

Neuroendocrine tumor of the breast: Is it primary or metastatic?

**Ornela A. Dervishaj, Alexandra S. Renzi, Romulo Genato,
Philip Q. Xiao, Armand P. Asarian**

ABSTRACT

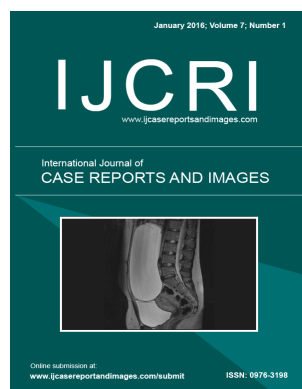
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Case Report: We present the case of a patient who was referred to our outpatient office with the diagnosis of a triple negative invasive breast carcinoma on an ultrasound-guided core needle biopsy. The patient subsequently underwent a lumpectomy with sentinel lymph node biopsy. Postoperative pathology revealed neuroendocrine carcinoma of the breast with sentinel lymph node biopsy negative for carcinoma. The tumor cells were positive for AE1/AE3, chromogranin, synaptophysin and CD-56 but negative for estrogen, progesterone and HER2. To exclude a primary carcinoma elsewhere, we obtained a whole body PET scan which showed a mildly hypermetabolic mesenteric mass in the midline with curvilinear calcification. Computed tomography scan of the abdomen and pelvis with oral and IV contrast showed a mass-like soft tissue within the terminal ileum with thickening of the cecum. An octreotide scan of the whole body revealed abnormal activity in the midline of the lower abdomen 6 hours and 24 hours after administration of octreotide. Colonoscopy showed a nodular friable mass in the ileocecal valve extending from the terminal ileum. Biopsy from the colonoscopy demonstrated a neuroendocrine carcinoma. The patient subsequently underwent a right hemicolectomy with primary anastomosis. Postoperative pathology was concordant with a neuroendocrine carcinoma and 9 of the 20 lymph nodes were positive for carcinoma. We performed a literature review to explore the reported incidence, diagnosis and treatment of this rare tumor metastasizing to the breast.

Conclusion: Differentiating between primary and metastatic tumor of the breast represents a challenge, albeit an important one, as the first disease can subject the patient to the morbidities of a mastectomy with axillary node dissection and the other is locally controlled.



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CASE REPORT

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Keywords: Breast cancer, Colorectal metastasis, Neuroendocrine tumor

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INTRODUCTION

Neuroendocrine tumors (NET) are low grade malignant neoplasms that occur most frequently in the gastrointestinal tract (74%) and respiratory system (25%)

[1]. When discovered in the gastrointestinal tract they are most commonly seen in the small bowel [2]. When NET of the breast is diagnosed, the question remains whether the tumor is a primary versus metastatic disease. Subtle yet important differences in radiological and pathological presentations may aid in the diagnosis. In our case, the patient had an initial presentation of NET within the breast and ultimate work-up revealed a primary elsewhere.

CASE REPORT

A 64-year-old female underwent a screening mammogram and bilateral breast ultrasound (Figure 1) that showed a nodule in the right breast that was initially read as BIRADS 3 due to its benign appearance. After comparison with a previous mammogram, the nodule was noted to be a new finding and was then read as a BIRADS 4. The right breast nodule measured 0.5x0.4x0.4 cm and was located in the 3 o'clock axis, 4 cm from the nipple. A core-needle biopsy with clip placement was performed and the pathology was reported as a triple negative invasive ductal carcinoma. At this time, the patient was referred to our office for further management of her newly diagnosed breast cancer. The patient denied any medical problems. Family and social history were noncontributory. On review of systems, she denied any unusual symptoms including weight loss, flushing, dyspnea, diarrhea, or palpitations. On physical examination, the breasts were symmetrical with no skin dimpling, nipple retraction or spontaneous discharge noted. No masses were appreciated on palpation.

Patient underwent an ultrasound-guided needle localized lumpectomy and sentinel lymph node biopsy. The post-procedure mammogram identified adequate resection. The sentinel nodes were negative. The right breast nodule pathology revealed three small foci of low grade neuroendocrine tumor with no lymphovascular or perineural invasion, and the surgical margins were negative for tumor cells. Immunostaining of the three small foci was positive for AE1/AE3, synaptophysin, chromogranin and CD56 (Figures 2 and 3) which supported the diagnosis of neuroendocrine tumor. Ki-67 highlighted around 5% of tumor cells. Hormone receptor studies were negative for ER, PR and Her2/neu.

Our suspicion was that this tumor was most likely a metastasis. To explore this option, the patient underwent a PET/CT scan, CT abdomen/pelvis, and octreotide scan of the whole body. The PET/CT scan showed a mildly hypermetabolic mesenteric mass with curvilinear calcification measuring 3 cm in the midline. The CT Abdomen and pelvis showed the presence of a mass within the terminal ileum with calcifications and mild thickening of the cecum. The octreotide scan showed (Figure 4) increased radionuclide accumulation at the midline of the abdomen, highly suggestive of a neuroendocrine malignancy.

The patient then underwent a colonoscopy which revealed a nodular, erythematous, and friable mass on the ileocecal valve that was extending from the terminal ileum. Biopsy of the mass revealed well differentiated neuroendocrine carcinoma.

At the same time patient underwent laboratory work-up which revealed normal basic metabolic panel, hepatic function panel and complete blood count. However, her 24-hour urine 5-HIAA and serum chromogranin A levels were elevated at 11.2 mg/24 hr (normal < 6) and 195 ng/cc (normal < 95 ng/cc), respectively.

The patient subsequently underwent a right hemicolectomy with primary ileocolic anastomosis. The final pathology demonstrated a low-grade neuroendocrine tumor grossly measuring 3.5x5x2 cm. Tumor invasion involved serosa and pericolic soft tissue, perineural and lymphovascular invasion. The appendix and nine of twenty lymph nodes were positive for metastatic neuroendocrine carcinoma. Patient was treated with sandostatin postoperatively and continues to be free of disease at least follow-up with chromogranin level at 27 ng/cc and repeat PET/octreoscan negative for recurrence.

DISCUSSION

Neuroendocrine tumors (NET) are endocrine-related tumors that are relatively slow growing with distinct molecular and clinical characteristics. The first NET detected by mammogram was in 1977 when mammograms were just starting to be utilized in clinical practice [3]. Prior to that, all NET of the breast presented as a mass, usually no more than 2 cm in size [3]. This is a case of a 64-year-old female with original diagnosis of invasive ductal carcinoma on a core biopsy who on complete resection was found to have metastatic NET to the breast.

According to a recent meta analysis of 13,715 NET, the most common location for this tumor within the gastrointestinal tract are small intestine, rectum

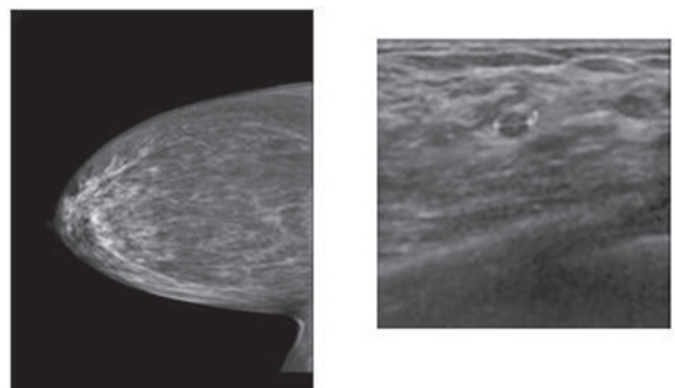


Figure 1: Diagnostic mammogram and ultrasound of right breast showing right breast nodule.

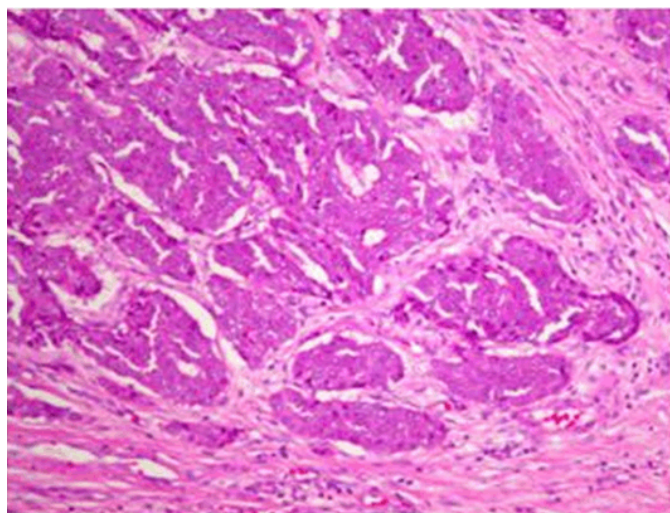


Figure 2: Microscopic examination reveals that tumor is composed of insular, trabecular monotonous small round cells showing peripheral palisading with moderate finely granular cytoplasm, small nucleoli, salt and pepper chromatin. Mitotic figures are present (H&E stain, x200).

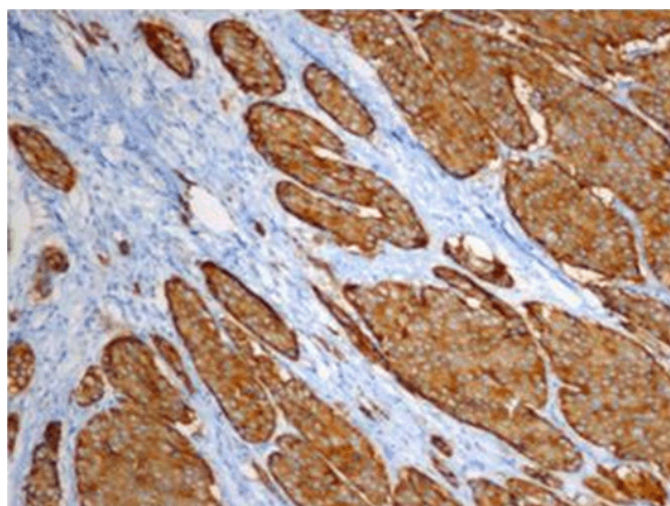


Figure 3: Immunohistochemical stain for synaptophysin is diffusely strong positive (H&E stain, x200).

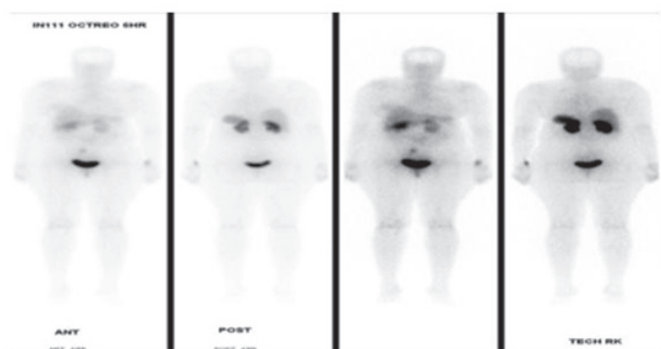


Figure 4: Octreotide scan showed increased radionuclide accumulation at the midline of the abdomen, highly suggestive of a neuroendocrine malignancy.

and stomach, respectively. Not the appendix as was previously believed [2]. The most common NET to have metastasized at time of diagnosis is that of the cecum, pancreas and small intestine (81.5%, 71.9%, and 58.3%, respectively). The most frequent sites of metastasis, excluding the lymph nodes (89.8%), are the liver (44.1%), lung (13.6%), peritoneum (13.6%), and pancreas (6.8%) [2]. It is unusual to find this rare tumor in the breast as a metastasis. NET metastases do not favor any particular quadrant of the breast, but they do occur more commonly on the right breast than the left [3]. In the review by Kalisher et al., the authors report on 59 cases of neuroendocrine tumors in literature. Thirty-eight of these were primary neuroendocrine tumors of the breast, while only nine were metastases [3].

The most common cancers to metastasize to the breast in decreasing frequency are contralateral breast carcinoma, malignant melanoma, prostate, lung, and renal cell carcinoma [3]. Primary breast NET comprise <2% of all primary breast cancers (Table 1) [1, 4–6]. In 2003, the World Health Organization (WHO) classified primary NET of the breast as tumors with expression of one or more immunohistochemical markers (neuron specific enolase, chromogranin A, and synaptophysin) in at least 50% of the tumor cells [1].

Our patient's initial finding was an oval-shaped hypoechoic lesion which was initially thought to be benign due to absence of irregularity. Multiple case reports have reported an initial benign appearing mammogram with a well-circumscribed mass with no calcifications [1, 3, 5]. In a review of 1845 breast cancers, Belgin et al. found 5 NETs of the breast. On mammogram, four of them appeared round, while only one patient had an irregularly shaped lesion.

Studies have demonstrated that diagnosing NET of breast on core needle biopsy may be difficult [7]. Angarita et al. also report a case of a patient who was diagnosed with IDC that was postoperatively found to have a NET, in their case a primary neuroendocrine tumor of the breast.

Fine needle aspiration (FNA) is also a common tool for the diagnosis of malignancy. However while it may help identify malignant cells, it has often proven difficult in distinguishing NET from other breast cancers [5]. Moreover, due to identification of malignant cells on FNA, it has sometimes led to an immediate mastectomy without further characterization of the cancer [5].

On gross pathology, metastatic NET tends to be less fixed to the surrounding tissues than primary tumors and is located in the subcutaneous tissue rather than breast tissue [3]. NET consists of a uniform cell population with abundant eosinophilic cytoplasm and nuclei with stippled (“salt and pepper”) chromatin [1]. Invasive ductal carcinoma (IDC), on the other hand, usually consists of atypical cells with occasional to numerous mitoses which is unlike the uniform round cells seen in NET [1, 3].

Lobular carcinoma in situ (LCIS) may be confused with NET because of the uniform cells with round nuclei lying in well-defined islands [3]. However, LCIS has no

Table 1: Different characteristics of primary versus metastatic neuroendocrine tumor of the breast

Feature	Primary	Metastatic
Prevalence	0.27–2%	0.4–0.7%
Age at diagnosis	6th or 7th decade of life [1, 2, 3]	5th decade of life most common
Symptoms of carcinoid syndrome	No cases reported to date	depends on primary
Axillary involvement	Commonly involved in tumors >3 cm in size	Not reported in literature
Radiology	–US: irregular margin, hypoechoic, homogenous texture, round nodule, absence of cystic component [1, 2] –MRI: homogeneous lobulated tumors with early contrast enhancement, suggesting malignancy [1, 2]	– Mammogram: most common appear as benign, well circumscribed nodules, absent micro-calcifications,
Gross Pathology	pale-yellow colored, fleshy or firm with either smooth or irregular margins [1, 2].	Mets tend to be less fixed to surrounding tissues and located in subcutaneous tissue adjacent to breast tissue [5]
Histological Markers	–strongly + ER/PR, Expression of GCDFP-15, mammaglobin and lack of TTF-1 , + for synaptophysin/chromogranin A	–negative for ER/PR, GCDFP-15, mammaglobin, or TTF-1 +synaptophysin and chromogranin A
Treatment	same recommendations as invasive ductal carcinoma	local excision only
Survival	Similar to Luminal Type A invasive ductal carcinoma	Depends on primary source

fibrosis and it preserves the pattern of markedly dilated terminal ducts filled with slightly dyshesive cells [3]. Infiltrating lobular carcinoma (ILC) can be distinguished from metastatic NET, since NET rarely “Indian file” [3]. Histologic confirmation of NET can be made by a positive argyrophil reaction and evidence of small membrane-bound neurosecretory granules [8]. Although the solid nests found in NET of the breast are also present in DCIS/LCIS and IDC/ILC, both of the latter can be excluded when considering E-cadherin positivity and p63 negativity of the palisading cells, respectively [6].

Once NET is diagnosed by histopathologic features, the question remains whether the tumor is a primary versus metastatic NET to the breast. The definite feature that makes the diagnosis of primary is intraductal component of NET, as metastatic NET has no intraductal component [3, 4]. Based on this finding, we advise screening of other sites using different imaging modalities once the diagnosis of metastatic NET is suspected.

Chromogranin A (CGA), chromogranin B (CGB), and synaptophysin (SYP) are considered the most sensitive and specific NET markers but they are relatively nonspecific when it comes to differentiating between primary versus metastatic NET to the breast [4, 6]. For breast tumor markers, more than 90% of diagnosed primary NET cases can express estrogen receptors (ER) while up to 75–80% express progesterone receptors (PR) [6]. However, presence of ER/PR is not sensitive nor specific enough to differentiate between primary versus metastatic NET to the breast. To the best of our

knowledge, we could not find a study that reported the presence of these markers in NET of the bowel. Hence we can assume that the presence of these markers in a case of NET of the breast can help exclude a metastasized NET from the bowel. However, there have been cases of bronchopulmonary NET which have been reported to be positive for ER/PR and metastasized to the breast. In one report of pulmonary NET, 40% of specimens expressed ER, and 70% expressed PR [1, 2, 4, 9]. Moreover, when these tumor markers are found to be negative, one has to assume that the tumor could be a metastasis from the bowel, lung or a primary of the breast.

Richter-Ehrenstein et al. looked at the expression of Gross cystic disease fluid protein (GCDFP-15), mammaglobin, and TTF-1 (thyroid transcription factor 1) to help assist in differentiation of a primary versus metastatic NET to the breast. In primary NET, they found that GCDFP-15 was expressed in 6 out of 9, mammaglobin was positive in 4 out of 9, and TTF-1 was not expressed in any of the breast tumors. One of these patients was found to have a primary in the midgut, and this was the only patient that had 0% expression of ER/PR and HER2. In evaluation of the 99 patients with primary NET of gut, they found no expression of GCDFP-15, mammaglobin, or TTF-1. Other studies have reported similar results using these tumor markers [1, 10–12].

It is the difference in treatment of primary versus metastatic NET to the breast that is most worrisome about misdiagnoses. Prior to lumpectomy and radiation treatment, a simple or radical mastectomy was the

standard treatment of primary carcinoid tumors, even in cases of correct diagnoses [3, 8]. This is because primary carcinoid tumor of the breast behaves similarly to IDC and hence is treated in the same manner. Whereas in cases of metastatic NET to the breast, an excision of the lesion is thought to be sufficient treatment and that radiation to the breast is not necessary [13].

CONCLUSION

In order to determine the appropriate treatment for our patient, we needed to know if there was a primary elsewhere which led to the eventual discovery of original tumor in the ileocecum. Our work-up included a PET/CT scan, octreotide scan and colonoscopy. All three studies helped us find and confirm the site of the primary as well as obtain tissue for diagnosis. We recommend the use of all three in the workup of a neuroendocrine tumor.

Author Contributions

Ornela A. Dervishaj – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Alexandra S. Renzi – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Romulo Genato – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Philip Q. Xiao – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Armand P. Asarian – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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