CASE REPORT

Triple receptor-positive primary neuroendocrine carcinoma of breast in a young patient

Manu Vats,¹ Vivek Sachan,¹ Sahaj Prajapati,¹ Shramana Mandal²

¹Department of General Surgery, Maulana Azad Medical College, New Delhi, India

²Department of Pathology, Maulana Azad Medical College, New Delhi, India

Correspondence to
Dr Manu Vats,
vatsmanu@gmail.com

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SUMMARY

Primary neuroendocrine carcinoma of breast is a very rare malignancy and preoperative diagnosis is difficult by clinical examination alone. Most often, histopathological examination (HPE) and immunohistochemistry (IHC) studies are required to establish the diagnosis. We describe here a case of a primary neuroendocrine carcinoma of right breast in a 32-year-old woman. The patient underwent a right modified radical mastectomy, and the diagnosis was conclusively established postoperatively by the HPE and IHC reports. The IHC report revealed positive status of oestrogen, progesterone and Herceptin receptors.

BACKGROUND

Neuroendocrine carcinomas of breast are a very rare entity; contributing less than 0.1% to all the breast malignancies, wherein primary neuroendocrine tumours (NETs) constitute only about 5–10%.^{1–2} They show morphological features of NETs identical to those found in gastrointestinal tract and lung, along with the expression of neuroendocrine markers in more than 50% of the tumour cells.¹ The disease is most commonly described in the age group ranging from 40 to 70 years, more frequently in women aged above 60 years.³ The patient described in this case is only 32 years old and is relatively young for a primary neuroendocrine carcinoma of breast. The patient was initially diagnosed with infiltrating ductal carcinoma (IDC; not otherwise specified, NOS), based on the core needle biopsy. However, she did not comply with the treatment and neglected her disease. After 1 year, she presented again with an advanced T4b disease.⁴ Kawasaki *et al* have proposed that neuroendocrine ductal carcinoma in situ (DCIS) is the preinvasive stage of neuroendocrine carcinoma of breast, and neuroendocrine DCIS is commonly underdiagnosed before surgery due to difficult sampling and further resemblance of the specimen to ductal hyperplasia and intraductal papilloma.⁵ The outcome of this is that patients are misdiagnosed and fail to receive the appropriate therapy on time.⁶ A preoperative diagnosis of primary neuroendocrine carcinoma with hormone receptor status on biopsy will help us in the early administration of appropriate targeted therapy. Furthermore, most of the neuroendocrine tumours (NETs) express oestrogen and progesterone receptors (ER and PR) but are usually negative for HER2/

Neu (Human Epidermal Growth Factor Receptor 2).⁷ However, the patient described in this report was positive for Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2/Neu. The purpose of writing this case report is to discuss the rare occurrence of a primary neuroendocrine carcinoma of breast with ER, PR and HER2/Neu receptor positivity in a young woman. The fact that primary neuroendocrine carcinomas of breast are often misdiagnosed on initial biopsy is highlighted, and appropriate strategies to address this problem have been discussed. Subsequently, although the patient did not receive any treatment after one cycle of neoadjuvant chemotherapy for 1 year, there was only locoregional progression of the carcinoma but no systemic metastasis despite the graver prognosis of primary neuroendocrine carcinomas of breast in comparison with invasive carcinoma breast NOS.

CASE PRESENTATION

A 32-year-old woman presented to the outpatient department (OPD) in April 2016, with the complaints of progressively increasing painless lump in the right breast since past 3 months. There was no history of nipple discharge, trauma to the breast, tuberculosis or any previous breast swelling or surgery. The patient attained menarche at the age of 14 years, and the menstrual cycles had been regular. The patient had two children, both of whom she breastfed, starting immediately after child birth and continuing until the age of 1 year. The patient gave no history of breast malignancy in the first or second degree relatives or of any malignancy-related deaths in the family. There was no history of oral contraceptive pills intake.

General physical examination was unremarkable. Local examination revealed a well-defined hard lump on the upper outer quadrant of the right breast measuring 6×4 cm, free from the overlying skin and underlying pectoralis major muscle. Single, mobile lymph node measuring 1.5×1 cm was palpable in the right axilla. No supraclavicular lymph nodes were palpable on either side. The contralateral breast and axilla were normal. Mammography of the right breast was suggestive of Breast Imaging Recording And Data System Category 5 (BIRADS-5). Core cut biopsy of the lump reported IDC, NOS grade 1. Tumour showed focal areas of haemorrhage and mild intratumour fibrosis. Immunohistochemistry (IHC) was positive for ER, PR and HER2/Neu.

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Figure 1 Preoperative photograph of the right breast (with gauze packed in wound cavity).

With a working diagnosis of advanced locoregional right breast cancer (stage IIIA, $T_3N_1M_0$),⁴ the patient was given only one cycle of neoadjuvant chemotherapy (doxorubicin–cyclophosphamide and paclitaxel–trastuzumab based) after which she was lost to follow-up. She then reported to our OPD after a span of 1 year, with the complaints of foul-smelling discharge and recurrent spontaneous bleeding from the ulceroproliferative lesion (figure 1) in the right breast since last 15 days.

Bilateral axillary examination revealed right side multiple matted lymph nodes and a single lymph node on the left side. Fine needle aspiration cytology of right axillary nodes was suggestive of metastatic carcinoma but only reactive lymphoid hyperplasia on the contralateral side. Contrast-enhanced Computed Tomography (CECT) chest and abdomen suggested no pulmonary or abdominal metastasis. Whole body Technetium-99m bone scan reported no evidence of skeletal metastasis. The patient now had stage IIIB disease (tumour, node, metastases (TNM) staging— $ycT_4N_2M_0$).⁴ Her haemoglobin level was 7.8 g/dL on presentation and decreased to 6.4 g/dL over the next 3 days.

INVESTIGATIONS

1. Bilateral mammography.
2. Core needle biopsy for HPE and IHC reports.
3. CECT chest and abdomen.
4. Technetium-99m whole body bone scan.

DIFFERENTIAL DIAGNOSIS

1. Invasive ductal carcinoma of breast NOS.
2. Metastatic neuroendocrine carcinoma.

TREATMENT

Owing to the ongoing blood loss from the lesion, the patient was transfused 3 units of packed red cells. Subsequently, right modified radical mastectomy was performed. Subcutaneous suction drain limbs were placed in the axilla and on the chest wall. The drains were removed on postoperative day 6 when the output had reduced to less than 30 mL over 24 hours. Central 3 cm of the suture line showed flap necrosis which was managed with serial debridement and dressing. The patient was discharged from the ward on Post Operative Day-13 and was followed up in the OPD.

Figure 2 Photomicrograph (H&E, ×4) showing the tumour cells arranged in sheets.

OUTCOME AND FOLLOW-UP

The histopathology examination revealed the diagnosis of primary neuroendocrine carcinoma of breast and reported a growth measuring 11×9×7 cm involving all the quadrants. Pathological TNM staging was $pT_{4b}N_2M_0$.⁴ The deep resected plane, nipple and areola complex were free of tumour; however, the upper and lower outer and lower inner quadrants were involved. The tumour was arranged in tubules, cords and small nests. The cells were found to have scant cytoplasm, round to oval nuclei and stippled chromatin. Tumour cells showed few mitosis and were surrounded by mild to moderate fibrosis. Tumour necrosis and lymphovascular invasion was present (figures 2, 3 and 4). Out of the 11 lymph nodes in the specimen, four showed tumour deposits. IHC showed the tumour to be positive for neuron-specific enolase (NSE), synaptophysin (figure 5), ER, PR and HER2/Neu. The patient was stable and on regular follow-up at the time of writing this paper. She is receiving adjuvant chest wall radiation therapy and adjuvant chemotherapy (doxorubicin, cyclophosphamide and paclitaxel–trastuzumab based) under the supervision of a medical oncologist.

Figure 3 Photomicrograph (H&E, ×10) showing tumour cells in nests and sheets with trabeculae.

Figure 4 Photomicrograph (H&E, ×40) showing round blue tumour cells with scant cytoplasm and stippled chromatin.

DISCUSSION

NETs were first described in 1907 by Siegfried Oberndorfer as 'karzinoide tumoren' or carcinoid tumours.⁸ Cubilla and Woodruff coined the term 'primary carcinoid tumour of the breast' in the year 1977.⁹ However, it was not until the year 2003 that WHO officially defined neuroendocrine carcinoma of the breast and classified it as a separate entity.¹⁰ In this classification, the tumours are defined as those which are positive, in at least 50% of cell population, for one or more neuroendocrine markers such as NSE, chromogranin A and synaptophysin.¹ The diagnosis of primary neuroendocrine carcinoma of breast requires two more criteria to be fulfilled: (1) exclusion of other primary sites and (2) histologically confirmed breast *in situ* component within the tumour.¹¹ WHO further subdivided them into solid NET, small cell carcinoma and large cell neuroendocrine carcinoma based on the HPE.¹² This classification was further revised by WHO in 2012. These were now named as 'breast carcinoma with neuroendocrine features' or BCNFs, and the tumours were classified under well-differentiated NET, invasive breast carcinoma with neuroendocrine differentiation and poorly differentiated NET or small cell carcinoma. The requirement of more than 50% of the neoplastic cell population to be positive for

Figure 5 Photomicrograph (×40) showing strong immunoreactivity for synaptophysin.

neuroendocrine IHC markers was also excluded.¹³ BCNFs are usually seen as hyperdense oval, round non-calcified masses with sharp and non-spiculated margins on mammography. On ultrasonography, they appear as irregular hypoechoic highly vascular solid masses with cystic components and ill-defined margins. Magnetic Resonance Imaging (MRI) reveals a hypointense, irregular lesion with early initial contrast enhancement on T1-weighted images.¹⁴ BCNFs usually present in the sixth and seventh decades of life; approximately 10 years later than the average age of other types of breast carcinoma.¹⁵ Usually, the chief presenting complaints are a lump in the breast and nipple discharge without enlargement of axillary lymph nodes. Making an accurate preoperative diagnosis of BCNF is a very formidable task for the clinicians and the pathologists. The presence of NE differentiation in the breast biopsy should arouse the suspicion in the pathologist's mind to look for a primary tumour elsewhere¹⁶ as 36% of BCNF cases presently available in the literature are actually metastasis.¹⁷ IHC usually reveals oestrogen and progesterone receptor positivity and is negative for c-erb2/HER2/Neu receptors, CK5/6, CK14, p63 and Epidermal Growth Factor Receptor (EGFR) protein.^{18 19} The most important histopathological features include cellular monotony, nuclear palisading and pseudorosette formation.²⁰ The histological differentiation grade is the most significant prognostic factor. oestrogen and progesterone receptor positivity and mucinosis differentiation are characteristics which favour a better prognosis.²¹ According to a study, patients with neuroendocrine carcinoma of the breast have a graver prognosis in the form of shorter overall survival and disease-specific survival when compared with the invasive breast carcinoma NOS in identical stages.⁷ Furthermore, histopathologically proven small cell type had the worst prognosis when compared with all other variants.⁷

In the absence of any specific distinguishing radiological features of the tumour, these tumours are susceptible to increased probability of inaccurate preoperative diagnosis. Characteristic features of carcinoma breast on mammography, such as microcalcifications and irregular margins, may be absent in these cases. The presence of certain cellular receptors in these tumours makes them susceptible to be diagnosed and, in some cases, treated by using somatostatin and interferons.²² Ultimately, tissue biopsy either in the form of Fine Needle Aspiration (FNA) or core needle or resected specimen is indispensable for the accurate diagnosis of the disease. Despite this, more than 67% of the cases which have been reported in literature have been initially misdiagnosed, and correct diagnosis was established only after surgery.²³ The reason for such a high rate of inaccurate diagnosis on biopsy can be attributed to the predominance of *breast in situ* component in the biopsy specimen, which is invariably diagnosed as IDC.⁶ If suspicion arises, one should not hesitate to test for IHC markers on the biopsy specimen. This would reduce the high rates of preoperative misdiagnosis and give an accurate diagnosis to the surgeon to plan the appropriate management.

The surgical treatment of the tumour is not different from that of IDC. The surgical procedure depends on the clinical stage and site of the tumour after confirming that this is the primary malignancy and not any metastatic deposit. The roles of breast conservation surgery and postmodified radical mastectomy immediate breast reconstruction remain to be investigated due to lack of studies in the available literature which, in turn, may be due to the misdiagnosis as IDC. However, because of the inaccuracy in delineation of the margins of this tumour type, breast reconstruction is often not advisable in these set of patients. Another part of the treatment which lacks a definite consensus is the cytotoxic therapy regimen. As of today, there are no fixed

guidelines as to which chemotherapy is most effective. However, recommendations based on the chemotherapy used commonly for breast carcinomas and pulmonary small cell neuroendocrine carcinomas are suggested. The chemotherapy agent selection is guided by the histopathological characteristics of the tumour. Poorly differentiated patients with BCNF have been administered cisplatin–etoposide and paclitaxel–carboplatin combinations, which are usually given in patients with small cell lung cancer, gynaecological malignancies and malignant melanoma.⁶ Hormonal receptor status positivity plays an important role, and it is recommended that patients get the appropriate hormone therapy based on the receptor status.⁶ Radiation therapy is used less commonly. Tumours which overexpress somatostatin receptors are amenable to be treated by long-acting somatostatin analogues (SSAs). Advanced metastatic and/or inoperable patients with BCNF may be treated with peptide receptor radionuclide therapy with radiolabelled SSA.²⁴ The disease is most commonly described in the age group ranging from 40 to 70 years, more frequently in women aged above 60 years.³ However, a few exceptions are present, and these tumours have been reported in a patient aged 22 years only.²⁵ Our patient was a 32-year-old young woman with a history and chief complaints complying with that of a typical case of carcinoma breast. Certain aspects of the case made it unique and inspired us to report it. First, her age of 32 years is relatively young for a primary neuroendocrine carcinoma of breast. Second, although the patient had first presented to us in the early stage of the disease and we had made a diagnosis of IDC NOS based on the core needle biopsy, she did not comply with the treatment and neglected her disease. Later on, she presented to us with an advanced T4b disease.⁴ Kawasaki *et al* have proposed that neuroendocrine DCIS is the preinvasive stage of neuroendocrine carcinoma of breast, and neuroendocrine DCIS is commonly underdiagnosed before surgery due to difficult sampling and further resemblance of the specimen to ductal hyperplasia and intraductal papilloma.⁵ The outcome of this is that patients are misdiagnosed and fail to receive the appropriate therapy on time.⁶ Third, most of the NETs express oestrogen and progesterone receptors but are usually negative for HER2/Neu.⁷ However, the patient described in this report was positive for ER, PR and HER2/Neu.

Learning points

- Though neuroendocrine carcinoma of the breast is mostly reported in the older population, possibility of the disease in a younger patient must be considered.
- Owing to the high probability of misdiagnosing or underdiagnosing the disease, the surgeon must actively involve the pathologist as well as the radiologist in reaching to an accurate diagnosis and implementing the treatment expeditiously.
- The pathologist must not hesitate to use immunohistochemistry markers on the biopsy specimen for an accurate reporting of the diagnosis.
- Multimodal approach is required for correct diagnosis and management of this disease.
- Primary neuroendocrine carcinoma of breast as a differential diagnosis, in a case of carcinoma breast, should be kept in mind.

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