Unusual presentation of more common disease/injury

An unusual presentation of breast cancer in a very young woman

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A healthy 27-year-old woman presented to an outside institution with unilateral nipple pruritus and a slight brown discolouration. When her symptoms failed to respond to topical therapy, nipple biopsy revealed Paget's disease of the nipple. The patient sought further evaluation and care at our institution. Further investigation revealed multifocal breast cancer and the patient underwent bilateral mastectomies with sentinel lymph node biopsy followed by adjuvant systemic therapy. She is currently more than 4 years out from surgery and chemotherapy and has had no evidence of breast cancer recurrence.

BACKGROUND

Breast cancer is a fairly common malignancy primarily affecting postmenopausal women above 50 years of age. However, it may also present in young women. Most commonly, early onset breast cancer is seen in women with a significant family history, usually affecting multiple generations.¹

Paget's disease of the nipple is a rare presentation of breast cancer and most commonly is identified in the setting of a scaly, erythematous nipple, often referred to as an eczematous rash. Nipple pruritus may also be a manifestation of Paget's.² Often when women present for evaluation of nipple itching in the setting of a normal appearing nipple, the possibility of Paget's disease is overlooked. Women presenting with such changes are frequently diagnosed with dermatitis or eczema and treated with topical regimens with the true diagnosis remaining elusive for long periods of time.

To avoid missing a diagnosis of Paget's disease of the nipple, the clinician must maintain a high level of clinical suspicion. The case we present is unusual in that the patient was under 30 years of age without any significant breast cancer risk factors and the presenting symptoms were nipple pruritus and mild hyperpigmentation without an eczematous rash. Failure to respond to topical treatment and the clinician's investigation with a nipple biopsy intended to exclude the diagnosis of breast cancer revealed the unsuspected diagnosis of Paget's disease of the nipple.

CASE PRESENTATION

Several months prior to presentation at our institution, this otherwise healthy 27-year-old woman noticed a mild brown discolouration of her left nipple in the setting of recent onset of itching. When the pruritus persisted for 1 month, she presented to her primary physician who prescribed a topical medication and suggested that she may be developing eczema despite the lack of eczematous skin changes. The pruritus failed to resolve and she returned

for further evaluation. She was referred to a local surgeon who felt that the likelihood of Paget's disease was very low given her age and lack of suggestive skin findings but recommended a biopsy of the nipple to exclude the possibility. However, nipple biopsy confirmed the unlikely diagnosis of Paget's disease of the nipple. Breast cancer risk factors included a family history of breast cancer involving two relatives in her maternal lineage (maternal grandmother at age 77 and maternal grandmother's sister at 52), and one paternal aunt diagnosed at 50 years of age. There is no family history of ovarian cancer.

Clinical examination revealed a healthy-appearing young woman. No axillary adenopathy was identified. Inspection of the breasts identified slight brown hyperpigmentation of the left nipple compared to the right with no other skin findings (figure 1). Specifically, no crusting or excoriation, papular lesions, ulcerations or eczematous lesions were present. Palpation revealed a focal mass-like area of density in the subareolar left breast and asymmetric nodularity in the upper outer and inframammary fold regions of the left breast concerning for multifocal breast cancer. Contralateral breast examination was unremarkable.

INVESTIGATIONS

Review of the outside institution's pathology slides by a breast pathologist at our institution confirmed both the diagnosis of breast cancer and the diagnosis of Paget's disease of the nipple (figure 2A,B). Specifically, special stains were negative for CK7, S-100 and melan-A and were strongly positive for CAM5.2 (not shown). This staining pattern was felt to be consistent with a diagnosis of Paget's disease of the nipple.

Diagnostic breast imaging including mammograms and ultrasound were performed. Mammographically, the patient had scattered fibroglandular density with no mammographic features suggestive of malignancy in either breast. There were no sonographic findings

Figure 1 Mild hyperpigmentation of the affected nipple. No skin changes typically associated with Paget's disease of the nipple (eg, eczematous rash) were seen.

Figure 2 (A,B) H&E staining of a surgical tissue specimen from the affected nipple shown in (A) 100 and (B) 400 magnification demonstrating Paget's disease. Pagetoid cells are noted (arrow).

of concern in the subareolar or upper outer left breast. However, the ultrasound evaluation of the left breast did reveal at least four suspicious nodules close in proximity to the inframammary fold in the inferior breast. These sonographically suspicious nodules were not seen mammographically, likely due to their anatomic position making them difficult to capture in the mammographic field of view (figure 3A). Axillary ultrasound revealed two prominent axillary lymph nodes with minimal cortical thickening to 3 mm that were sonographically indeterminate (figure 3B). Bilateral breast MRI was then performed which revealed bilateral progressive and diffuse uptake in both breasts consistent with physiologic uptake of the fibroglandular tissue, and no focal abnormalities concerning for malignancy were identified. However, the pronounced physiologic enhancement in this patient was noted to be a factor that could limit the sensitivity for detecting early lesions.

Ultrasound-guided core needle biopsy of two of the sonographically suspicious breast nodules revealed grade

I (of III) invasive ductal carcinoma, ER/PR positive. Fine needle aspiration of an indeterminate axillary lymph node revealed reactive changes without evidence of malignant cells.

Given her young age in the setting of a family history of breast cancer, she was referred to Medical Genetics for genetic counselling.³ After careful evaluation, she was estimated to have approximately a 22% likelihood of a mutation based on her maternal family history. Her likelihood based on her paternal family history was estimated to be 19%. There is no consanguinity between the maternal and paternal lineage. The patient elected to undergo *BRCA1* and *BRCA2* gene mutation testing which did not reveal a deleterious mutation. The patient was offered *BRCA* ½ rearrangement testing (BART) to evaluate for a large deletion or duplication⁴ (estimated at the time to provide an additional 3% detection rate), which the patient declined. She had no family history of malignancy suggestive of another hereditary cancer syndrome and the patient elected not to pursue additional testing.

Figure 3 Diagnostic digital mammogram (A, B) and ultrasound (C) of affected breast. No abnormalities were seen mammographically but several suspicious masses were seen sonographically.

After further discussion and consideration of treatment options, the patient elected to proceed with bilateral skin-sparing mastectomies with implant reconstruction.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes dermatitis, nevoid hyperkeratosis of the nipple⁵ and, much less likely, cutaneous T cell lymphoma.⁶

TREATMENT

Final surgical pathology of the left mastectomy specimen demonstrated infiltrating ductal carcinoma, Nottingham grade I (of III) forming three distinct masses ranging in size from 0.3 cm to 0.9 cm. Low grade DCIS was also identified and comprised approximately 5% of the tumour volume. No angiolymphatic invasion was identified. The nipple

showed Paget's disease consistent with the original pathologic diagnosis. Sentinel lymph node biopsy was negative for axillary nodal involvement. In addition, a single left intramammary lymph node was negative for tumour involvement. Pathologic review of the right breast showed no malignancy. The patient recovered well after surgery. The patient was then treated with intravenous doxorubicin and cyclophosphamide every 2 weeks for four cycles followed by intravenous docetaxel every 2 weeks for four cycles. She then initiated adjuvant tamoxifen therapy.

OUTCOME AND FOLLOW-UP

The patient completed adjuvant chemotherapy more than 4 years ago and is nearing initiation of her final year of tamoxifen therapy. With the exception of mild vasomotor symptoms due to tamoxifen she continues to tolerate

it well. She is seen for regular oncologic follow-up and continues to have no evidence of recurrent breast cancer.

DISCUSSION

Paget's disease of the nipple is a rare malignant condition with a reported incidence among all primary breast cancers of 1–3%.^{7–11} Underlying carcinoma is identified in the majority of cases but may be absent in up to 33% of cases.^{12–14} It typically presents as an excoriated lesion of the nipple-areolar complex and may be associated with pruritus. Rarely, it may present with pruritus alone. It is extremely uncommon in young women, with typical age of onset in the sixth decade of life. This is one of the few reports in the literature of a woman presenting at a young age with Paget's disease of the nipple, and this patient represents the second youngest such woman. To our knowledge, there are only two other reports of very young women diagnosed with Paget's disease of the nipple. One was a case series, also from our institution, that included a 36-year-old woman as the youngest identified between 1975 and 2000.¹⁵ The other represent the youngest reported case represented in the literature and describes a 24-year-old woman who presented with an ulcerative nipple-areolar lesion that started as a scaly plaque involving the nipple-areolar complex 1 year prior to medical evaluation.¹⁶ Consistent with other reports in the literature, our patient's underlying malignancy was multifocal.¹⁷ While our patient presented with nipple pruritus, she did not have any of the classic dermatologic changes associated with Paget's disease of the nipple. However, hyperpigmentation of the nipple was observed which the patient noted to be a change from her normal nipple appearance.

Despite description well over 100 years ago¹⁸ and a generally widely recognised typical clinical presentation, it remains relatively common for women presenting with classic clinical findings of Paget's disease of the nipple to be misdiagnosed with either eczema or dermatitis. Often such patients are treated with topical steroids with no improvement and may elude accurate diagnosis for months or longer. Thus, women presenting with non-classical clinical indicators of Paget's disease may remain undiagnosed for extended periods of time resulting in more locally or locoregionally advanced disease at diagnosis.

Both Paget's disease of the nipple specifically and breast cancer in general are uncommon in women of our patient's age and thus we referred her to our Medical Genetics group for evaluation preoperatively. Though her probability of having a mutation in *BRCA1* or *BRCA2* was relatively high, testing was negative. The patient elected to proceed with bilateral mastectomy to minimise her future breast cancer risk given her diagnosis at a young age and the concern that genetic testing does not detect all cancer-causing mutations. Bilateral mastectomy reduces breast cancer risk by 90–95% in women at increased breast cancer risk.¹⁹ Given the lack of ovarian cancer in any family member and the lack of a defined *BRCA* gene mutation, there is no published data to suggest an increased risk of ovarian cancer. Thus, no interventions for ovarian cancer risk have been recommended.

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Learning points

- Breast cancer, and specifically Paget's disease of the nipple, although quite rare, may occur in very young women.
- Excoriation of the nipple-areolar complex is not always associated with Paget's disease of the nipple.
- Subtle changes to the nipple-areolar complex warrant careful follow-up and possible biopsy.
- A high index of clinical suspicion is necessary to avoid overlooking a breast malignancy.
- Very young women with breast cancer, even in the absence of a first degree family history of breast cancer, should be considered for the possibility of a *BRCA* gene mutation.

Competing interests None.

Patient consent Obtained.

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