lymph node biopsy. *Am J Surg* 2006, 192(4), 481-3.
- Rzaca M, Tarkowski R. Paget's disease of the nipple treated successfully with cryosurgery: a series of cases report. *Cryobiology* 2013, 67(1), 30-3.
- Burke ET, Braeuning MP, McLelland R. et al. Paget disease of the breast: a pictorial essay. *Radiographics* 1998, 18(6), 1459-64.