Neoadjuvant chemotherapy for primary invasive ductal carcinoma of the nipple: A case report

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Abstract. Breast cancer typically arises from the terminal duct-lobular unit of the mammary gland and rarely from the ducts inside the nipple. The present paper reports a rare case of primary invasive ductal carcinoma of the papilla, which was a locally advanced triple-negative breast cancer that was treated with 6 cycles of neoadjuvant chemotherapy with a nab-paclitaxel, epirubicin and cyclophosphamide regimen. Surgical pathology confirmed that a pathological complete response was achieved and adjuvant radiotherapy was performed postoperatively. No recurrence or metastasis occurred as of April 2024. A review of previous similar cases revealed that primary invasive breast cancer of the nipple has several manifestations. Changes in the nipple should be treated cautiously and a pathological biopsy should be performed in a timely manner. Breast cancer occurring in the nipple can be treated with reference to the same type of common breast cancer, and neoadjuvant chemotherapy can also be performed first if neoadjuvant chemotherapy is indicated.

Introduction

Invasive breast cancer originating in the nipple is very rare, occurring in 0.25% of breast cancers (1). Sanders *et al* (2) was the first to term this rare condition as nipple-invasive primary carcinoma. Nipple-invasive primary carcinoma has previously been described in two conditions: i) Secondary to Paget's disease, where tumor cells of the epidermis invade directly into the dermis; and ii) invasive carcinoma arising from the internal ducts or lobules of the papilla (2). The present case belonged to the latter. Previous cases have reported that this rare condition may have multiple clinical manifestations (2-11). Only 6 out of 23 (26%) cases presented with a nipple mass, 12 (48%) had pagetoid changes such as eczema, pruritus or erosion, and 6 presented with only an edematous thickened nipple (Table I) (2-11). Imaging examinations occasionally show no significant abnormalities, and only 11 of the 21 cases with imaging findings reported abnormal changes, such as masses or microcalcifications in the nipple (2-11). Atypical clinical manifestations and imaging findings are considered to lead to missed diagnoses despite the absence of definitive statistical studies. Axillary lymph node metastases have been identified in up to 8 (40%) of the previous 20 cases in which axillary surgery was performed, and it can be speculated that this may be associated with delayed diagnosis (2-11). Therefore, the present report aims to increase attention of this condition.

Case report

A 40-year-old female patient was admitted to the Second Hospital of Jilin University (Changchun, China) on 16 August 2022 due to an enlarged firm mass on the left nipple with an ulcerated surface and exudation of clear fluid (Fig. 1). X-ray examination revealed an enlargement and increased density of the left nipple, measuring ~ 3.5x3.2 cm, and MRI demonstrated a mass-like abnormal signal shadow in the left papillary region and axillary lymphadenopathy (Fig. 2).

A total of three months prior, the patient had noticed left nipple enlargement and then underwent pathological biopsy of the nipple skin at The First Hospital of Jilin University (Changchun, China), which showed spongiform dermatitis of the nipple skin with lymphedema. However, the mass continued to enlarge in the following 3 months and showed enlarged axillary lymph nodes, therefore a second pathological biopsy was performed. A core needle biopsy was performed on the nipple mass and axillary lymph nodes, and the results revealed invasive ductal carcinoma of the nipple (World Health Organization classification of breast tumors) and axillary lymph node metastasis (12). The immunohistochemistry (IHC) results were negative for estrogen receptor (ER; Fig. 3), progesterone receptor (PR; Fig. 4) and human epidermal growth factor receptor-2 (HER-2; Fig. 5). Ki-67 index was measured manually as 60% (Fig. 6). IHC staining was performed using paraffin-embedded breast cancer tissue sections of 3 μm thickness soaked in 10% neutral formaldehyde for 6-12 h at room temperature. Antigen retrieval was performed by soaking the sample in sodium citrate buffer (pH 6.0; 0.01 M), heating the water barrier to 92-98˚C for 15-20 min, and then cooling at room temperature for 20-30 min followed by rinsing with distilled

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water and PBS buffer. Permeabilization was performed in 0.1-0.3% TritonX-100 at room temperature for 25 min, and rinsed with PBS three times for 5 min each. Blocking was performed with 2-5% bovine serum albumin at room temperature for 10-30 min. Sections were soaked in 3% hydrogen peroxide for 20 min to block endogenous peroxidase activity. Primary antibodies used for ER, PR, HER2 and Ki-67 were EP1 (Origene Technologies, Inc.; cat. no. ZA-0102; 5 μg/ml), EP2 (Origene Technologies, Inc.; cat. no. ZA-0255; 5 μg/ml), UMAB36 (Origene Technologies, Inc.; cat. no. ZM-0065; 1:50) and UMAB107 (Origene Technologies, Inc.; cat. no. ZM-0166; 1:300), respectively, and incubated with the tissues at 37˚C for 32 min. Secondary antibodies were provided by the ultraView Universal DAB Detection Kit (Roche Tissue Diagnostics; cat. no. 760-500) and incubated for 8 min at 37˚C. The chromogen detection reagent was DAB. Counterstaining was performed with hematoxylin for 10 sec at room temperature. The OLYMPUS BX51 Fluorescence Microscope (Olympus Corporation) was used for observation. Staging examinations included bilateral supraclavicular ultrasound, liver ultrasound lung CT, and whole-body bone scintigraphy, which revealed no distant metastasis (The American Joint Committee on Cancer) (13).

Considering the locally advanced disease, the patient was administered 6 cycles of neoadjuvant chemotherapy with nab-paclitaxel [intravenously guttae (i.v.gtt); 260 mg/m^2], epirubicin (i.v.gtt; 75 mg/m^2) and cyclophosphamide (i.v.gtt; 500 mg/m^2) -, and each cycle was 21 days (Fig. 7). The first administration of chemotherapy was performed in August 2022. Subsequently, the patient underwent a modified radical mastectomy in December 2022 and achieved a pathological complete response (pCR), which included the axillary lymph nodes. A total of 25 cycles of adjuvant radiotherapy was administered postoperatively. The patient was last reviewed in April 2024 and showed no signs of recurrence or metastasis.

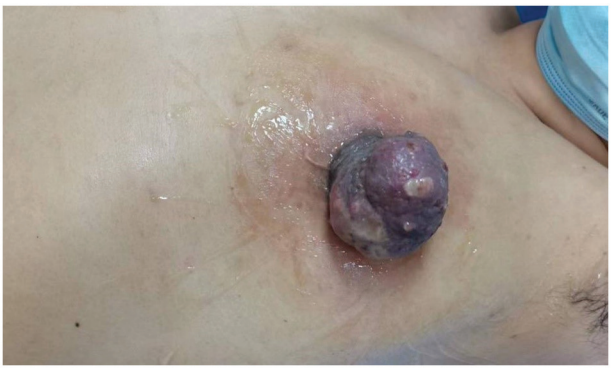

Figure 1. Left nipple showing a large, firm mass.

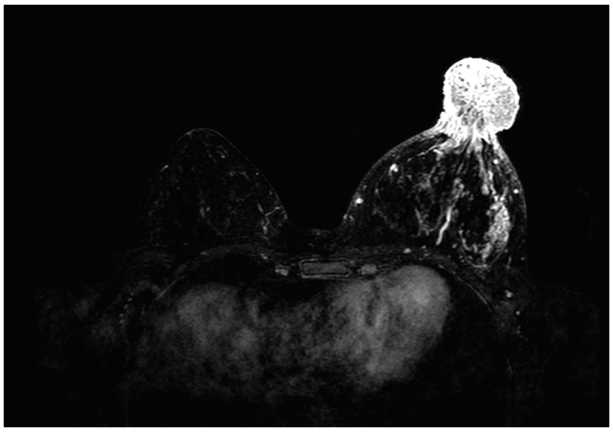

Figure 2. Magnetic resonance imaging of the breast showing an enlarged mass located on the left nipple.

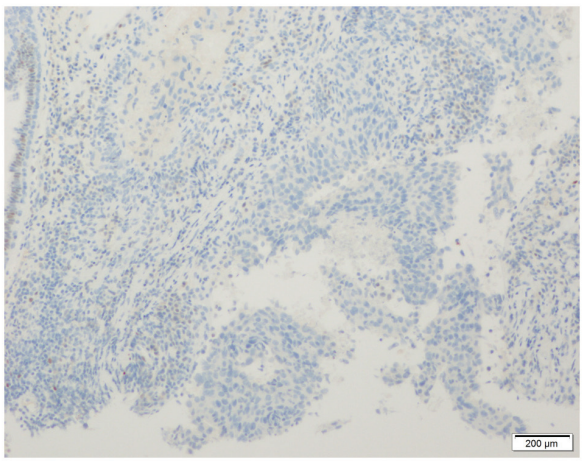

Figure 3. Estrogen receptor expression in the breast cancer cells.

Discussion

Table I presents the previously reported cases of nipple-invasive primary carcinoma (not secondary to Paget's disease). Previous cases have reported that this invasive carcinoma arising in the nipple has several manifestations, such as nipple mass, eczematous changes, edematous thickened nipples or nipple bleeding (2-11). Notably, eczematoid lesions do not equate to epidermal invasion, and there are certain cases in which Paget's disease-like changes are present but there are no Paget's cells present in the epidermis; therefore, Paget's disease is excluded (2,4-9). Imaging studies can sometimes detect abnormal changes, such as masses or microcalcifications in the nipple, but there are also cases in which eczematous changes in the nipple are only present, whilst imaging studies do not show any abnormalities, suggesting that a pathological biopsy can actively be performed (2,4,6-8).

Core needle biopsy can be performed for nipple masses and suspicious lymph nodes, whilst open freehand biopsy can be performed for eczematous changes. Notably, certain cases have no epidermal infiltration, so epidermal scraping alone may lead to a missed diagnosis 4. The patient in the present case presented to another healthcare facility with nipple enlargement 3 months prior to diagnosis. Punch biopsy of the nipple skin and core needle biopsy of the axillary lymph nodes revealed spongiform dermatitis of the nipple skin with dermal lymphedema, and no carcinomatous infiltration of the axillary lymph nodes. This could have been due to small lesions or inadequate biopsy sampling at that time.

Core needle biopsy pathology confirmed the present case as triple-negative breast cancer (TNBC), that is, lack of expression of ER, PR, and HER-2; however, most previous reported

Table I. Characteristics of reported cases.

First author/s, year	Age, years	Clinical presentation	Imaging	Histological type	ER	PR	HER-2	Other focus	Paget's disease	Surgical method	Lymph nodes metastasis	Other therapy	(Refs.)
Kasuga *et al*, 1993	38	Eczematoid changes and pruritus	No	Scirrhous carcinoma	NR	NR	NR	No	No	Modified radical mastectomy	No	Tamoxifen and 5-fluorouracil for 2 years	(4)
Ohsumi *et al*, 1996	71	Eczematoid change and	Yes (MGR: mass and US: mass) a mass	IDC and solid-tubular	NR	NR	NR	No	No	Modified radical mastectomy	Yes	Tamoxifen	(5)
Ahmed and Basit, 2011	47	Eczematous change	No	carcinoma IDC	+	NR	-	No	No	Central segmentectomy and sentinel node biopsy	Yes (1/18)	Radiation therapy, chemotherapy and hormonal treatment	(6)
Erben *et al*, 2012	65	Asymmetrically enlarged nipple	No	ILC	+	+	-	No	No	Central lumpectomy and sentinel node biopsy	Yes	Radiation therapy and anastrozole	(7)
Moennich *et al*, 2015	47	Erosion and bloody discharge	No	IDC	NR	NR	+	No	No	Lumpectomy with nipple removal and sentinel node biopsy	No	Radiation therapy	(8)
Pasquali *et al*, 2016	65	Yellowish tinge and appeared infiltrate	Yes (US: pseudonodular and hypoechoic aspect)	ILC	+	+	-	No	No	NR	Yes	NR	(9)
Moliere *et al*, 2018	45	Swollen nipple	Yes (MGR: accentuated density and MRI: mass)	IDC	+	+	-	No	No	Excision of the nipple-areolar complex associated with sentinel lymph node dissection	No	Radiation therapy and tamoxifen	(3)
Sanders *et al*, 2018	67	Nipple mass	NR	IDC	+	-	-	NR	No	NR	No	NR	(2)
	51	Erythema and exudative crust	No	IDC	+	-	-	NR	No	NR	No	NR	
	37	Nipple mass	No	IDC	+	+	-	NR	Yes	NR	No	NR	
	77	Pruritus	No	IDC	+	+	+	NR	No	NR	Yes	NR	

Table I. Continued.

First author/s, year	Age, years	Clinical presentation	Imaging	Histological type	ER	PR	HER-2	Other focus	Paget's disease	Surgical method	Lymph nodes metastasis	Other therapy	(Refs.)
	62	Skin changes	No	IDC	+	+	-	NR	No	NR	No	NR	
	44	Nipple thickening	Yes (MGR: calcifications)	IDC	+	+	+	NR	No	NR	Yes	NR	
	86	Nipple thickening	Yes (MGR: Nipple thickening)	IDC	+	-	-	NR	No	NR	NR	NR	
	55	Erythema and exudative crust	No	IDC and ILC	+	+	-	NR	Yes	NR	Yes (1)	NR	
	68	Erythema	Yes (MRI: Nipple thickening)	IDC and ILC	+	+	-	NR	No	NR	Not sampled	NR	
	60	Pruritus and exudative crust	No	IDC and ILC	+	-	-	NR	Yes	NR	No	NR	
	58	Nipple mass	Yes (US: mass and MRI: mass)	IDC and ILC	+	+	-	NR	No	NR	No	NR	
	80	Nipple thickening	NR	ILC	+	NR	-	NR	No	NR	Not sampled	NR	
	61	Nipple mass	Yes (US: mass)	ILC	+	+	-	NR	No	NR	No	NR	
	85	Nipple retraction	Yes (US: mass and MGR: Distortion)	ILC	+	+	-	NR	No	NR	Not sampled	NR	
Tan and Mihir, 2019	69	Nipple mass	Yes (MGR: mass; US: mass; and MRI: non-mass) enhancement	IDC within the nipple and DCIS within the breast	-	-	+	Yes	No	Mastectomy and sentinel lymph node biopsy	No	Adjuvant chemotherapy, targeted therapy and radiation therapy	(10)
Hamzah *et al*, 2019	62	Bloody discharge and pagetoid changes of nipple	Yes (MGR: pleomorphic microcalcifications in nipple and US: distended retroareolar ducts and a small indeterminate echogenic focus)	IDC within the nipple and DCIS within the breast	+	-	+	Yes	Yes	Mastectomy and axillary clearance	Yes (1/29)	Adjuvant chemotherapy, targeted therapy, radiotherapy and hormonal therapy	(11)

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; PR, progesterone receptor; HER-2 human epidermal growth factor receptor-2; MGR, mammogram; US, ultrasound; MRI, magnetic resonance imaging; NR, not reported.

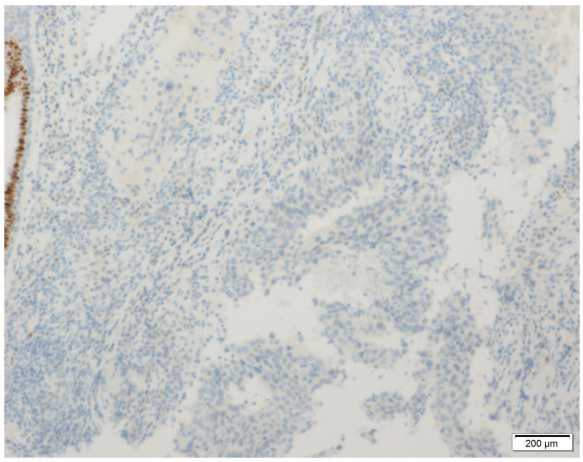

Figure 4. Progesterone receptor expression in the breast cancer cells.

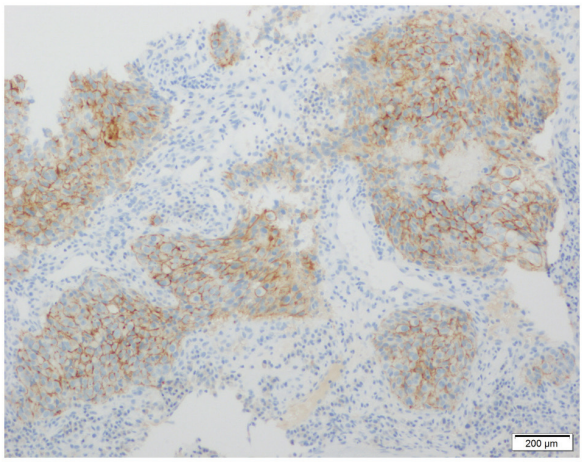

Figure 5. Human epidermal growth factor receptor-2 expression in the breast cancer cells.

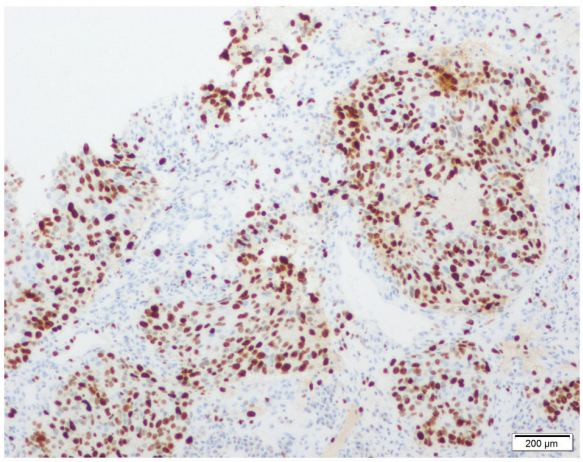

Figure 6. Ki-67 expression in the breast cancer cells.

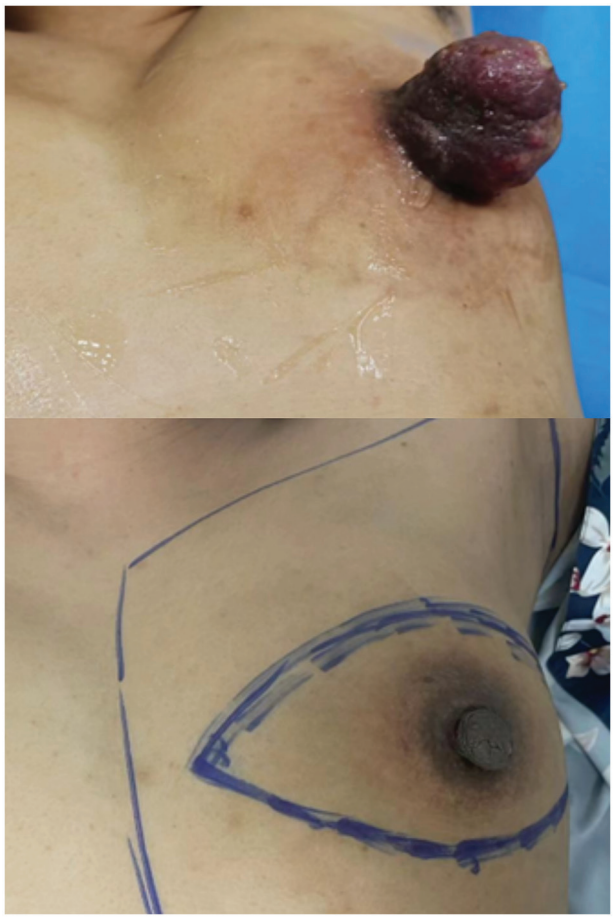

Figure 7. Comparison of papillary morphology before and after neoadjuvant chemotherapy.

cases were hormone receptor-positive (95%) (2,3,6,7,9,11). Compared with other molecular subtypes, TNBC has a more unfavorable prognosis, but is more sensitive to chemotherapy, and pCR is more likely to be achieved after neoadjuvant chemotherapy (14). According to the National Comprehensive Cancer Network guidelines for breast cancer, neoadjuvant chemotherapy is recommended for TNBC that is >2 cm in diameter or TNBC with positive lymph nodes (15). In the present case, Ki-67 proliferation index was relatively high at 60%. Ki-67 index is used as an indicator of proliferative activity and also as a predictor of response to treatment (16). Many previous studies have reported that patients with TNBC with high Ki-67 protein levels are more likely to achieve pCR after receiving neoadjuvant chemotherapy (17). Pathologic response to neoadjuvant chemotherapy is associated with long-term prognosis, with prolonged survival in patients achieving pCR than in those with residual tumor, and this association has been reported to be strongest in TNBC (14).

To the best of our knowledge, the present case is the first case of neoadjuvant chemotherapy for invasive breast cancer originating in the nipple. Following the Chinese Society of Clinical Oncology guidelines for breast cancer, the present case administered a TEC regimen and the patient achieved pCR (including axillary lymph nodes) after 6 cycles of chemotherapy (18). Other regimens have also demonstrated efficacy in neoadjuvant chemotherapy for TNBC, but anthracycline- and taxane-based regimens remain the first choice (19). Furthermore, a retrospective study by Liedtke *et al* (14) reported that anthracycline combined with taxane had the highest pCR rate compared with anthracycline alone, taxane

alone, or other regimens. It was concluded that anthracycline + taxane was the most effective regimen for TNBC.

In the choice of the surgical approach, total mastectomy is performed in most cases, and the surgical principles of the axilla are identical to those of invasive breast cancer (4,5,10,11). However, Moliere *et al* (3) performed central breast-conserving surgery with negative margins followed by postoperative radiotherapy in the absence of other suspicious lesions on MRI, suggesting that, although nipple breast cancer may occur with other breast lesions, central breast-conserving surgery is also an option under the premise of adequate imaging assessment.

To summarize, the present paper reports a rare case of primary invasive carcinoma of the nipple. For abnormal changes in the nipple, clinicians should be aware of the possibility of breast cancer in the nipple and timely select the appropriate way for pathological biopsy to avoid delay in diagnosis and treatment. The present case also suggests that for primary breast cancer of the nipple suitable for neoadjuvant therapy, the choice of treatment can also refer to common breast cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KS proposed the main conceptual ideas, developed the structure, wrote and edited the manuscript. MZ obtained medical images, collected data, assisted with the preparation of tables and figures and polished the language. GC performed biopsy procedures, managed the patient during diagnosis and treatment, revised the manuscript and provided guidance and supervision throughout the writing process. BL made treatment decisions, advised on neoadjuvant chemotherapy, performed surgical treatment and provide financial support for this project. All authors have read and approved the final manuscript. KS and BL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The verbal informed consent was obtained from the patient for the publication of their anonymous information in the present article. Written informed consent was not obtained due to the personal circumstances of the patient.

Competing interests

The authors declare that they have no competing interests.

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