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Case Report

An Unusual Presentation of Paget's Disease After Breast Conserving Surgery and Radiotherapy: A Case Report and Literature Review

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Abstract

Mammary Paget's Disease (MPD) is a malignant noninvasive proliferation of glandular epithelial cells (in situ carcinoma or DCIS) in the nipple. MPD is a rare presentation of Breast Cancer (BC), accounting for 1% to 3% of all BCs. Even rarer, secondary mammary MPD as a relapse of a primary BC is seen. If recognized and treated early, MPD is known to have an excellent prognosis. The clinical presentation of MPD as an eczematous eruption of the Nipple-Areola Complex (NAC) makes a differential diagnosis with benign presentations of the nipple, e.g., nipple eczema, erythema or other malignancies, e.g. cutaneous melanoma. The clinical signs of MPD, redness and erythema are also seen as typical side effects of Radiotherapy (RT) which makes it difficult to diagnose MPD after recent RT, risking a diagnostic delay. Preferential treatment of Paget's malignancy is based on the principles of primary BC approach, including surgery ± RT and/or systemic therapy. This case report presents a MPD in a 70-year-old patient shortly after postoperative RT following Breast Conservative Surgery (BCS). We focus on the difficulties of diagnosing MPD in this setting.

Keywords: Breast cancer; Morbus paget; Radiotherapy; Secondary breast cancer; Hypertension

Abbreviations

BC: Breast Cancer; BCS: Breast Conserving Surgery; DCIS: Ductal Carcinoma *In Situ*; GP: General Practitioner; MPD: Mammary Paget's Disease; MP: Morbus Paget; NAC: Nipple-Areola Complex; RT: Radiotherapy

Introduction

Paget's disease of the breast, also known as Morbus Paget Disease (MPD) or MP, is a rare presentation of a malignant process in the breast, affecting both nipple and areola [1]. Primary MPD is diagnosed in 1% to 3% of all BCs, however the prevalence of secondary MPD is 0.8% to 2.2% [2-5]. Time to relapse as a secondary MPD after a primary BC can vary among cases. On average, this interval comprises a period of 2 years, but cases of 0.5 up to 20 years are also described in literature [4,6]. Although the exact pathogenesis remains unclear, literature reports two hypotheses [6]. The epidermotropic hypothesis is based on the migration of malignant cells of an underlying BC [7]. Another theory claims the malignant transformation of cells that are already present in the dermis [8]. Nowadays, no specific risk factors for MPD have been reported yet. Pathological investigation reports infiltration of neoplastic cells with glandular properties, invading the NAC [4,5]. Not very often, infiltration in the dermis is seen, such as in our case. However, according to current knowledge, this is not linked with a minor clinical outcome [9,10].

Since MPD is generally associated with abnormalities of the Nipple-Areola-Complex (NAC), clinical signs of secondary MPD can be detected by means of a thorough clinical examination. Furthermore, in advanced stages, an eczematous, erythematous or ulcerative change of the nipple can be found [11]. Patients can also complain of an itching and burning sensation of the affected area. Differential diagnosis with eczema, erythema and rare cutaneous melanoma must be made [4,12]. Redness and ulceration are common after Radiotherapy (RT), often causing a risk of diagnostic delay in case of secondary MPD [6].

Our case is unique since the presentation of secondary MPD is only 14 months after original BC treatment. The case emphasizes the importance of clinical and pathologic research in case of persisting redness or ulceration despite treatment with corticosteroids or antibiotics.

Case Presentation

A 70-year-old woman presents after referral by her General Practitioner (GP), with a scale crust on the right nipple. She underwent 09/2020 Breast-Conserving Surgery (BCS) for an extensive DCIS (5 cm) of the right breast. Final pathology report shows a pT1bNx G2 Invasive Ductal Carcinoma (IDC) in the DCIS with a positive margin for DCIS. A second operation with re-excision and sentinel lymph node procedure was performed 09/2020 and final staging shows a pT1cN0(sn) G2 IDC, ER 8/8, PR 8/8, HER2 negative with

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negative margins (R0). Adjuvant RT (breast+boost 40/56 Gy) and endocrine therapy (upfront aromatase-inhibitor) were proposed after a multidisciplinary board meeting. After the irradiation therapy, a crusted lesion on the right nipple occurred that was alternating present and absent, despite treatment with a Hydrocortisone Butyrate/Isobetadine cream prescribed by the GP. The lesion caused a progressively increasing pain and itching around the nipple. Because of the persistent clinical presentation, the patient was referred for a check-up at the breast clinic.

The patient is known with a medical history of hypertension, intrinsic asthma, fracture of the left ankle and depression. Her medication includes Bisoprolol 5 mg once a day, Omeprazole EG 20 mg once a day, Sipralexa 10 mg once a day and Symbicort (turbohaler 4, 5 mcg/dos-160 mcg/dos). On occasion, she takes Alprazolam EG 0.5 mg and De icol (fl coll 5 ml) 1 drop, LOC eye bilateral. She takes Exemestane 25 mg as endocrine therapy.

Physical examination

Clinical examination shows a scale crust lesion at the lateral border of the right nipple, circa one centimeter in cross section and not elevated from the skin (Figure 1). Initially she was treated in a conservative way. As skin changes around the nipple-areola complex persisted and were refractory from local treatment, a punch biopsy was performed to exclude MPD after reassessment with the dermatology department.

Diagnostic interventions

An additional mammography and ultrasound of the breast show classical postoperative and post-radiotherapy changes (BIRADS II) (Figure 2). Magnetic Resonance Imaging (MRI) confirms a postoperative distortion of the mammary tissue with clips, overlying skin retraction and – thickening, but no pathological contrast captation in the previous surgery zone. A significant contrast captation in the right areola and peri-areolar region over 6-7 cm is found. Yet no suspicious underlying mammary lesions were found. The left breast does not show any suspicious contrast captations, nor any abnormal skin or nipple contour. Furthermore, no enlarged axillary and internal mammary lymph nodes are noticed (Figure 3).

Pathological examination

Pathological examination of a punch biopsy confirms the diagnosis of Paget's disease of the nipple. Since there are no arguments for the presence of invasive breast carcinoma, no further investigation for distant metastases is performed.

Figure 1: Scale crust of the right nipple after recent therapy with Isobetadine cream.

Figure 2: Mammography MP.

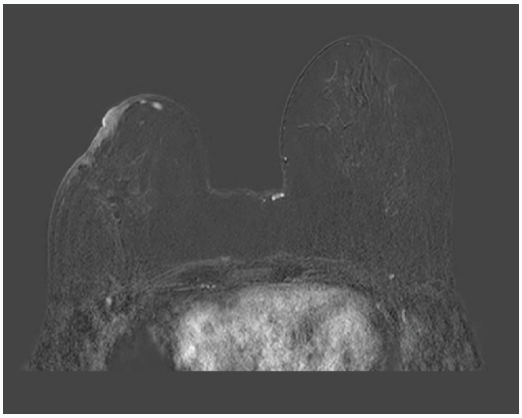

Figure 3: Magnetic resonance imaging shows a peri-areolar contrast captation of the right nipple.

Therapeutic intervention

This case is discussed in a preoperative multidisciplinary board meeting, and local therapy with excision of the NAC without sentinel lymph node procedure is proposed.

Outcome intervention

Excision of the lesion with tumor free margins is successfully performed without any complications. The resection specimen is 6.8 cm × 4.7 cm × 2.7 cm (mediolateral × craniocaudal × anteroposterior) and weighs 28 g (Figure 4). Microscopic investigation shows extensive presence of MP cells in the right nipple, remarkably associated with maximal spread of atypical cells intradermal up to 1.4 cm (Figures 5 and 6). Further investigation indicates a retro-areolar non-invasive grade 3 DCIS with CK5/6 negativity. The lesion is ER and PR negative.

The case is again discussed at the postoperative multidisciplinary board meeting, which decides to perform a strict follow-up, given the patient's recent history of irradiation of the breast.

Discussion

Triple assessment remains crucial in BC diagnosis. The diagnosis of MPD is mostly a clinical diagnosis confirmed by histology. In recently irradiated BC patients, the diagnosis of MPD may be difficult. It may present as an isolated MPD, but it can be associated with underlying intramammary pathology. Mammography, breast ultrasound and MRI also play an essential role in diagnosis, staging and therapy planning of MPD.

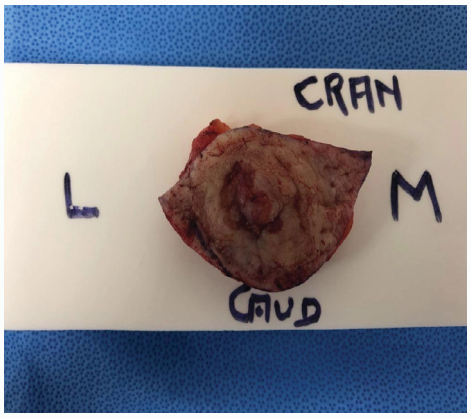

Figure 4: Perioperative resection specimen of the right nipple.

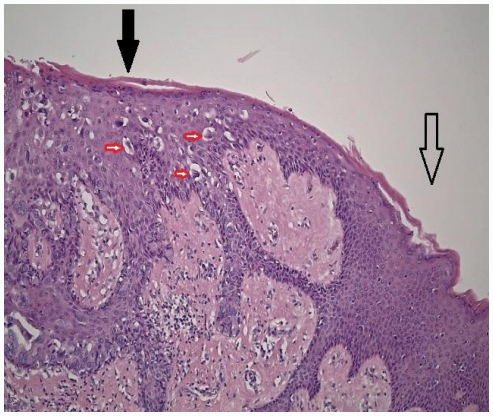

Figure 5: Small magnification (21B11573-2): open vertical arrow normal epidermis, full vertical arrow affected epidermis, with scattered tumor cells; horizontal arrows at some Paget cells.

Mammography and ultrasound provide a good assessment of abnormalities such as skin thickening and -retraction, asymmetry, calcifications and masses localized at the NAC, but some lesions are missed because of a non-specific presentation [13-15]. In a recently irradiated breast, imaging will be more difficult to interpret. MRI is known to have an excellent sensitivity of 98% to 100%, making it an important player in the detection of both primary invasive breast tumors and cutaneous infestation that is seen in MPD, especially if the lesions are difficult to evaluate on mammography and ultrasound, like our case [14,16,17]. However, a subgroup of MPD patients will not show any radiologic changes at all [18,19].

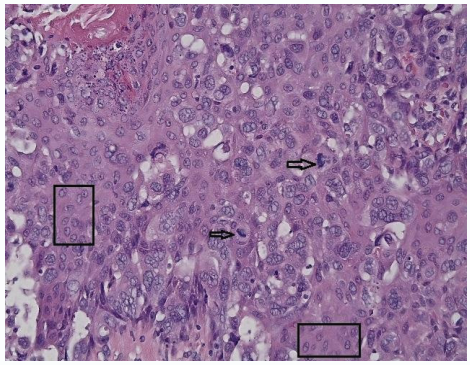

Figure 6: Higher magnification (21B11573-4): numerous Paget cells with some smaller, normal keratinocytes in between, for example in the rectangles. Arrows at single cells in mitosis.

Treatment of MPD, without any other underlying BC, is based on the principles of primary BC therapy. To date, the optimal therapy for MPD remains undetermined, but different therapeutic options are investigated, ranging from local excision and/or RT to mastectomy [20,21]. Selection of the most appropriate option is based on the staging and potential presence of an underlying invasive carcinoma. BCS with removal of the NAC and tumor free margins followed by RT has an equal outcome compared to mastectomy, causing it to be the preferential therapy in case of invasive and non-invasive restricted MPD [2,22,23]. On the other hand, in more advanced stadia, mastectomy remains therapy of first choice. Treatment options of the axilla follow the principles of primary BC management, depending on the presence of a positive sentinel node [24]. Recommendations regarding systemic therapy in (neo-)adjuvant setting are determined by the presence of an underlying invasive carcinoma or DCIS [3]. Additionally, few cases defend the possible role of exclusive RT as a treatment option for MPD in an early stage. Given the limited amount of evidence in literature, in rare cases of secondary MPD such as our case, not only clinical and technological elements, but also preference and history of the individual patient are considered [21,25].

Our patient with confirmed diagnosis of secondary Paget's disease after primary pT1cNoG2 IDC underwent a successful excision of the affected NAC, followed by strict follow-up. As our patient already underwent RT for her primary BC, no further RT is performed. It remains remarkable that our patient previously treated for a small invasive cancer within a large zone of DCIS with negative section margins develops MPD shortly after irradiation. We are convinced that patients within extensive DCIS may be more at risk. Though literature describes exclusive RT as a treatment option for MPD, this cannot be compared with the classical adjuvant RT after BCS. Although MPD is known to have a good prognosis, provided an early diagnosis and multidisciplinary approach, an important diagnostic delay is seen too often [26]. A strict follow-up after BC, including a thorough clinical investigation and imaging, is crucial. Patients presenting with new or persistent skin changes should undergo a punch biopsy.

Conclusion

In patients treated with BCS plus RT presenting with persistent skin changes and pain in the NAC, resistant to local treatment, the diagnosis of MPD should be considered. Clinical examination and histology (punch biopsy) remain essential to differentiate between post-radiotherapy changes and the unlikely diagnosis of secondary MPD of the nipple.

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