

Metastatic Primary Neuroendocrine Carcinoma of the Breast: A Case Report Describing Successful Treatment using Letrozole and Abemaciclib Combination Therapy

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ABSTRACT

Neuroendocrine carcinoma of the breast (NECB) is a rare invasive tumor characterized by low/intermediate grade, neuroendocrine morphology, and supported by immunoreactivity for neuroendocrine markers such as chromogranin A and synaptophysin. Given their low incidence, there is very limited evidence-based guidelines for the management, and this can pose great challenges for the treating clinician. In this case report we describe a patient with diffusely metastatic hormone receptor positive, Her2neu negative well differentiated neuroendocrine tumor of breast who had an excellent response to a combination of aromatase inhibitor and CDK4/6 inhibitor combination.

KEYWORDS

Neuroendocrine carcinoma; Chromogranin A; CDK4/6 inhibitor

INTRODUCTION

Neuroendocrine neoplasms are a rare subset of tumors arising from neuroendocrine cells through-out the body [1]. Most commonly, neuroendocrine neoplasms are associated with the gastrointestinal and respiratory systems, with primary neuroendocrine tumors of the breast being exceedingly rare. These neuroendocrine breast malignancies account for less than 0.1% of all breast cancers and less than 1% of all neuroendocrine tumors [2]. Because of their low incidence, there is significant lack of evidence regarding the optimal management of neuroendocrine carcinoma of the breast (NECB).

In this review, we describe a case of metastatic NECB successfully treated with a combination of endocrine therapy (Letrozole) in combination with CDK4/6 inhibitor (Abemaciclib).

CASE REPORT

A 71-years old Caucasian woman presented for evaluation of a mass of the left breast. The mass had been present for more than 1 year, but the patient had deferred follow-up during that time due to the COVID pandemic. Her medical history was unremarkable, and she had no prior personal or family history of breast or ovarian cancer.

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On initial evaluation, a large necrotic mass of the left breast was readily identified as well as multiple palpable abnormal masses of the right breast (Figure 1). Mammogram imaging and PET scan revealed multicentric left breast cancer with ulcerating skin involvement and pectoralis invasion, multi-focal lesions of the right breast, multiple hypermetabolic peritoneal and subcutaneous meta-static implants, multiple bilateral pulmonary metastases, and hypermetabolic left axillary mediastinal and bilateral hilar nodal metastasis. Patient had visual changes in the left eye, however, declined MRI brain for staging due to claustrophobia. She was seen by ophthalmologic oncologist and diagnosed with left choroidal metastasis.

The patient underwent core needle biopsy of the left breast mass which showed Hormone receptor (HR) positive, Her2 negative well differentiated neuroendocrine tumor of the breast.



Figure 1: Large fungating mass of left breast seen on initial clinical encounter.

The markers were ER: 99% 2-3+ (positive). -PR: 99% 2-3+ (positive). -Her2: 0+ (negative). -Ki67: 25% (high proliferation). For staging purposes, patient also under-went core biopsy of a subcutaneous lesion around right lateral chest wall. Pathology confirmed metastases from well differentiated neuroendocrine carcinoma with identical molecular marker.

Given the diffusely metastatic nature of her disease, she was deemed inoperable and subsequently treated with systemic therapy. She was started on combination therapy consisting of Letrozole 2.5 mg once a day and Abemaciclib 150 mg two time a day. Patient tolerated the treatment very well except for occasional episodes of diarrhea, well controlled with loperamide. At 2-months follow-up, excellent clinical response was already apparent with a significant decrease in tumor size (Figure 2). Repeat PET scan also showed excellent response (Figure 3 and Figure 4). Follow up evaluation by the ophthalmologic oncologist showed near complete response in the left choroidal metastasis.



Figure 2: Clinical exam after 2 months of combination therapy showing significant decrease in tumor size.

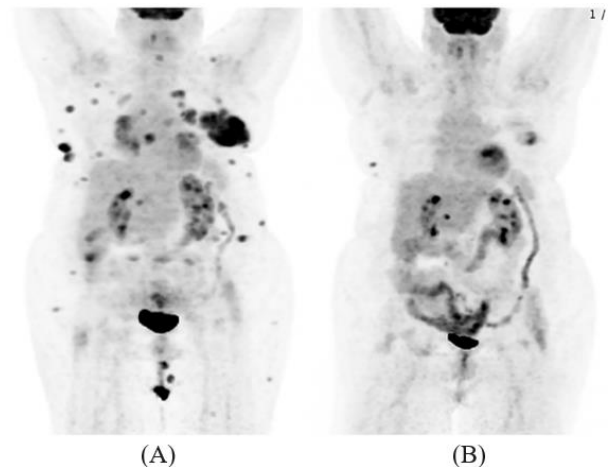


Figure 3: A) Maximum Intensity Projection (MIP) seen on initial presentation in May 2021. B) Compared to MIP 4 months into treatment in September 2021.

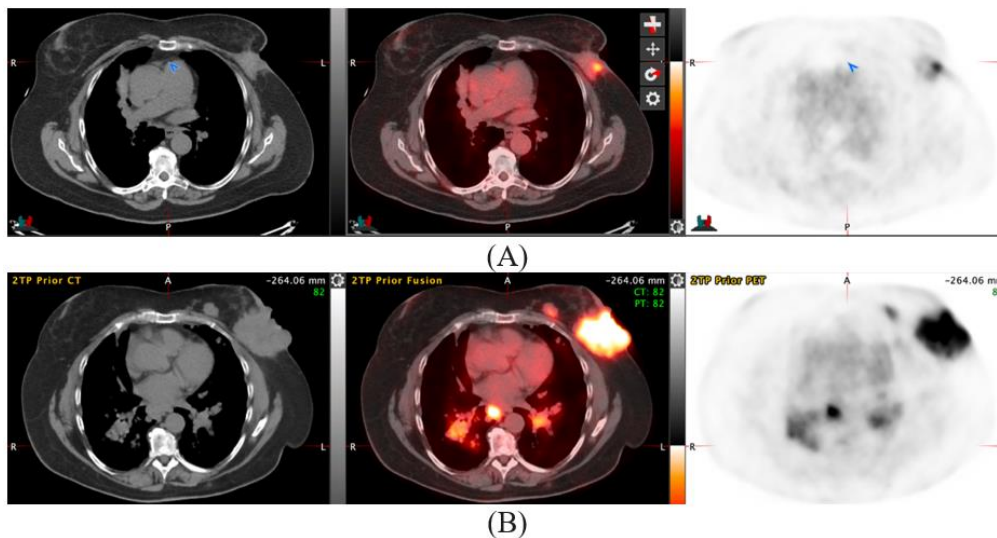


Figure 4: Positron emission tomography (PET). (A) Initial PET scan obtained May 28, 2021, showing high level of radiotracer uptake at primary tumor within left breast as well as multiple areas of metastatic disease to bilateral lungs. (B) PET scan im-aging obtained on September 20, 2021, 4 months into treatment, showing remission of met-astatic lesions within lungs as well as significant decrease in primary tumor burden.

DISCUSSION

Neuroendocrine carcinoma of the breast (NECB) represents a very rare subtype of breast cancer. NEBC was first described in 1963 by Feyrter and Hartmann in 2 patients with breast cancer as carcinoid growth pattern [3]. Subsequently, in 1977, Cubill and Woodruff described eight patients with breast masses were found to have histologic features resembling carcinoids of other sites [4]. Classically found within the gastro-intestinal and respiratory systems, neuroendocrine neoplasms are described as heterogeneous tumors arising from neuroendocrine cells throughout the body [5]. Although foci of neuroendocrine differentiation can be detected in up to 30% of invasive ductal carcinomas of the breast, a diagnosis of primary NECB is very rare and accounts for less than 0.1% of all breast cancer cases [2]. NECBs are more commonly positive for estrogen and progesterone and negative for human epi-dermal growth factor receptor 2 (HER2) negative [6,7].

The clinical presentation of NEBC is similar to that of other subtypes of invasive breast cancer [8]. Most commonly, patients will present in their sixth and seventh decades of life with complaints of a painless retro-areolar lump [9,10].

Radiologic findings of NEBCs are nonspecific and a core needle biopsy is needed to establish a definitive diagnosis. The diagnosis of NEBC is based on the presence of morphological features shared with gastrointestinal and lung neuroendocrine tumors in combination with specific neuroendocrine markers. Given the rarity of a primary NECB, diagnosis requires exclusion of metastasis from an extramammary site. Because neuroendocrine markers are not routinely used in breast cancer diagnosis, the exact incidence of NEBC is not definitively known, though, it is generally accepted that NEBC is a very uncommon subtype of breast carcinoma.

Primary NECB is so rarely reported that there is no established standard treatment protocol, and the adopted therapeutic approach is similar to that used for other breast cancer subtypes [11]. Surgery remains the focus for those masses amenable to re-section, and the type of surgery depends on tumor location and stage. When surgery is not feasible, the use of chemotherapy either in the adjuvant, neoadjuvant or palliative setting provides further treatment options. However, the optimal chemotherapy regimen has not been clearly delineated.

The current consensus in regard to medical management of NEBC is to use chemotherapeutic regimens similar to those used for other types of breast cancer as well as small-cell carcinoma of lung [12,13].

Abemaciclib is an antitumor agent and dual inhibitor of cyclin-dependent kinases 4 (CDK4) and 6 (CDK6) [14]. Both CDK4 and CDK6 play important roles in regulating the cell cycle and are involved in the promotion of cancer cell growth in the case of unregulated activity. Abemaciclib has not been well studied in the setting of NEBC, however, it has proven promising in the treatment of other more common sub-types of metastatic breast carcinoma. It is FDA approved as a monotherapy and in combination with Fulvestrant for HR positive, Her2neu negative advanced or meta-static breast cancer with disease progression following endocrine therapy. On October 12, 2021, Abemaciclib was FDA approved in combination with endocrine therapy for adjuvant treatment of patients with HR positive, Her2neu negative node positive, early breast cancer with high risk of recurrence and KI-67 $\geq 20\%$.

Abemaciclib added to standard adjuvant endocrine therapy was shown to significantly improve invasive disease-free survival in patients with ER+, HER2- early breast cancer [15]. In our patient, we used a combined therapeutic modality consisting of Letrozole and Abemaciclib with excellent clinical response and near complete tumor regression with medical treatment alone.

CONCLUSION

In summary, NECB is a rare subtype of breast cancer with histologic characteristics similar to carcinoids of other sites [16]. Lack of clinical experience owing to the rarity of this tumor highlights the need for further investigation of tumor specific markers and diagnostic methods to guide targeted treatment specific for patients with primary neuroendocrine carcinoma of the breast. A combination of endocrine therapy with CDK4/6 inhibitor can potentially provide excellent response in metastatic well differentiated hormone receptor positive, Her2neu negative breast cancer.

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