



Case Report

Intraepidermal malignancy in breast skin: A tale of two tumours

Zitong Zhao^a, Timothy Kwang Yong Tay^{a,*}, Rashi Agrawal^b, Veronique Kiak Mien Tan^c,
Yah Yuen Tan^d, Puay Hoon Tan^{a,e}

^a Department of Anatomical Pathology, Singapore General Hospital, Singapore

^b Parkway Laboratories, Mount Elizabeth Hospital, Singapore

^c Division of Surgical Oncology, National Cancer Centre Singapore, Singapore

^d BreastCare Surgery, Mount Elizabeth Medical Centre, Singapore

^e Division of Pathology, Singapore General Hospital, Singapore



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ABSTRACT

Mammary Paget's disease most commonly affects the nipple areolar complex and is frequently associated with an underlying in-situ or invasive breast carcinoma. Pagetoid Bowen's disease of the breast is extremely rare and contains cells which morphologically resemble those of Paget's disease and may also express CK7 on immunohistochemistry. Here, we report two unusual cases of a 42-year-old Chinese woman with a recurrence of high grade ductal carcinoma in-situ presenting as mammary Paget's disease away from the nipple areolar complex, and a 65-year-old Chinese woman with pagetoid Bowen's disease of the breast skin. To our knowledge, there are only two case reports that are similar to the former and one to the latter.

1. Introduction

Paget's disease was first described by James Paget in 1874, as a neoplastic condition that exclusively affects the nipple areolar complex (NAC) from which it may spread to the surrounding skin [1]. It comprises approximately 2% of all cases of breast carcinoma, often associated with an underlying high grade disease with multifocality [2]. It is clinically characterized by eczematoid changes of the nipple. The most common cause of Paget's disease in the breast is in-situ or invasive carcinoma extending from the breast into the epidermis of the NAC.

Bowen's disease, also known as squamous cell carcinoma in-situ, is a malignant neoplasm restricted to the epidermis, without evidence of dermal invasion. While it can occur in the head and neck, trunk and extremities, it is extremely rare in the breast.

Here, we report two uncommon cases: a high grade ductal carcinoma in situ (DCIS) recurring in the skin of the breast as Paget's disease but away from the NAC, and a Pagetoid Bowen's disease of the breast skin. Informed consent for publication was obtained from both patients.

1.1. Case 1

1.1.1. Clinical history

A 42-year-old Chinese woman underwent a right skin-sparing mastectomy 2 years prior to the current episode, for high grade DCIS

diagnosed pre-operatively on core biopsy. At that time, she had presented with a 6-month history of an enlarging 5 cm lump in the upper outer quadrant of her right breast, measured on ultrasound as 5.7 cm and subsequently assessed as 5.5 cm of high nuclear grade DCIS on pathological examination of the resected specimen. No invasive disease was seen. The DCIS was positive for HER2 and negative for hormone receptors (ER and PR). The nipple was free of malignancy and Paget's disease. Four sentinel lymph nodes that were biopsied were negative for metastasis. The superficial margin, however, was focally involved by tumour. Approximately 18 months after the skin-sparing mastectomy, the patient noticed a skin rash on the breast. Clinical examination found a 4–5 mm erythematous lesion at the 8 o'clock position of the right breast, resembling a hypertrophic scar that corresponded to the site of the original core biopsy scar, and hence no diagnostic skin biopsy was performed then. Upon review 6 months later, the appearance remained similar with no lesional enlargement. Two months later however, the patient underwent a punch biopsy of the persistent skin lesion (Fig. 1), followed by excision.

1.1.2. Pathologic features

Histological examination of the skin showed a relatively sharply-demarcated, acanthotic region of the epidermis involved by intraepidermal malignant cells and glands (Fig. 2A). The malignant cells showed moderate to marked nuclear pleomorphism with distinct

* Corresponding author.

E-mail address: timothy.tay.k.y@singhealth.com.sg (T.K.Y. Tay).

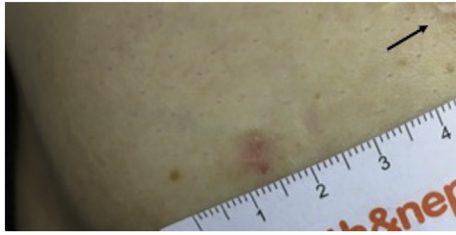


Fig. 1. Clinical picture of Case 1 showing an erythematous, mildly crusted skin rash at the lower outer quadrant of the right breast measuring about 0.5 cm in size (Arrow: the nipple-areolar complex).

nucleoli and several of the malignant cells extended into the deep rete pegs (Fig. 2B). This was associated with a mild to moderate chronic inflammatory infiltrate in the superficial dermis. There was no invasive disease present. A few sebaceous glands, eccrine glands and small hair follicles were seen in the dermis but otherwise no breast tissue was observed. Focal dermal scarring was noted.

On immunohistochemistry (Fig. 3), the malignant cells were diffusely and strongly positive for CK7, while CK14 highlighted only background epidermal cells. Scattered malignant cells were also decorated by GATA3 and GCDPF-15. Tumour cells were negative for ER and PR but diffusely positive for HER2 with 3+ cytoplasmic membranous staining.

1.2. Case 2

1.2.1. Clinical history

A 65-year-old Chinese woman presented with a skin rash on the left breast for 1 year. It was a 2 cm erythematous, scaly lesion at the 6 o'clock position, approximately 5 cm from the nipple (Fig. 4), without active bleeding, discharge or nipple retraction. There were no palpable breast lumps or enlarged axillary lymph nodes. Radiological investigations, including mammogram, ultrasound and magnetic resonance imaging (MRI), did not reveal any breast parenchymal lesions. Ultrasound showed a well-circumscribed cutaneous lesion in the left breast, predominantly macular, with only a small nodular focus measuring 0.2 cm in maximum thickness. This was associated with slightly increased vascularity in the surrounding tissue.

1.2.2. Pathologic features

A punch biopsy of the skin lesion showed an acanthotic epidermis with hyperparakeratosis. A pagetoid band of malignant cells were seen within the epidermis (Fig. 5A), featuring nuclear pleomorphism with increased mitotic activity (up to 4 per high power field) and abnormal mitoses (Fig. 5B). The tumour cells showed enlarged hyperchromatic as well as vesicular nuclei with prominent nucleoli, without definite intercellular bridges. No glandular formation was observed. There was a superficial dermal chronic inflammatory infiltrate involving parts of the dermoepidermal junction, with accompanying vacuolation of the basal epidermal cells.

On immunohistochemistry (Fig. 6), the tumour cells stained positive for CAM5.2 and showed focal reactivity with CK7. PAS, PAS-D and Alcian blue histochemical stains were negative. A diagnosis of Paget's disease was favoured initially. However, the case was further reviewed due to the rarity of mammary Paget's disease away from the NAC without an underlying breast lesion, as well as the unusual staining profile of the tumour. Additional stains performed revealed that the tumour cells were positive for p63 and 34betaE12, although slightly weaker than the background benign epidermal cells. They were focally positive for GATA3 and EMA. HER2, polyclonal CEA, GCDPF-15, CK20, S100 and HMB45 immunohistochemical stains as well as mucicarmine were all negative. In view of the clinical findings, p63 and 34betaE12 positivity and HER2 negativity, the overall features were regarded to be more in keeping with a pagetoid Bowen's disease. Subsequent wide

excision confirmed the diagnosis, with CK7 reactivity in only 30% of the tumour cells and p63 in 90% of the tumour cells.

2. Discussion

The differential diagnoses of a skin rash on the breast include tumours such as Paget's disease, Bowen's disease, basal cell carcinoma, superficial spreading malignant melanoma (particularly in a pigmented lesion) and inflammatory conditions (3). If a neoplastic process is suspected, it is important to distinguish between Paget's disease, Bowen's disease and malignant melanoma. With a combination of morphology and immunohistochemistry, the diagnosis in most cases is straightforward. However, cases with an unusual clinical presentation or limited biopsy material may pose significant challenges and lead to an erroneous diagnosis.

Mammary Paget's disease is most common in the nipple and usually arises in association with an underlying breast carcinoma. The presentation of Paget's disease at a non-NAC location is extremely rare, and even rarer as a manifestation of recurrent breast carcinoma. Our patient in Case 1 had DCIS diagnosed at the right upper outer quadrant and the initial core biopsy was performed through an inferior-superior approach, leaving a biopsy scar at about 8 o'clock on the breast skin. Subsequent Paget's disease was at the same location. While we were not able to review the original high grade DCIS histologically as the pathology was rendered elsewhere, the high nuclear grade appearance of the intraepidermal cells together with similar immunoprofiles and location close to the initial core biopsy site favour the Paget's disease being a recurrence of the underlying breast DCIS. A search of the literature revealed only 2 other case reports of mammary Paget's disease at a non-NAC location presenting as a recurrence of breast carcinoma: one occurred over the prior biopsy site [4] while the other at the previous mastectomy scar [5]. The first case occurred in a 38-year-old woman with a history of right skin-sparing mastectomy for DCIS with microinvasion. There was no adjuvant therapy given. One and a half years later, she had an erythematous skin lesion over the previous core biopsy site which was diagnosed as Paget's disease. The second case involved a 57-year-old woman who had a simple mastectomy and axillary clearance for invasive mucinous breast carcinoma and unifocal Paget's disease of the nipple with clear surgical margins. There was no lymph node metastasis and she was given adjuvant tamoxifen therapy. Four years later, she presented with an eczematoid erythematous lesion at the surgical scar of the previous mastectomy. This lesion remained stable for another 4 years with little disease progression. An excision was then performed which revealed Paget's disease. In our Case 1, the presence of focal dermal scarring in the skin specimen, indicating a prior procedural site, could be secondary to the recent punch biopsy, although the more temporally remote pre-mastectomy core biopsy or even the mastectomy scar are other possibilities. In addition, the documented focal involvement of the superficial margin in the previous resection, despite without record of its exact location, is another risk factor contributing to local recurrence.

Several mechanisms of Paget's disease have been proposed [4]. Away from the NAC, Paget's disease can arise from an ectopic nipple which usually occurs along the normal milk line. Extramammary Paget's disease is thought to arise from apocrine glands as it usually occurs in the genital, perianal, and axillary regions, or rarely from eccrine glands when occurring in skin without apocrine glands. In Case 1, there was no breast tissue present in the specimen. The presence of a few benign sweat glands unrelated to the lesion also excludes the likelihood of apocrine/eccrine gland origin. The similar location of newly developed Paget's disease of the breast skin to the previous preoperative core biopsy position that found DCIS supports the consideration of tumour recurrence at the biopsy site. On review of the two other cases in the literature of recurrent Paget's disease at the prior biopsy site/surgical scar, it is also possible that the Paget's disease in our case also occurred via displacement of tumour cells from the original in-situ carcinoma to

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