

Metastatic Carcinoid Tumor Presenting as a Breast Mass: A Case Report and Review of the Literature

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Abstract

Carcinoid tumors are indolent neoplasms derived from the enterochromaffin cells which have a wide anatomic distribution. Most common primary sites include gastrointestinal tract and bronchopulmonary system. Despite their slow growing nature, carcinoid tumors possess metastatic potential, and breast is a rare but known site of metastasis. We report a case of breast metastasis from carcinoid tumor of the terminal ileum in a 53 year old woman who initially presented with a breast mass detected by screening mammography. A review of literature was performed for this rare presentation of breast as the initial site of detection of metastatic carcinoid tumor.

Keywords: Breast; Metastasis; Carcinoid tumor

Introduction

Unlike primary malignancy of the breast, metastatic lesions to the breast are very rare and represent 0.5% - 2% of all breast tumors [1-3]. The most common primary site for breast cancer metastasis is the contralateral breast but various extramammary malignancies may also metastasize to the breast. Breast metastasis from carcinoid tumor is a rare manifestation accounting for about 7% of breast metastases, and often requires additional investigative studies to establish the correct diagnosis [3]. Carcinoid tumors are slow-growing neuroendocrine tumors arising from enterochromaffin cells which are present throughout the body. They most commonly develop in the gastrointestinal tract and bronchopulmonary system but also may arise in other organs such as kidney and ovary. The main sites of metastases include regional lymph nodes, liver, peritoneum, and lung [4]. Breast mass may be the initial presentation of a metastatic extramammary carcinoid tumor and thorough work up should be undertaken to localize the primary tumor for appropriate treatment planning.

Case Report

A 53 year old post-menopausal female with only medical history of hypertension underwent screening mammography which revealed a 1.1 cm mass in the upper outer quadrant of the right breast. Sonographic exam confirmed the presence of a hypoechoic mass with irregular borders (Figure 1). A core needle biopsy was performed under sonographic guidance yielding the diagnosis of infiltrating carcinoma with neuroendocrine features. This patient was evaluated at an outside institution and underwent right breast lumpectomy with wire localization. The histologic examination of the surgical specimen revealed infiltrating well-to-moderately differentiated carcinoma with neuroendocrine features, present at the anterior margin (Figure 2). The

tumor diffusely stained positive with CDX2, suggesting a neuroendocrine tumor of midgut origin, and showed focal non-specific staining with mammaglobin and BRST2. Ki-67 staining was positive in approximately 5% of cells.

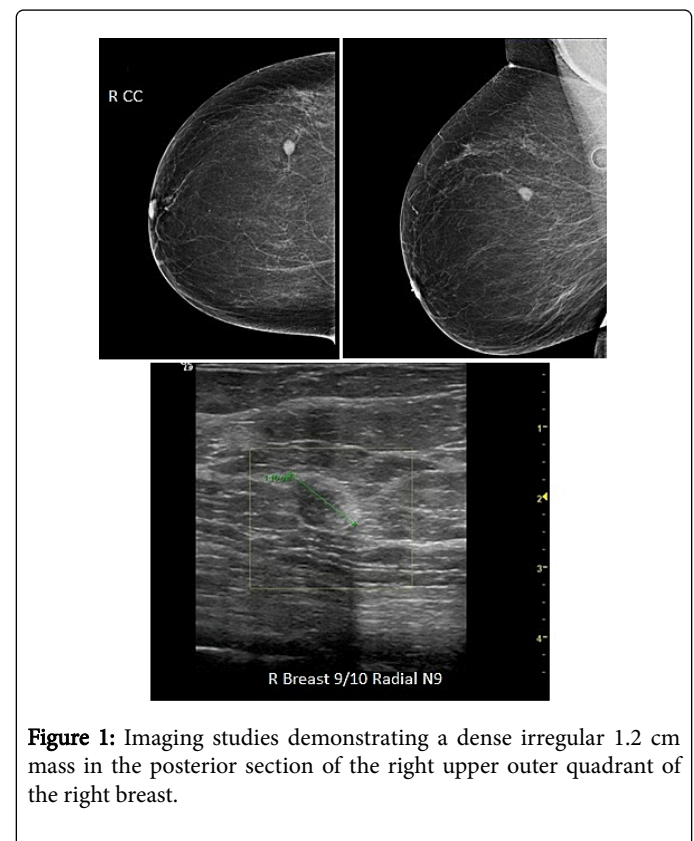


Figure 1: Imaging studies demonstrating a dense irregular 1.2 cm mass in the posterior section of the right upper outer quadrant of the right breast.

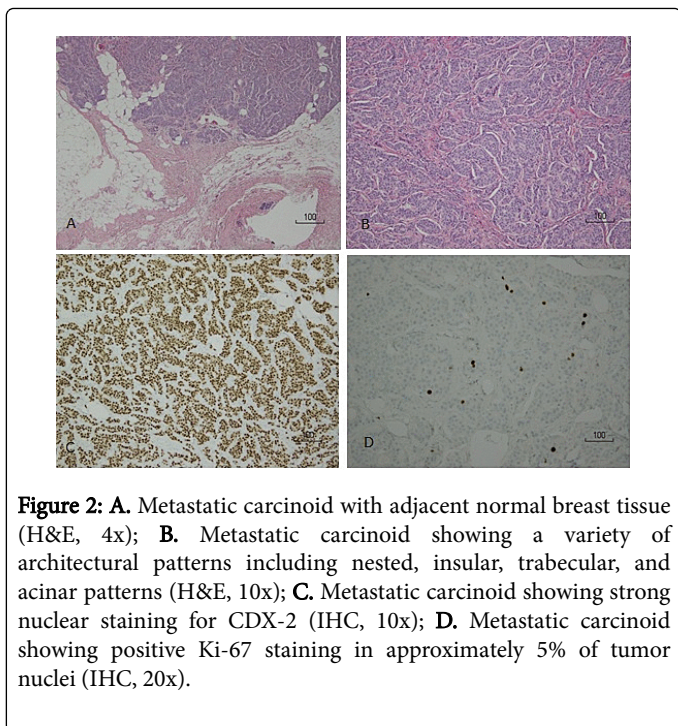


Figure 2: A. Metastatic carcinoid with adjacent normal breast tissue (H&E, 4x); B. Metastatic carcinoid showing a variety of architectural patterns including nested, insular, trabecular, and acinar patterns (H&E, 10x); C. Metastatic carcinoid showing strong nuclear staining for CDX-2 (IHC, 10x); D. Metastatic carcinoid showing positive Ki-67 staining in approximately 5% of tumor nuclei (IHC, 20x).

At this point, the patient was referred to our institution for further management. On further inquiry regarding symptoms associated with carcinoid syndrome, the patient did not report any abdominal cramping or diarrhoea but did admit to intermittent flushing. Having recently undergone menopause, she attributed these symptoms to “hot flashes”. Further work-up to localize the primary tumor site was undertaken. Evaluation of serum for biomarkers showed elevated Chromogranin A (96, reference range 0-95 ng/ml) and Serotonin (1676, reference range 50 ng/ml - 220 ng/ml). Octreotide scan revealed an isolated ileal lesion (Figure 3) without any liver metastasis. A subsequent colonoscopy confirmed the presence of an avascular mass in the terminal ileum which was biopsied. Pathologic examination was consistent with neuroendocrine tumor and immunohistochemical stains were positive for synaptophysin and chromogranin.

The patient underwent laparoscopic right hemicolectomy and re-excision of right breast during the same operation to achieve clear margins. Post-operative course was unremarkable. Histologic exam of the hemicolectomy specimen revealed 3 nodules of low-grade neuroendocrine tumor measuring 3 cm, 0.4 cm, and 0.3 cm in the ileum with mitotic activity 0 - 1/10 per high power fields. The larger tumor was noted to infiltrate the entire bowel wall up to the subserosal adipose tissue and extensive lymphovascular invasion and perineural invasion were present. Three of thirteen lymph nodes were positive for metastasis and immunostain Ki-67 showed a proliferative index of up to 10% (Figure 4). The breast re-excision specimen contained residual infiltrating neuroendocrine carcinoma which was histologically similar to the ileal tumors and the margins were negative (Figure 5).

This patient recovered from surgery without any complications. On follow-up, she reported cessation of facial flushing and is asymptomatic six months following the surgery with normal serum serotonin and chromogranin A.

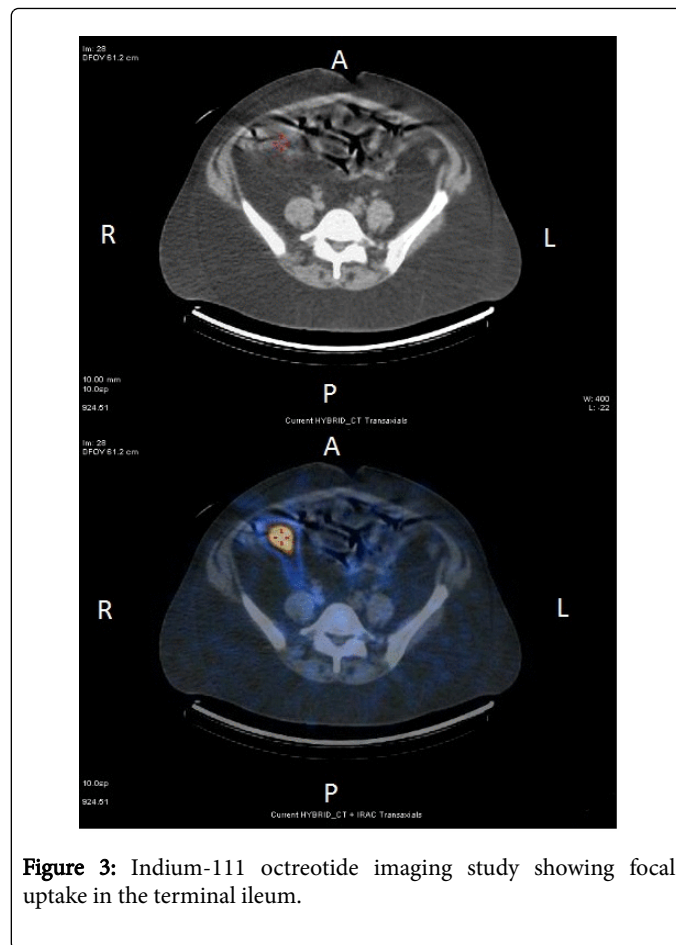


Figure 3: Indium-111 octreotide imaging study showing focal uptake in the terminal ileum.

Discussion

The incidence of carcinoid tumors has increased in the past two decades and improved survival duration has been observed [5]. The overall 5 year survival rate for all carcinoid tumors, regardless of site or stage, ranges from 70% - 80% [6]. Prognosis for localized carcinoid tumor is favorable with observed median survival of 111 months in a Surveillance, Epidemiology, and End Results (SEER) database analysis. Even those with metastatic disease can have significant survival and may benefit with appropriate treatment [5,6]. The most common primary site of carcinoid tumors is the gastrointestinal tract with 42% originating from the small bowel [7]. Despite the indolent nature of these tumors, 13% - 22% of patients have distant metastases at the time of diagnosis [6,7]. Molecular cytogenetic studies have shown overexpression of neoplasia-related genes such as nucleosome assembly protein (NAP1L1), melanoma antigen D (MAGE-2D), and metastasis-associated protein 1 (MTA1) in small intestine carcinoids. Currently, however, there are no well-established predictors for metastatic potential as lesions with bland morphology and no mitotic activity have been shown to produce distant metastases [7-9].

Metastasis of carcinoid tumor to the breast is a very rare occurrence. The first report of carcinoid tumor metastatic to the breast appeared in the literature in 1957. The patient displayed multiple symptoms of carcinoid syndrome which was not yet a known entity at the time of her presentation, 30 years prior to the publication of the report. This patient reportedly had multiple breast nodules, which were confirmed

to be metastases from carcinoid tumor arising from the ileum after an autopsy was performed [10]. There are also reports of patients with known extramammary carcinoid tumors who developed breast metastases over a variable time period after primary diagnosis [4,11]. In some cases, however, breast metastasis is the first manifestation of an occult carcinoid tumor.

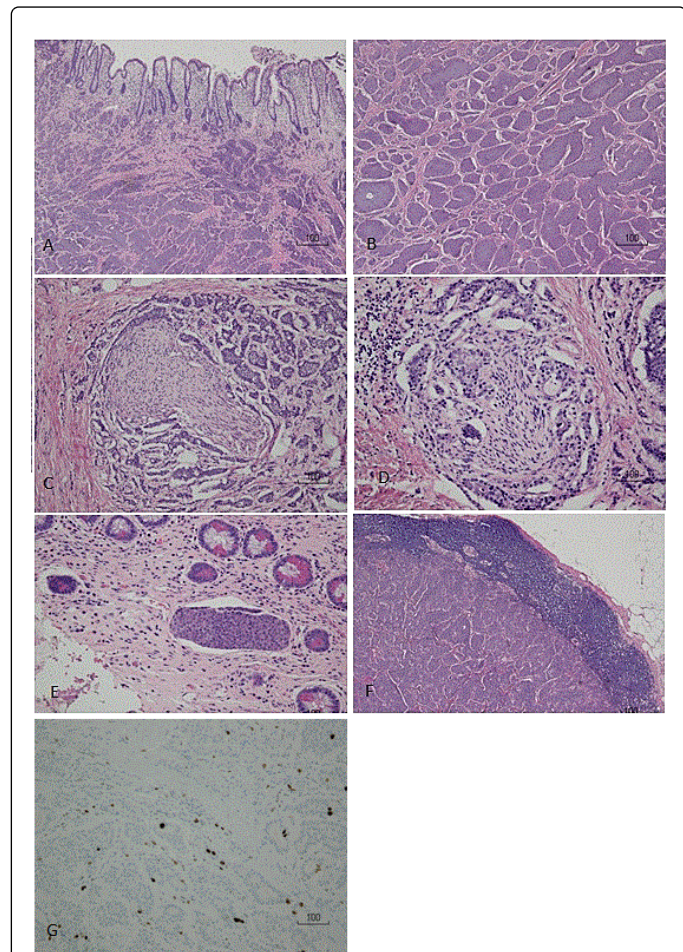


Figure 4: A. Tumor with overlying normal colonic mucosa (H&E, 4x); B. Carcinoid tumor (H&E, 4x); C. Perineural invasion (H&E, 10x); D. Intraneural invasion (H&E, 20x); E. Lymphatic invasion (H&E, 20x); F. Lymph node with metastatic carcinoid (H&E, 4x); G. Carcinoid showing positive Ki-67 staining in approximately 10% of tumor nuclei (IHC, 20x).

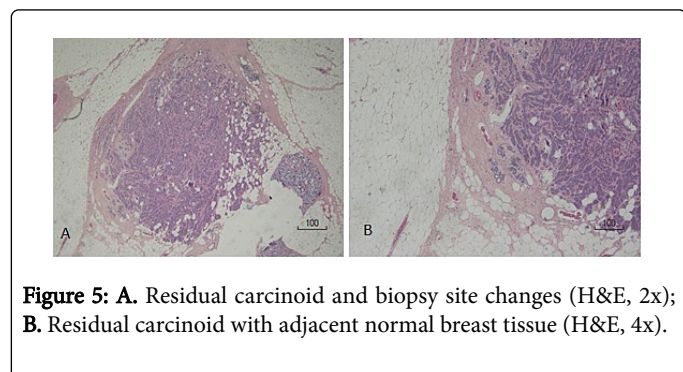


Figure 5: A. Residual carcinoid and biopsy site changes (H&E, 2x); B. Residual carcinoid with adjacent normal breast tissue (H&E, 4x).

A review of the literature indicates that there are 12 previously reported cases of breast as the initial site of presentation for metastatic carcinoid tumor (Table 1). Average age at presentation was 56 (range 23 - 73). The majority of cases presented as palpable or radiographically detected solitary mass in the breast. In more than half of the cases, the tumor was initially mistaken for carcinoma of the breast. Half of the patients displayed at least one symptom of carcinoid syndrome. The most common primary location of carcinoid tumor was the ileum / small bowel with only two cases having different sites: appendix and ovary. Surgical treatment of the breast lesion included mastectomy and lumpectomy, with lumpectomy being more common in later years. Axillary surgery was performed in 6 cases - 3 sentinel lymph node biopsies and 3 axillary lymph node dissections - all of which were initially misdiagnosed as having primary breast carcinoma. In one case, one of thirty axillary lymph nodes removed was positive for micrometastasis while all the other cases were negative for axillary disease.

	Author	Year	Age	Primary Site	Solitary mass	Treatment
1	Turner and Gallager [21]	1969	61	Appendix	Yes	Mastectomy
2	Schurch et al. [12]	1980	53	Ileum	Yes	Mastectomy
3	Nielsen et al. [1]	1981	73	Ileum	N/A	N/A
4	Kashlan et al. [13]	1982	69	Ileocaecum	Yes	Mastectomy
5	Di Palma et al. [22]	1988	54	Ileum	Yes	Lumpectomy
6	Fishman et al. [23]	1994	52	Ovary	Yes	Mastectomy
7	Kaltsas et al. [24]	1998	23	Ileocaecum	Yes	Lumpectomy
8	Mosunjac et al. [7]	2004	60	Ileum	Yes	Lumpectomy
9	La Rosa et al. [25]	2007	50	Ileum	Yes	Lumpectomy
10	Shahrokni et al. [26]	2009	64	Small Bowel	Yes	Lumpectomy
11	Geyer et al. [2]	2010	52	Ileum	Yes	Lumpectomy
12	Glazebrook et al. [5]	2011	53	Ileum	No	N/A
13	Dervishaj et al. [27]	2015	64	Ileocaecum	Yes	Lumpectomy
14	Ahn et al. (this report)	2015	53	Ileum	Yes	Lumpectomy

Table 1: Summary of case reports of breast as first presentation of carcinoid.

Metastasis to other sites was present in seven cases, all of whom had liver lesions. One patient was found to have metastases to omentum and femur in addition to the liver. Metastatic carcinoid lesion in the breast may present as a palpable mass or as an abnormality on imaging study. Because of its rarity, imaging characteristics have not been well described in the literature. From the available reports, these lesions are not associated with calcifications on mammography and may appear as sharply circumscribed masses, leading to misinterpretations as

fibroadenoma, medullary carcinoma, or mucinous carcinoma [2,4,6,12-14]. On magnetic resonance imaging, they seem to display a rapidly enhancing mass with Type 3 kinetics [4].

Once tissue diagnosis has been established, search for a possible primary site should be undertaken to determine whether the lesion is a metastasis or a primary carcinoid tumor of the breast. Primary carcinoid tumor of the breast is reported to account for less than 1% - 5% of breast cancers and is usually treated in the same manner as other types of invasive breast cancer including a combination of surgery, chemotherapy, radiation, and endocrine therapy [15]. Clinically, there are no reliable ways to distinguish a primary lesion from a metastasis. However, thorough histological examination and the use of various stains can help determine the diagnosis. The presence of intraductal or in-situ proliferation in a biopsy sample is strongly suggestive of a breast primary [12]. Also, primary neuroendocrine carcinoma of the breast is often positive for hormone receptors and almost always negative for Her2 [15]. The staining patterns of metastatic lesions often resemble that of the primary tumor although it may vary from case to case. Historically, gastrointestinal carcinoid tumors contain argyrophil and argentaffin cytoplasmic granules. Tumors from foregut and hindgut tend to be argentaffin negative and argyrophil positive while those of midgut origin display mostly argentaffin positive granules [12,13,16]. Modern antibodies are now used to help determine the primary site. When biopsied tissue tests positive for immunohistochemical marker CDX-2, the primary tumor is more likely to be in the midgut. If the tumor is positive for CDX-2 and negative for other transcription factors including pancreatic and duodenal homeobox factor-1 (PDX-1), neuroendocrine secretory protein-55 (NESP-55), and thyroid transcription factor-1 (TTF-1), the primary tumor is highly likely to be arising from the ileum. In the absence of CDX-2 positivity, expression of TTF-1 is suggestive of a pulmonary origin [9]. PDX-1 is highly specific, with very good overall diagnostic accuracy for pancreatic primary [17]. In our case, the breast tumor was negative for hormone receptors and breast specific markers such as BRST2 and mammoglobin. It expressed chromogranin and synaptophysin, immunohistochemical markers sensitive and specific for neuroendocrine tumors when used together. In addition, the tumor stained diffusely positive for CDX2, consistent with the final diagnosis of metastasis from carcinoid tumor arising in the terminal ileum.

Surgical treatment is the mainstay of therapy for primary carcinoid tumors and can be curative. Unlike the treatment of most carcinomas with distant metastases which often involve various combinations of systemic therapy, surgery can play a significant role in the setting of metastatic carcinoid tumors. In a retrospective review and analysis of 169 cases of breast metastasis from non-breast solid organ primary tumors, neuroendocrine histology was found to be a significant favorable predictor of survival [3]. Complete resection of metastases may be beneficial for patients with resectable primary tumors in the absence of widely disseminated disease in terms of both improved survival and quality of life. Long term follow-up and survival rates for these patients who presented with carcinoid tumors metastatic to breast were not available for all cases. However, resection of more commonly encountered metastatic sites such as liver is known to impact survival and surgery is often advocated in patients with limited liver metastases [18]. One study showed that long-term survival can be achieved with hepatic resection of metastatic carcinoid tumors with reported 10 year overall survival rate of 50% [19]. Survival benefit of resection of breast metastasis is unknown and likely will remain so due to the rarity of the entity. However, an analysis of SEER data for patients with metastatic carcinoid tumor highlighted a survival benefit

in patients undergoing resection of either the primary or metastasis, and an even greater benefit for resection of both sites [20]. Therefore, surgery should be strongly considered in those with good functional status who may have meaningful survival benefit from resection of metastasis. In cases of relapse, it would be reasonable to re-resect isolated recurrent breast tumor if the patient remains free from diffuse metastatic disease and still maintains good health overall.

There is paucity of data supporting adjuvant therapy for carcinoid tumor metastatic to the breast. Generally, somatostatin analogues are used in patients with unresectable metastatic disease or those with carcinoid syndrome. However, there is little or no effect on tumor growth and no clear role have been demonstrated in patients with resectable tumors who do not suffer from effects of excess serotonin. The indication for chemotherapy is narrow in treatment of carcinoid tumors and is often reserved for high-grade malignancies [6]. External radiation therapy also has limited value and is only recommended for bone and brain metastases [8]. In three cases identified in this report, mastectomy with axillary surgery was performed because the breast lesion was first mistaken as breast carcinoma. With a solitary metastatic nodule in the breast, mastectomy is not typically required for metastasectomy. Unlike primary neuroendocrine tumor of the breast, there is little data to suggest a benefit for axillary staging in carcinoid tumor metastatic to the breast. For these lesions lumpectomy with clear margins likely provides optimal local control with minimal morbidity.

Conclusion

- Carcinoid tumor of the breast is rare and may be the first manifestation of metastatic disease from an extramammary site.
- Metastatic carcinoid tumor in the breast can be mistaken as primary carcinoma and can result in overtreatment.
- Search for primary site should be undertaken to establish the correct diagnosis and guide treatment planning.
- Lumpectomy without axillary surgery is adequate to obtain local control.

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