Primary Neuroendocrine Tumor of Breast: Diagnosing and Treating a Rare Case

Abstract

Neuroendocrine carcinoma breast is a distinct entity. Although clinical features and morphology cannot distinguish it from invasive carcinomas, immunochemistry plays an important role in it. Due to its rarity and lack of clinical data, treatment is followed on the lines of invasive breast carcinoma. Some studies have suggested the use of cisplatin and etoposide for its treatment, but none of them is standard. The prognosis is poor compared to invasive breast cancer.

Keywords: *Breast, immunohistochemistry, invasive carcinoma, neuroendocrine carcinoma*

Poorva Vias, Kislay Dimri, Awadhesh Kumar Pandey, Nidhi Prinja, Ranjeev Bhagat[1]

Departments of Radiation Oncology and [1]Pathology, GMCH, Chandigarh, India

Introduction

Neuroendocrine tumors (NETs) are rare, slow-growing tumors derived from neuroendocrine cells, which are present throughout the body; they arise most commonly in the bronchopulmonary system and gastrointestinal (GI) tract but may arise anywhere in the body. They account for <0.1% of all breast cancers and <1% of all NETs.[1] There are limited data on neuroendocrine tumors available in India. Majority of the data is in the form of case reports which showed the mean age at diagnosis is 55 years in India with equal prevalence in males and females.

Focal neuroendocrine differentiation can be found in different histological types of breast carcinoma, including *in situ* and invasive ductal, lobular, colloid, or papillary breast cancer. However, the term "neuroendocrine carcinoma" is applied when more than 50% of tumor shows such differentiation.[2] They occur in older women and are often positive for the estrogen receptor.[3]

In 2003 WHO divided neuroendocrine carcinomas into solid, small cell, and large cell neuroendocrine carcinoma.[4] The term neuroendocrine carcinoma of the breast was revised to carcinomas with neuroendocrine features in 2012 WHO Classification of Tumors of the Breast[5] and were grouped as:

1. Well-differentiated
2. Poorly differentiated
3. Invasive breast carcinoma with neuroendocrine differentiation.

Well-differentiated tumors resemble carcinoid tumors of other sites but lack characteristic neuroendocrine nuclei. Poorly differentiated neuroendocrine or small cell carcinoma resembles their pulmonary counterparts. Breast carcinoma with special or no special type with neuroendocrine differentiation forms invasive breast carcinoma with neuroendocrine differentiation. Neuroendocrine differentiation, seen in up to 30% of invasive breast carcinomas, is most commonly associated with mucinous and solid papillary carcinomas. The diagnosis of neuroendocrine differentiation requires the expression of the neuroendocrine markers mainly, synaptophysin and chromogranin. The main differential diagnosis is a metastatic NET from an extramammary site. Here, we present a patient with primary neuroendocrine carcinoma breast, and its management followed a brief discussion and review of literature.

Case Report

A 50-years-old, postmenopausal female, noticed a lump in upper outer quadrant of the left breast of size 3 cm × 3 cm approximately. On positron emission tomography (PET)-scan [Figure 1] there was an ill-defined heterogeneously enhancing soft-tissue nodule in upper outer quadrant

How to cite this article: Vias P, Dimri K, Pandey AK, Prinja N, Bhagat R. Primary neuroendocrine tumor of breast: Diagnosing and treating a rare case. Clin Cancer Investig J 2019;8:254-6.

Address for correspondence:
Dr. Poorva Vias, Department of Radiation Oncology, GMCH, Sector 32, Chandigarh, India.
E-mail: poorvavias.1989@gmail.com

Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_79_19

Quick Response Code:

of the left breast measuring 2.7 cm × 2.7 cm × 3.1 cm with low-grade uptake in the left axilla and left supraclavicular region. She underwent fine-needle aspiration in a private hospital which was suggestive of malignancy, but no characterization was possible. The patient was then taken up for breast-conserving surgery with axillary dissection in the same hospital. On detailed histopathological examination, the tumor was 4.7 cm × 4 cm × 3.8 cm, with tumor type of invasive carcinoma with neuroendocrine features which was unifocal. Microscopic examination showed sheets of tumor cells separated by area of coagulative necrosis [Figure 2], cells showing mild-to-moderate pleomorphism, high nuclear to cytoplasm ratio, fine, granular nuclear chromatin, and scant cytoplasm [Figure 3]. The skin and resection margins were free of tumor. Lymphovascular emboli were present. A total of 21 lymph nodes were examined, and none was positive for tumor. Hormone status was negative for estrogen, progesterone, and Her2-neu receptors. Further, immunohistochemistry (IHC) was advised for the exact characterization of disease which was positive for synaptophysin, chromogranin, and neuron-specific enolase. Ki-67 was positive in 20%–25% of cells. CD56, carcinoembryonic antigen, cytokeratin 7, and E-cadherin were also positive. Overall, the above features were suggestive of neuroendocrine tumor breast, WHO Grade III.

On DOTA PET-scan, there was low-grade uptake in the left axilla and left supraclavicular region. The treatment was challenging as it was Grade III, so radiotherapy was started at 50 Gy in 25 fractions over 5 weeks by two tangential fields and one supraclavicular field followed by chemotherapy using Adriamycin and paclitaxel.

Discussion

The estimated prevalence of NETs is 1–2 cases/100,000 people, of which GI tract is the most common site.[6] Primary neuroendocrine tumor of the breast is unique but rare entity with a different biological behavior. The incidence has been reported to <1%–5% depending on various studies.[7] However, the exact incidence is difficult to assess as IHC was not used routinely in breast cancer patients. These tumors are often positive for hormonal receptors, whereas HER2 is almost always negative. In our case, the receptor status was triple negative.

The clinical presentation is not distinct from other breast cancers. They present with isolated hard lump breast with or without axillary lymphadenopathy. The disease is commonly seen in older patients in sixth or seventh decade. The radiological features are nonspecific. However, some studies reported primary neuroendocrine tumor breast on mammogram as a round, sharply circumscribed, hyperdense mass, and on ultrasound as a hypoechoic solid mass with increased vascularity and enhanced posterior echo. Magnetic resonance imaging shows homogeneous low signal intensity with heterogeneous rapid initial enhancement on the T1-weighted image.[8]

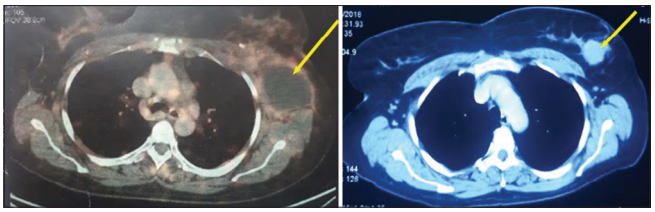

Figure 1: Positron emission tomography-computed tomography showing heterogeneously enhancing soft-tissue nodule in upper outer quadrant of the left breast (arrowhead)

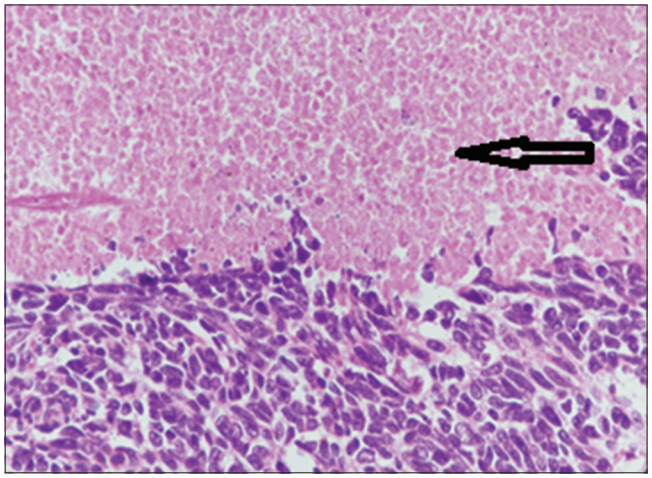

Figure 2: Sheet of tumor cells seen, separated by area of coagulative necrosis (arrowhead) (H and E, ×400)

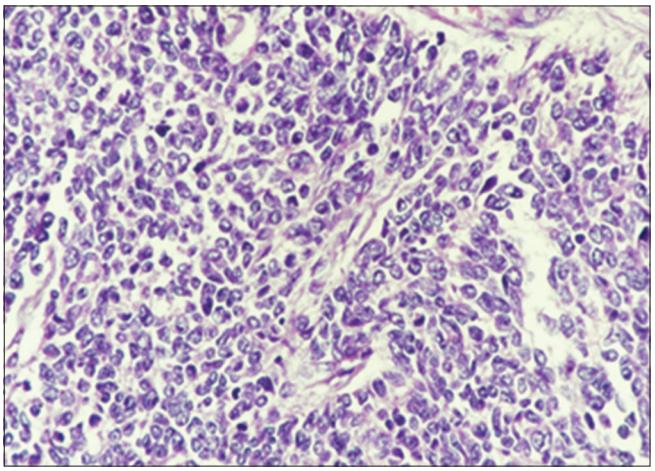

Figure 3: Tumour cells show mild to moderate pleomorphism, high nuclear:cytoplasmic ratio, fine, granular nuclear chromatin, and scant cytoplasm (H and E, ×400)

Cytology may be inconclusive thus core needle biopsy should be done. Keeping in mind, the NETs metastatic to the breast. The presence of an associated ductal carcinoma *in situ* component is a valid proof of the primary nature of the tumor in breast.[1] While diagnosing a primary neuroendocrine carcinoma breast, the metastasis from other primary sites should be ruled out by appropriate imaging. Carcinoid syndrome (including diarrhea, flushing, and bronchospasm) can appear in 5%–10% of patients with a neuroendocrine tumor[9] which were not seen in our patient.

As clinical features and morphology cannot distinguish it with invasive breast cancer, IHC with neuroendocrine markers such as synaptophysin and chromogranin help in confirmation of diagnosis which were positive in our case also.

Surgery is the mainstay of treatment which can be breast-conserving surgery or mastectomy. In the above case, the patient underwent breast-conserving surgery. There are no specific recommendations of adjuvant radiotherapy, but should be considered as for other invasive breast cancers. The choice of chemotherapy is individualized depending on the stage of disease and the risk of relapse. For locally advanced tumors, neoadjuvant chemotherapy is administered, and adjuvant therapy is used in patients with a high risk of relapse. Chemotherapy regimens for the treatment of both invasive breast cancer and small cell carcinoma lung were used. In a small study,[10] the chemotherapy regimen was decided based on the percentage of Ki67, if its value was <15% then anthracycline-based chemotherapy was used, and if the value was more than 15% then cisplatin and etoposide were used. Due to the scarcity of data, regimen using anthracyclines with or without taxanes are commonly indicated, and the patients are usually treated like invasive duct cell carcinoma. In this case, the patient was treated on the lines of invasive breast carcinoma.

The prognostic relevance of neuroendocrine differentiation is debated due to conflicting results of different case reports. In a study by Wang *et al*.,[7] neuroendocrine tumor breast had poorer overall survival and disease-specific survival compared to invasive breast carcinoma not otherwise specified at the same stage. In a multivariate analysis, including other prognostic factors such as age, tumor size, nodal status, histological grade, and neuroendocrine differentiation was another adverse factor.[7] In another study, as it is a slow-growing tumor, it seems that global disease-free survival is greater in patients with primary neuroendocrine tumors of the breast than in patients with other breast tumors.[11]

Conclusion

This study discusses various challenges in diagnosis and treatment of such patients. In view of advances in IHC, more number of such cases are expected. Due to its rare presentation and lack of robust data, the treatment of such patients should be individualized.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ogawa H, Nishio A, Satake H, Naganawa S, Imai T, Sawaki M, *et al.* Neuroendocrine tumor in the breast. Radiat Med 2008;26:28-32.
2. Tavassoli FA, Devilee P. Pathology and Genetics: Tumours of the Breast and Female Genital Organs. (WHO Classification of Tumours Series). 3rd ed., Vol. 4. Lyon, France: IARC Press; 2003.
3. Maluf HM, Koerner FC. Carcinomas of the breast with endocrine differentiation: A review. Virchows Arch 1994;425:449-57.
4. Ellis IO, Schnitt SJ, Sastre-Garau X, Bussolati G, Tavassoli FA, Eusebi V, *et al*. Invasive breast carcinoma. In: Tavassoli FA, Devilee P, editors. Pathology and Genetics of Tumours of the Breast and Female Genital organs. World Health Organization Classification of Tumours. Vol. 4. Lyon, France: IARC Press; 2003. p. 32-4.
5. Bussolati G, Badve S. Carcinomas with neuroendocrine features. In: Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van der Vijver MJ, editors. WHO Classification of Tumours of the Breast. World Health Organization Classification of Tumours. Vol. 4. Lyon, France: IARC Press; 2012. p. 62-3.
6. Sippel RS, Chen H. Carcinoid tumors. Surg Oncol Clin N Am 2006;15:463-78.
7. Wang J, Wei B, Albarracin CT, Hu J, Abraham SC, Wu Y, *et al.* Invasive neuroendocrine carcinoma of the breast: A population-based study from the surveillance, epidemiology and end results (SEER) database. BMC Cancer 2014;14:147.
8. Yoon YS, Kim SY, Lee JH, Kim SY, Han SW. Primary neuroendocrine carcinoma of the breast: Radiologic and pathologic correlation. Clin Imaging 2014;38:734-8.
9. Amin AL, Kong AL. Metastatic neuroendocrine tumor found on screening mammogram. WMJ 2011;110:140-3.
10. Oberg K. Management of neuroendocrine tumours. Ann Oncol 2004;15 Suppl 4:iv293-8.
11. Laabadi K, Jayi S, El houari A, Tawfic H, Bouguern H, Chaara H, *et al.* Primitive mammary neuroendocrine tumor: About a rare case. Pan Afr Med J 2013;16:92.