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Squamous Cell Carcinoma In Situ (SCCIS) of the Nipple Following Breast Conserving Therapy: Case Report

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Abstract

Background

Squamous cell carcinoma in situ (SCCIS), also known as Bowen's disease, is a precancerous intradermal lesion that commonly arises in sun-exposed areas. Other risk factors include radiation, inflammation, carcinogen exposure, and human papilloma virus exposure. Its presentation on the nipple-areolar complex is extremely rare with 14 cases reported in literature.

Case Presentation

We report a case of a postmenopausal woman with remote history of breast cancer and DCIS treated with bilateral breast conserving surgery followed by adjuvant radiation. She developed SCCIS of the right nipple nearly 30 years later. Associated symptoms included bloody nipple discharge, nipple rash, and nipple pruritus for 1.5 years. A punch biopsy of the right nipple lesion identified epithelioid cells in the intradermal space staining CK7 (+) and p40 (+)/p63 (+), classifying the lesion as Paget's disease. The patient elected to proceed with bilateral mastectomies without reconstruction. Final surgical pathology revealed radiation induced atypia and atypical keratinocytes that focally extend throughout the full epidermal thickness. Immunohistochemical staining demonstrated CK7 (-), CK5/6 (+), p40 (+), HER2 (-) and GCDFP15 (-) consistent with the diagnosis of SCCIS.

Conclusion

Paget's disease of the nipple and SCCIS may present with similar clinical and histopathologic features; however, they are managed differently. Nipple lesions in the setting of prior radiation should raise concern for SCCIS. Clinicians should be aware of this rare, but potential sequelae in patients with a history of breast cancer treated with breast conserving therapy and nipple complaints.

List of abbreviations

BCC = basal cell carcinoma
BRCA = breast cancer gene
DCIS = ductal carcinoma in situ
IHC = immunohistochemistry
SCC = squamous cell carcinoma
SCCIS = squamous cell carcinoma in situ

INTRODUCTION

Squamous cell carcinoma *in situ* (SCCIS), also known as Bowen's disease, is an intraepidermal lesion that usually arises in sun-exposed areas. It is considered an early, non-invasive form of squamous cell carcinoma (SCC) with malignant potential, first described in 1912 by dermatologist John T Bowen.[1] Annual incidence in the United States is approximately 15 per 100 000. There is a slight female predominance with most patients diagnosed in their 60s or 70s.[2-4] SCCIS usually occurs in the head and neck in men compared to the lower limbs and cheeks in women. While less common, SCCIS has also been known to occur in sun protected areas such as the torso or anogenital regions.[5] Its presentation in the breast, and specifically the nipple-areolar complex, is extremely rare with 14 case reports published in PubMed as of April 2025. This case report describes a postmenopausal woman with a history of breast cancer treated with breast conserving therapy who subsequently developed SCCIS of the nipple.

CASE PRESENTATION

This patient is a 69-year-old White female with a past medical history significant for right cheek basal carcinoma and bilateral breast cancer. In 1992 she was diagnosed with right breast ductal carcinoma *in situ* (DCIS) and underwent partial mastectomy and axillary dissection followed by adjuvant radiation. In 2004 she was diagnosed with early stage left breast hormone positive invasive ductal carcinoma and underwent partial mastectomy and axillary dissection followed by adjuvant radiation and anti-endocrine therapy. Her family history was significant for a sister and maternal aunt with breast cancer and 2 paternal cousins with breast cancer. Genetic testing revealed a breast cancer gene (BRCA) variant of uncertain significance. Her social history was notable for prior tobacco use (9 pack-year smoking history; she quit smoking 29 years ago). She initially presented to her primary care physician for new onset right bloody nipple discharge as well as rash and pruritus of 1.5 years duration.

Diagnostic work up including bilateral diagnostic mammogram and targeted right breast ultrasound were negative for suspicious findings. She was referred to a dermatologist who performed a punch biopsy. Histological analysis of the intra-epidermal lesion demonstrated broad islands and infiltrating clusters of atypical epithelioid cells. Immunohistochemical (IHC) stains demonstrated focal superficial CK7

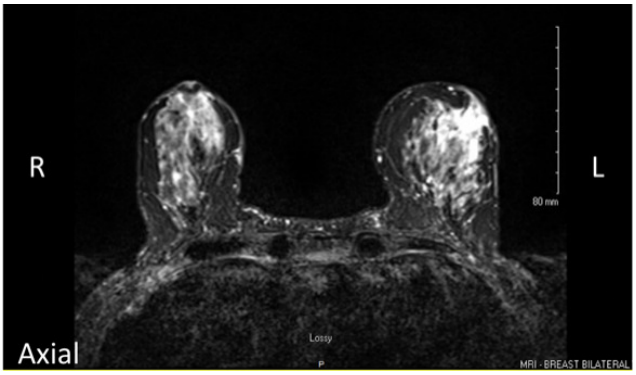

Figure 1. Bilateral Breast Magnetic Resonance Imaging.

Non-mass enhancement in the right inferior retroareolar breast.

(+) with diffuse GATA-3 expression, p40 (+), p63 (+), ER (-), PR (-) classifying the lesion as most consistent with Paget's disease with squamous differentiation. She was subsequently referred to a breast surgical oncologist.

Breast MRI was recommended and revealed an area of non-mass enhancement in the right inferior retroareolar breast for which biopsy was recommended **(Figure 1)**. MRI-guided biopsy of the right breast demonstrated focal intraductal epithelial atypia. Given the diagnosis of Paget's disease with atypia, an in-depth discussion was had with the patient and her husband regarding surgical options including breast conservation vs mastectomy. She ultimately elected to proceed with right mastectomy without reconstruction as well as contralateral risk reducing mastectomy due to her personal history of bilateral breast cancer.

Final surgical pathology demonstrated SCCIS of the right nipple with underlying radiation induced parenchymal changes **(Figures 2a-c)**. Histologically, the nipple lesion demonstrated full thickness epidermal involvement by atypical keratinocytes. IHC staining demonstrated CK7 (-), CK5/6 (+), p40 (+), HER2 (-), GCDFP15 (-), GATA 3 (+), EMA (+), and AR (focal) (+). The breast parenchyma showed changes consistent with radiation atypia, including lobular sclerosis and atrophy with foci of epithelial atypia in a background of diffuse dense stromal fibrosis. There was no recurrence observed at 3-year follow-up. The timeline of events from initial presentation to final diagnosis is summarized in **Figure 3**.

DISCUSSION

The differential diagnosis for nipple lesions and nipple pruritus includes benign and malignant etiologies. Though Paget disease of the breast represents only 1-3% of breast cancers with the highest incidence seen in the 5th decade of life, this diagnosis should be high on the differential for women with nipple lesions and pruritus.[6] It commonly presents as eczematous patches over the nipple and areolar complex, which is histologically composed of malignant intraepithelial cells, also called Paget cells. Underlying breast cancer can extend from the lactiferous ducts to the nipple epidermis, possibly due to de novo transformation of epithelial cells.[7] Paget's disease is associated with underlying breast malignancy in approximately 50% of cases, with some literature citing incidences of over 90%.[6-8] Thus, the diagnostic workup and management should be prompt and thorough.

For patients with prior history of radiation and nipple complaints, squamous cell carcinoma *in situ* (SCCIS) should also be included in the differential. If left untreated, SCCIS has a 3-5% rate of progression to invasive carcinoma.[9] Other risk factors include carcinogens such as arsenic, immunosuppression, and history of human papillomavirus (HPV) infection.[10] Sun-exposed areas such as the head, neck and extremities are commonly affected. SCCIS rarely occurs in the nipple-areolar complex. Histologically it is described as a population of atypical cells that spans across the epidermis and it is usually not associated with underlying breast malignancy. To date, there is only 1 reported case of SCCIS and concurrent breast cancer.[11] A brief comparison of Paget's disease and SCCIS is shown in **Table 1**.

Prior radiation treatment is a known risk factor for future precancerous and cancerous lesions arising at the site of radiotherapy. There are few studies regarding the incidence of radiation induced SCCIS. One case report demonstrated occupational radiation exposure induced SCCIS of the hands.[12] Another study done by Lichter et al evaluated the relative risk of developing basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) after receiving therapeutic ionizing radiation.[13] The authors found an increased risk for BCC (age and sex-adjusted OR, 1.88; 95% CI, 1.24-2.87) and for SCC although not significant (age- and sex-adjusted OR, 1.56; 95% CI, 0.95, 2.55). The study also noted an increased risk of developing BCC and SCC if the patients received their first radiation treatment prior to 20 years of age. There was a latency period of approximately 40 years before a diagnosis of SCCIS. There is also 1 documented case of a woman who developed SCC of the nipple 9 years after breast conserving surgery and adjuvant radiation for DCIS of the ipsilateral breast.[14] Similarly, the patient in this study received ionizing radiation treatment for right breast DCIS 30 years prior to her diagnosis of SCCIS.

It is important to distinguish SCCIS from Paget's disease, which may demonstrate significant clinical and histologic overlap, particularly in challenging cases. A rare subtype of SCCIS known as the pagetoid variant can closely mimic Paget's disease and presents as large, pale vacuolated cells in the epidermis; there are 3 cases reported in the literature.[15] SCCIS and Paget's disease are, however, fundamentally different in pathogenesis, histopathological features, and treatment.

Diagnostic work-up of a nipple or skin lesion requires a full thickness biopsy through the nipple and areola or complete excision followed by comprehensive IHC analysis of the tissue sample. Distinct histopathological features of SCCIS include full-thickness epidermal atypia, abnormal mitosis, and dyskeratosis. In comparison, Paget's disease demonstrates the presence of intraepidermal spread of Paget cells (cells with large, pale, abundant clear cytoplasm, atypical nuclei and prominent nucleoli) on histology.

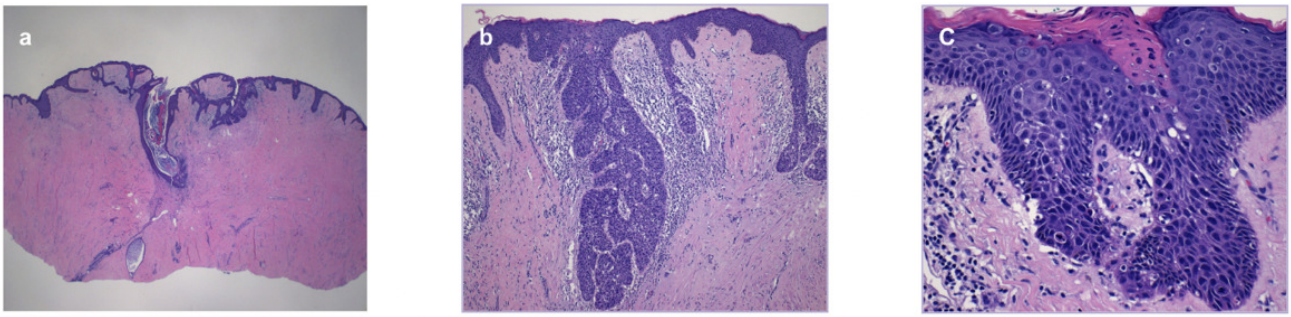

Figure 2. Histology of Nipple Specimen

(a) Nipple with squamous cell carcinoma in situ extending into the lactiferous duct. H&E, 20x. (b) Squamous epithelium with full thickness atypia; scattered mitotic figures and dyskeratotic cells are present. H&E, 100x. (c) Squamous epithelium demonstrating atypical intraepidermal keratinocytic proliferation with pagetoid spread of pale to clear-staining atypical keratinocytes. H&E, 400x.

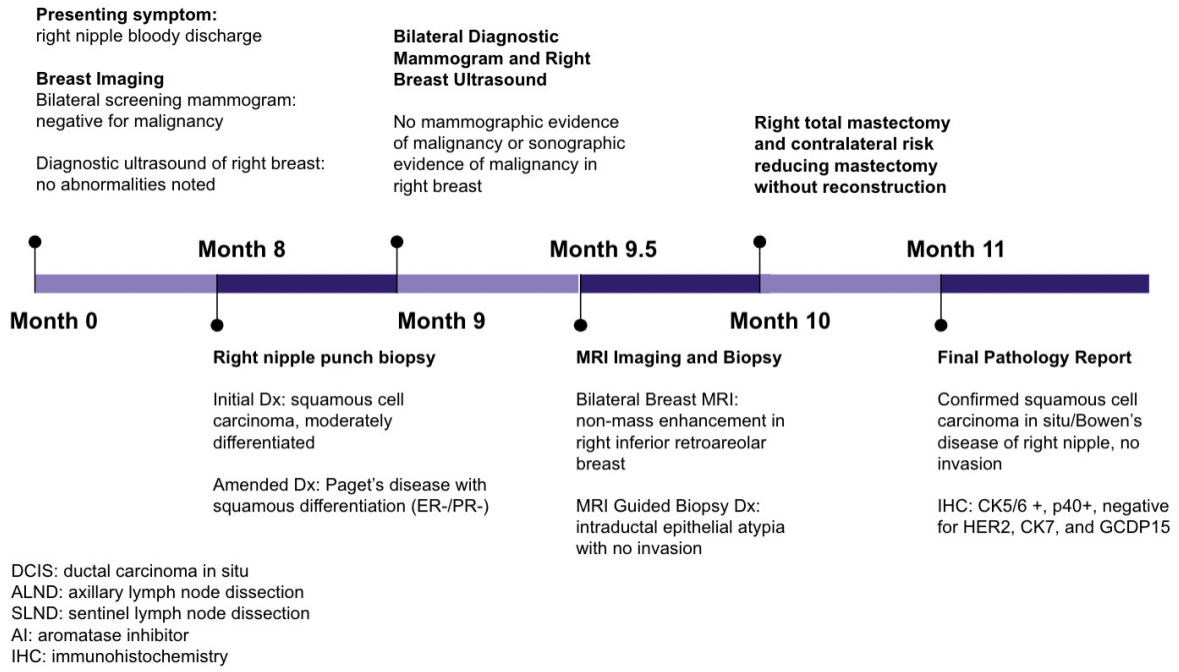

Figure 3. Timeline of Events of Symptom Presentation, Diagnosis and Treatment

In this report, the initial punch biopsy demonstrated histologic staining consistent with Paget's disease with squamous cell differentiation given positive staining for CK7 and p40/p63. However, surgical pathology of the lesion demonstrated IHC staining consistent with SCCIS: CK7 (-), CK5/6 (+), p40 (+), HER2 (-) and GCDFP15 (-). What made the final diagnosis particularly challenging was the presence of aberrant CK7 staining, pagetoid spread, marked inflammation, and radiation induced atypia of the breast parenchyma. Although it is known that radiation of breast tissue can induce atypia, the propensity for inducing primary SCCIS in the breast is understudied. This report highlights key clinicopathologic features that may arise as a late complication of radiation.

Surgical resection is the primary treatment modality for Paget's disease. This entails a mastectomy with axillary staging or central lumpectomy followed by radiation. This is in contrast to SCCIS for which treatment options vary and include topical creams (ie 5-fluorouracil, Imiquimod), photodynamic therapy, cryotherapy, and surgical excision.[10] With the drastically different treatment regimens, it is imperative to attain an accurate diagnosis.

The patient was very grateful to have undergone a risk reducing procedure given her personal history of breast cancer and extensive work up in the past which was anxiety provoking. This contributed to her decision to elect for bilateral mastectomies. Given that the nature of disease was radiation induced given the radiation atypia histology seen in the breast, it may have complicated future screening leading to more anxiety. Overall, the patient is happy with the risk reduction and outcome.

CONCLUSION

This case illustrates a rare cause of nipple lesion and demonstrates the need to include SCCIS in the differential

Table 1. Comparison of Paget's and Squamous Cell Carcinoma *in situ* (SCCIS)

	Paget's Disease	SCCIS (Bowen's Disease)
Clinical Features	Eczematous patches ± pruritus, tingling, erythema, discharge	
Underlying Breast Malignancy	Yes, ~50% of the time	No
Pathological Features	Paget cells (large, pale, abundant clear cytoplasm, atypical nuclei with prominent nucleoli)	Full-thickness epidermal atypia, pleomorphic abnormal mitoses, giant cells with multiple nuclei, and dyskeratosis
Immunohisto-chemical Features	LMWCK (+) p40/p63 (-) CK7 (+) CK 5/6 (-) GCDFP-15 (+) HER2 (+)	HMWCK (+) p40/p63(+) CK7 (-) CK 5/6 (+) GCDFP-15 (-) HER2 (-)
Treatment	Mastectomy with axillary staging or central lumpectomy with radiation	Topical creams (ie 5-fluorouracil, imiquimod), photodynamic therapy, cryotherapy, or surgical excision

diagnosis for patients with a history of breast cancer treated with adjuvant radiation who present with nipple complaints. While Paget's disease of the nipple is more clinically recognized, patients with a history of radiation to the breast should raise concern for SCCIS. Clinicians should be aware of this rare sequela of breast cancer treatment.

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Authors' contributions

Shirley Cheng wrote the main manuscript text, prepared manuscript figures, and performed the literature review. Jared Su revised the manuscript. Jessica Kieu revised the manuscript. Amelia Wong revised the manuscript. Koah Vierkoetter prepared manuscript figures and revised the manuscript. Ashley Marumoto collected patient information and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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