ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS

Case Report

The First Case Report of Neuroendocrine Tumor of the Breast with Metachronous Invasive Mammary Carcinoma

Mohammed Al Duhileb[1], Nadeen AlMushcab[1], Ayedh Al Qarni[2], Shakir I Shakir[3], Alaa Nour[3] and Jamila AlAzhri[1]*

[1]*Breast and Endocrine Surgery Section, Department of Surgery, King Fahad Specialist Hospital, Dammam, Saudi Arabia*

[2]*Department of Pathology, King Fahad Specialist Hospital, Dammam, Saudi Arabia*

[3]*Section of Radiation Oncology, King Fahad Specialist Hospital, Dammam, Saudi Arabia*

***Corresponding Author:** Jamila AlAzhri, Breast and Endocrine Surgery Section, Department of Surgery, King Fahad Specialist Hospital, Dammam, Saudi Arabia.

Received: September 26, 2022; **Published:** October 07, 2022

Abstract

Introduction: Primary neuroendocrine carcinoma of the breast (NECB) is a rare type of breast malignancy which is scarcely reported in the literature. As a result, there is no consistent criterion regarding the management approach. Well-differentiated tumors show architectural similarity to carcinoids of other sites but lack characteristic neuroendocrine nuclei. While poorly differentiated neuroendocrine tumors are morphologically identical to small cell carcinoma of the lung. Due to its similarities with other forms of tumours, its diagnosis has become more challenging and is starting to pose a clinical dilemma. This report presents an unusual case of primary neuroendocrine carcinoma of the breast in a patient with history of invasive ductal carcinoma of the contralateral breast.

Case Presentation: A 42-year-old lady with a history of oligometastatic right breast invasive mammary carcinoma with micropapillary features diagnosed in March 2019 and managed with neoadjuvant chemotherapy followed by surgery then adjuvant radiation to both (primary site and solitary bone lesion) then continued on adjuvant chemotherapy. Later, she presented to our clinic in June 2020 with a palpable left breast mass. Further investigations were confirmatory for a poorly differentiated neuroendocrine tumor with negative lymph node malignancy and imaging showed also oligometastatic deposit at left adrenal.

Conclusion: Due to the rarity of primary breast neuroendocrine tumors, no standard therapy exists, and the prognosis remains difficult to determine. The approach of managing these patients is complex and should be tailored towards the individual patient until further studies and guidelines are established.

Keywords: *Breast Cancer; Neuroendocrine Tumor; Bilateral Breast Cancer; SBRT; Rare Breast Cancer*

Introduction

Primary neuroendocrine carcinoma of the breast (NECB) is a rare form of breast cancer with variable biologic behavior and prognosis [1]. The incidence of NECB is controversial, with some suggesting an incidence as low as 1% [2] and others as high as 20% [3]. The true incidence is yet to be established, as immunohistochemical staining for breast tumors is not routine [1]. In a study retrospectively analyzing cases of breast cancer with immunohistochemical staining, neuroendocrine differentiation was found in 10.4% of tumors [4]. However, it played little role in the prognosis of the patients.

Due to its rarity and unique histologic types, there is little guidance in the literature regarding the optimal treatment approach for NECB. This fact presents a challenge to the treating physician, who must implement a careful and meticulous plan. Therefore, the treatment and prognosis of NECB deserves in-depth discussion. We report a rare case of a patient with NECB who had a history of metachronous contralateral invasive breast carcinoma. We analyzed the clinical course of the disease and highlighted the diagnostic and therapeutic management of this patient.

Case Presentation

Our patient is a 42-year-old lady with a history of right breast triple positive (estrogen receptor (ER) positive 90%, progesterone receptor (PR) positive 80%, HER2-Neu positive (+3), Ki67 20%) invasive mammary carcinoma with micropapillary features, diagnosed in March 2019. Imaging showed oligometastatic deposit at the sternum, so, clinical staging was cT2N1M1. She received neoadjuvant chemotherapy in form of Docetaxel-Carboplatin-Pertuzumab-Trastuzumab and then underwent wide local excision with axillary sentinel lymph node biopsy (SLNB) in September 2019. Final pathology revealed ypT1bN0 with negative surgical margins and absent lymph nodes metastasis. The patient received adjuvant radiation therapy to the breast and regional nodal stations (as of 40.05 Gy in 15 fractions plus Boost to the operative bed (as of 10Gy in 4 fractions) then Stereotactic body radiotherapy "SBRT" to the oligometastatic bone lesion in the sternum as of 30 Gy in 5 fractions) along with adjuvant anti-Her2-neu and TDM-1 as systemic treatment. She was maintained on adjuvant hormonal therapy (tamoxifen) until her second presentation.

In June 2020, the patient was admitted with severe anemia for further investigations. Upper gastrointestinal endoscopy was evident for erosive gastric ulcer and she was also diagnosed with iron deficiency anemia, and was properly treated for both. As part of the workup of the severe anemia, PET-CT was performed and it showed (Figure 1), an incidental finding of an FDG avid suspicious lesion in the left breast. She was referred to the breast surgery clinic for further assessment. On examination, there was a palpable small left breast mass measuring 1 x 1 cm at 1 o'clock, 12 cm from the nipple with a palpable left axillary lymph node, a right breast healed scar with no evidence of recurrence on examination. Mammogram and breast ultrasound (Figure 2) revealed a suspicious mass in the left upper outer quadrant of the breast, corresponding to the palpable lesion, with a borderline left axillary lymph node. Breast MRI (Figure 3) showed three enhancing lesions in the left upper outer quadrant of the breast with suspicious features suggestive of multifocal disease. A core needle biopsy (Figure 4) of the left 1 o'clock mass showed poorly differentiated neuroendocrine tumor, ER positive 95%, PR positive 20%, HER2-Neu negative and Ki67: 90%. Left axillary lymph node biopsy was negative for malignancy. The left breast cancer stage at this point was cT1N0M. The case was discussed in the breast multidisciplinary tumor board and planned for upfront surgery followed by adjuvant therapy (radiation for both sites: the primary disease and the solitary left adrenal deposit). The patient was given the options of mastectomy or breast conserving surgery. She decided to preserve the breast and accepted to receive postoperative radiation therapy. A left breast wire guided (3 wires) wide local excision with left axillary SLNB was performed in October 2020. The SLNB showed one out of 3 metastatic axillary nodes with extra nodal extension, and axillary dissection of level 1 and 2 was performed. Surgical pathology stage was consistent with pT1cN1aMx with surgical resection margins are free of carcinoma with sentinel lymph node biopsy showed one out of three lymph node was positive for metastasis and the final left axillary lymph node dissection showed 3 out of 22 lymph nodes are positive for metastasis.

After surgery, the patient was offered adjuvant radiotherapy to the left breast (as of 40.05 Gy in 15 fractions plus Boost to the operative bed (as of 10Gy in 4 fractions)) then chemotherapy due to the aggressiveness of this poorly differentiated tumor and the lymph node metastasis, but she strongly declined chemotherapy. Then, she was maintained on adjuvant hormonal therapy in the form of Tamoxifen.

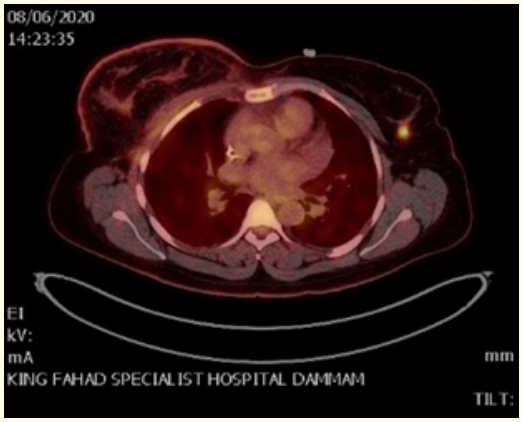
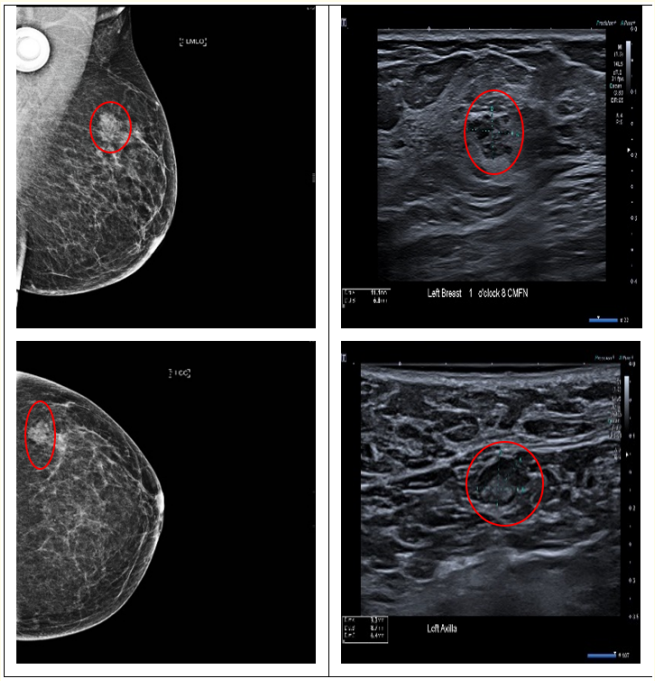


Figure 1: *PET CT axial view showing the development of left breast upper outer quadrant suspicious FDG avid focal lesion measuring 0.9 x 1.6 cm with SUV max of 7.*



(A) *(B)*

Figure 2: *(A) MLO and CC views of mammogram showing focal asymmetry at the upper outer quadrant, of the left breast, suspicious for malignancy. (B) Ultrasound of the left breast showing a 1 x 0.7 cm irregular shape heterogeneous mass at 1 o'clock, that is highly suspicious for malignancy (BIRADS 5) and a left axillary lymph node with a borderline thickened cortex.*

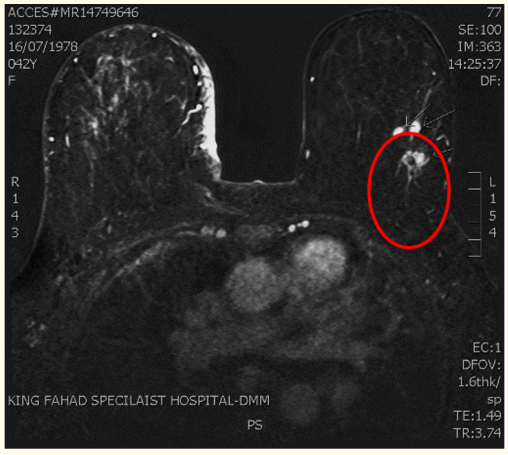


Figure 3: *Breast MRI showing three left upper outer quadrant enhancing lesions with suspicious features, suggestive of multifocal disease.*

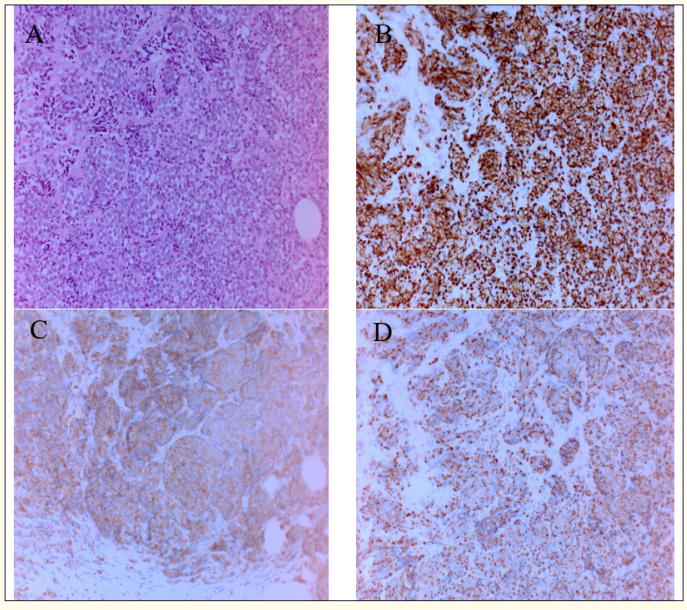


Figure 4: *H&E section showing clusters of monomorphic carcinoma cells with round nuclei showing fine (salt and pepper) chromatin (A). Tumor cells are diffusely positive for (B) Cytokeratin 7, (C) Synaptophysin, (D) Chromogranin, and Estrogen Receptor (not shown).*

Four months postoperatively, a surveillance PET scan (Figure 5) was done and showed metastatic malignant NECB in the left adrenal gland. There was no evidence of recurrence in the right breast. She subsequently received adjuvant Left breast and regional nodes radiotherapy with sternum and left adrenal SBRT (35Gy in 5 fractions) (Figure 6). A repeated PET scan on May 2021 showed no evidence of

local recurrence, resolution of left adrenal nodule, but unfortunately, demonstrated widespread osseous metastatic disease. She was seen by the medical oncology team to treat her aggressive tumor and was then initiated on palliative treatment in the form of hormonal therapy with ovarian suppression (letrozole/goserelin) and immunotherapy using palbociclib/the patient was still refusing any chemotherapy. Upon further discussion with the pathology, the review of the left breast histology showed lobular features that is strongly positive for Synaptophysin, Cytokeratin 7 and Estrogen Receptor (ER) which goes with primary neuroendocrine tumor of the breast with adrenal metastasis.

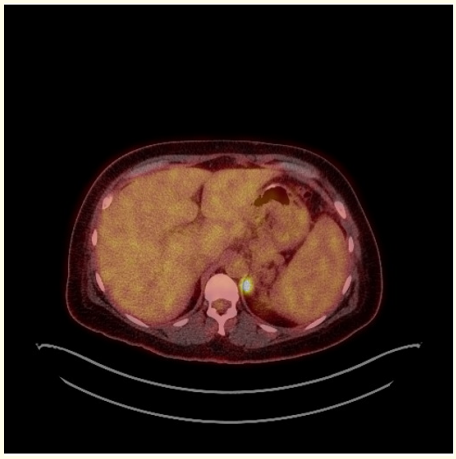


Figure 5: *PET CT showing the left adrenal metastasis.*

(A) (B)

Figure 6: *(A) SBRT to Sternum (30Gy in 5 fractions) and (B) SBRT to left adrenal (35Gy in 5 fractions).*

The patient was refereed to genetics and continue on the palliative treatment provided by the medical oncology as palbociclib 125 mg with last follow up on November 2021.

Discussion

Neuroendocrine carcinoma of the breast (NECB) is extremely rare and may allude to a primary lesion or a metastatic one [5]. Neuroendocrine tumors can occur in various parts of the body such as the lung, larynx, trachea, gastrointestinal tract, ovary, cervix, breast, larynx, prostate, and bladder [3]. It is estimated that NECB incidence ranges between 1 - 20% [2,3]. Yet, this number remains an area of controversy. This could be attributed to the inability to distinguish between primary and metastatic lesions with clinical and preoperative histopathological measures. Since the clinical presentation and imaging findings are not distinct from other types of breast cancer, diagnosis of NECB can only be made by the pathologist [5].

Given the aggressive nature of this tumor, it is prudent to correctly diagnose it as early as possible. To this day, diagnosing NECB is a great challenge and managing such tumor is of even greater challenge. Some studies recommend the use of somatostatin receptor scintigraphy (SRS) or PET-CT with 68-Gallium-labeled somatostatin analogs to detect well-differentiated neuroendocrine tumors (NECB) with a low proliferation index and 18-fluorodeoxyglucose (FDG) PET-CT to be used in poorly differentiated NEC with a high proliferation rate [6,7]. This is to be used in conjunction with ultrasound and mammography. Our patient was successfully diagnosed with the use of 18-fluorodeoxyglucose (FDG), PET-CT, despite the very small size of the tumor. This may be due to the poorly differentiated tumor grade with a very high proliferation indicated by the high KI67 of 90%.

Once NECB is diagnosed by histopathologic features, the question remains whether it is a primary or a metastatic tumor. One study [5,8] found that GCDFP-15 and mammaglobin receptors were expressed more in solid neuroendocrine tumors of the breast. While the cohort of patients with non-mammary neuroendocrine were found to be absent of the expression of these receptors. This would aid in the accurate differentiation between primary and metastatic lesions and play a crucial role in surgical management of such patients. The other clue that helps differentiate between NEBC and metastatic NECB is the histological feature. The definite feature that makes the diagnosis of primary is intraductal component of NECB, as metastatic NECB has no intraductal component. Based on this finding, it is advisable to screen the other sites using PET-CT or octreotide scan once the diagnosis of metastatic NECB is suspected. The presence of an in-situ carcinoma component within the breast was highly suggestive of a primary breast carcinoma rather than a metastatic tumor [14,15]. Despite the non-expression of GCDFP-15 and mammaglobin in our patient, the histopathology revealed lobular features that is strongly positive for Synaptophysin, Cytokeratin 7 and Estrogen Receptor (ER) which goes with primary neuroendocrine tumor of the breast along with adrenal metastasis rather than being secondary metastasis of the neuroendocrine tumor to the breast [16].

Given the low incidence of neuroendocrine breast cancer, it is recommended that NEBC be staged and treated similarly to conventional breast cancer. However, the optimal treatment strategy remains controversial. It is evident that the principal treatment is surgery and that primary breast tumors must be dealt with in a similar fashion to ductal carcinoma of the breast. Surgical management, like conventional breast cancer, is based on breast size, tumor size, location and stage [5].

The use of hormone therapy is based on receptor status [10]. In two studies [7,11], patients with NEBC treated with endocrine therapy and radiotherapy had longer overall survival (OS) and disease-free survival than those who did not receive treatment, while patients who received chemotherapy had lower OS and disease-free survival than those who did not. The poor response to chemotherapy is hypothesized to be due to either chemoresistance commonly seen in neuroendocrine tumors of other sites, or the lack of an appropriately determined regimen [7,9]. For patients with well differentiated NECB, the recommended treatment is cytotoxic therapy similar to that for conventional breast cancer. In contrast to patients with poorly differentiated NECB where they are recommended to be treated with similar protocols as for small cell lung carcinoma which our patient did not receive as she refused chemotherapy.

Several chemotherapy regimens have been reported in literature, including anthracyclines and/or taxanes containing combinations routinely used for other types of breast cancer and also combinations of platinum agents and etoposide, usually administered for small-cell lung cancer. Some examples of the chemotherapy regimens reported in the literature include fluorouracil/epirubicin/cyclophosphamide followed by docetaxel; docetaxel/epirubicin/cyclophosphamide; cyclophosphamide and doxorubicin; cyclophosphamide/methotrexate/fluorouracil; paclitaxel alone; carboplatin/paclitaxel; carboplatin or cisplatin and etoposide; and cisplatin and irinotecan. In a small series, the type of adjuvant chemotherapy was decided on the bases of the Ki67 index, according to a modified therapeutic algorithm initially developed for gastrointestinal neuroendocrine tumors. In this series, anthracycline-based chemotherapy was given to patients with Ki67 < 15% and cisplatin/etoposide to patients with Ki67 ≥ 15% [17].

Cloyd., *et al*. were the first to examine prognosis for NECBs by histologic subtype. NECB had a worse 5-year overall survival (OS) than invasive ductal carcinoma not otherwise specified (IDC-NOS). Well-differentiated NECBs and inflammatory breast cancer neuroendocrine differentiation (IBC-NED) had a similar 5-year OS and disease-specific survival (DSS), while poorly differentiated NECB had a significantly poorer 5-year OS and DSS [5,6]. This is evident in our patient who developed recurrence and distal progression of the disease within 4 months of the initiation of her treatment.

Advanced well-differentiated NECB that are ineligible for resection are managed in most cases with somatostatin analogs (SSAs), such as octreotide and lanreotide, peptide receptor radionuclide therapy and targeted agents, such as everolimus and sunitinib [12,13]. In contrast, poorly differentiated carcinomas are associated with rapid progression and a poor long-term prognosis. Therefore, be they should be approached aggressively in a similar manner to small cell carcinoma of the lung. The prognostic relevance of neuroendocrine differentiation in breast carcinoma is still debated because several studies have been published with mixed results. The locoregional surgical option of non-metastatic NECB depends on the stage of the disease with the recommendation to go for mastectomy due to lack of the literature to the evidence of outcome of breast conserving surgery along with adjuvant radiation on the Overall Survival (OS) and Disease-Free Survival (DFS). There are few studies supporting adjuvant radiation therapy for NECB, but radiotherapy should be considered according to the recommendations given for the other types of invasive breast cancer [18]. Hence, total mastectomy might be a better surgical choice in more aggressive type of NECB like poorly differentiated patients or patients with locally recurrent NECB. For chemotherapy, in the absence of robust data on the role of platinum compounds and etoposide for the adjuvant treatment of NECB, it is recommended to treat these tumors with the same principles adopted for ductal breast carcinoma; therefore, if chemotherapy is indicated, a regimen including anthracyclines and/or taxanes should be preferred [16].

To our knowledge, this is the first reported case of a patient who presented with metachronous invasive ductal carcinoma and neuroendocrine tumor of the breast. The difference in disease aggressiveness and prognosis is very evident in our patient. Which posed a clinical challenge in terms of management and diagnostic approaches. As there is a lack of large clinical studies, there are almost no standardized recommendations for treatment of NECB. Most treatments of NECB reported in the literature and in the present study (only in regard to well/moderately differentiated NECB) are similar to the treatment of ductal-type, while Anlauf., *et al*. highlight the importance of treatment according to ENET guidelines. According to both guidelines, surgery is the mainstay of treatment for early NECB. The surgical procedure (breast conserving partial mastectomy, total mastectomy) depends on the location of the tumor and the clinical stage. Especially with poorly differentiated NEBC where the recurrence is high, counseling the patient regarding mastectomy is a reasonable approach.

Conclusion

Primary neuroendocrine carcinoma of the breast is a rare aggressive tumor and an under-diagnosed entity. Current strategies in the diagnosis and therapy of NECB rely on radiology with the gold standard being histopathological diagnosis as well as on cytotoxic chemotherapy and somatostatin analogs, respectively.

Neuroendocrine carcinoma of the breast should be tackled aggressively in a multidisciplinary sittings giving its aggressive behavior and poor prognosis with the focus on reaching an accurate diagnosis to differentiate between primary neuroendocrine carcinoma of the breast and metastatic neuroendocrine carcinoma to the breast. Keeping in mind the aggressive approach with mastectomy as best surgical option, adjuvant chemotherapy, hormonal treatment and the utility of radiotherapy.

Due to lack of established guidelines, the surveillance of NECB should be more frequent than the patient with invasive ductal carcinoma giving the worse disease progression in NECB.

Consent

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

Conflict of Interest

The authors declare that they have no conflict of interest.

SCARE Checklist Statement

The manuscript was prepared and revised according to the SCARE guidelines (2018).

Bibliography

1. Feyrter F and Hartmann G. "On the carcinoid growth form of the carcinoma mammae, especially the carcinoma solidum gelatinosum mammae". *Frankf Z Pathol* 73 (1963): 24-39.

2. Wang J., *et al*. "Invasive neuroendocrine carcinoma of the breast: a population-based study from the surveillance, epidemiology and end results (SEER) database". *BMC Cancer* 14 (2014): 147.

3. Miremadi A., *et al*. "Neuroendocrine differentiation and prognosis in breast adenocarcinoma". *Histopathology* 40.3 (2002): 215-222.

4. Bogina G., *et al*. "Neuroendocrine differentiation in breast carcinoma: clinicopathological features and outcome". *Histopathology* 68.3 (2016): 422-432.

5. Byssolite G and Badve S. "Carcinomas with neuroendocrine features". In: Lakhani SR, EllisIO, Schnitt SJ, Tan PH, van der Vijver MJ, editions. WHO Classification of Tumours of the Breast. Lyon, France: IARC Press World Health Organization Classification of Tumours 4 (2012): 62-63.

6. Akhtar K., *et al*. "Primary neuroendocrine carcinoma of the breast". *Indian Journal of Pathology and Microbiology* 52 (2009): 71-73.

7. Yao JC., *et al*. "One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States". *Journal of Clinical Oncology* 26 (2008): 3063-3072.

8. Richter-Ehrenstein C., *et al*. "Solid neuroendocrine carcinomas of the breast: metastases or primary tumors?" *Breast Cancer Research and Treatment* 124.2 (2010): 413-417.

9. Li YQ, Du F, Zhu WJ, Xu BH.

10. Li YQ., *et al*. "Primary neuroendocrine carcinoma of the breast: clinical, imaging, and histologic features". *The American Journal of Roentgenology* 3 (2014): W221.

11. Mizukami Y., *et al*. "Pleomorphic adenoma of the breast". *Radiation Medicine* 26.7 (2008): 442-445.

12. PET Clin. 9 (2014): 323-329.

13. Inno A., *et al*. "Neuroendocrine Carcinoma of the Breast: Current Evidence and Future Perspectives". *Oncologist* 21 (2016): 28-32.

14. Bosman FT., *et al*. "WHO Classification of Tumours of the Digestive System, 4th edition.; WHO Press: Geneva, Switzerland (2010).

15. Rinke A., *et al*. "Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results of Long-Term Survival 104.1 (2017): 26-32.

16. Dongfang Yu and Yi Zhou. "Metastatic well-differentiated neuroendocrine tumor in the breast: A case report and literature review". *Human Pathology: Case Reports* (2019).

17. Inno A., *et al*. "Neuroendocrine Carcinoma of the Breast: Current Evidence and Future Perspectives". *Oncologist* 21.1 (2016): 28-32.

18. Alessandro Inno., *et al*. "Neuroendocrine Carcinoma of the Breast: Current Evidence and Future Perspectives". *Oncologist* 21.1 (2016): 28-32.

Volume 5 Issue 10 October 2022