

## ORIGINAL ARTICLE

# Imaging features of carcinoid tumors metastatic to the breast

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### Abstract

The objective of this study was to describe the imaging findings of carcinoid tumors metastatic to the breast, with pathologic and clinical correlations. We searched our surgical database for cases of pathologically proven carcinoid tumors metastatic to the breast from October 1, 2000, to May 31, 2010. Of the approximate 10,000 breast biopsies identified, 7000 had malignant findings. Ten cases of metastatic carcinoid (0.1% of all malignancies), all with imaging studies available for review, were included in the study. All patients were women and had their primary carcinoid in the gastrointestinal tract ( $n=9$ ) or lung ( $n=1$ ). One patient presented with a palpable breast mass and no history of carcinoid tumor; an ileal carcinoid was discovered after the pathologic diagnosis of metastatic carcinoid was established. In the breast, tumors presented as solitary lesions in half the cases. Metastases to the breast typically presented as circumscribed masses mammographically and as hypoechoic circumscribed masses ultrasonographically; some showed increased through-transmission and increased vascularity with color Doppler evaluation. Five patients had octreotide scans; of these, 4 had increased focal activity in the region of metastasis within the breast. Six patients underwent computed tomography. Without contrast, nodular masses were observed; with contrast, the masses showed rapid enhancement during arterial phase imaging. Magnetic resonance imaging ( $n=4$ ) also showed rapid enhancement and washout kinetics after contrast administration. Recognition of carcinoid metastases to the breast in patients with known or occult primary carcinoid tumors is important to avoid unnecessary treatment for primary breast cancer.

**Keywords:** Biopsy; pathology; treatment.

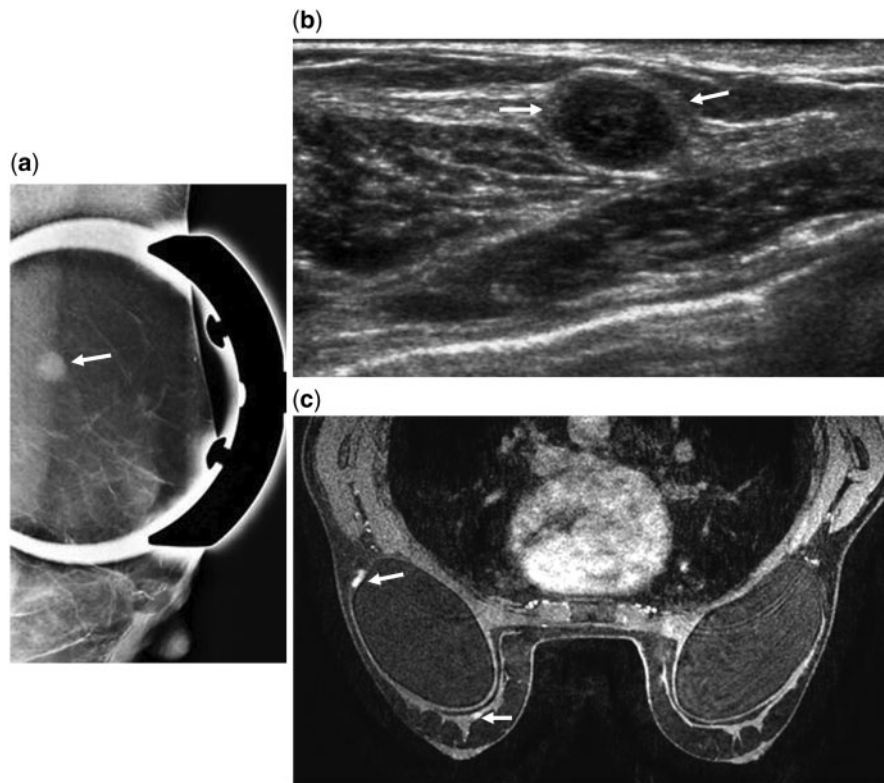
### Introduction

Carcinoid tumors are derived from enterochromaffin or Kulchitsky cells, which are most commonly found in the bronchopulmonary system and gastrointestinal tract. The main sites of metastases are regional lymph nodes, liver, peritoneum, and lung. Metastases to the breast are rare. The imaging characteristics of this rare tumor have not been well described in the literature. They have been reported as circumscribed or irregular masses when identified mammographically<sup>[1–5]</sup>; sonographically, they are hypoechoic masses that may exhibit increased vascularity with color Doppler ultrasonography<sup>[1,2,4]</sup>. Radionuclides such as octreotide can be used to localize

the tumor and treat metastatic disease<sup>[3]</sup>. To our knowledge, the magnetic resonance and computed tomographic (CT) appearance of carcinoid tumors metastatic to the breast have not been described previously. In this study, we describe findings of carcinoid metastases to the breast with multiple imaging modalities.

### Methods

With approval of our institutional review board, we retrospectively reviewed our institution's surgical pathology database for records of patients with a diagnosis of carcinoid tumor metastatic to the breast. Patients were seen



**Figure 1** A 43-year-old woman with an ileal carcinoid diagnosed in 2002. A palpable metastasis in the right breast was surgically removed in 2003. A screening mammogram detected a new mass in the left breast in 2008. (a) Spot compression of the left breast during a diagnostic mammogram (mediolateral view) shows a round mass with indistinct margins (arrow). (b) Sonography shows an isoechoic mass with microlobulated margins and a thin, echogenic halo (arrows). (c) Axial, immediate post-gadolinium, T1-weighted, fat-saturated magnetic resonance image of both breasts shows 2 rapidly enhancing, irregular masses in the left breast, adjacent to the breast implant (arrows). Both lesions had washout kinetics (not shown) with CADstream imaging (Confirmix, Inc, Bellevue, WA).

from October 1, 2000, to May 31, 2010. For all patients, diagnosis was made by percutaneous needle biopsy, surgical biopsy, or both. In all cases identified for this study, a dedicated breast pathologist confirmed the diagnosis of metastatic carcinoid. All identified patients had imaging studies and clinical histories available for review.

## Results

During the study period, approximately 10,000 breast biopsies were performed at our institution. Of these, 7000 specimens were malignant. The diagnosis of carcinoid tumor metastatic to the breast was made in only 10 cases (0.1% of all breast malignancies). Imaging methods included mammography ( $n = 10$ ), sonography ( $n = 10$ ), CT ( $n = 6$ ), octreotide scan ( $n = 5$ ), and magnetic resonance imaging ( $n = 4$ ). All patients were women. The mean age at the time of diagnosis of breast metastases was 56 years (range, 43–79 years). One patient had a primary pulmonary carcinoid, and the other 9 had their primary carcinoid in the gastrointestinal tract. One patient presented with a palpable breast mass and no history of carcinoid tumor. An ileal

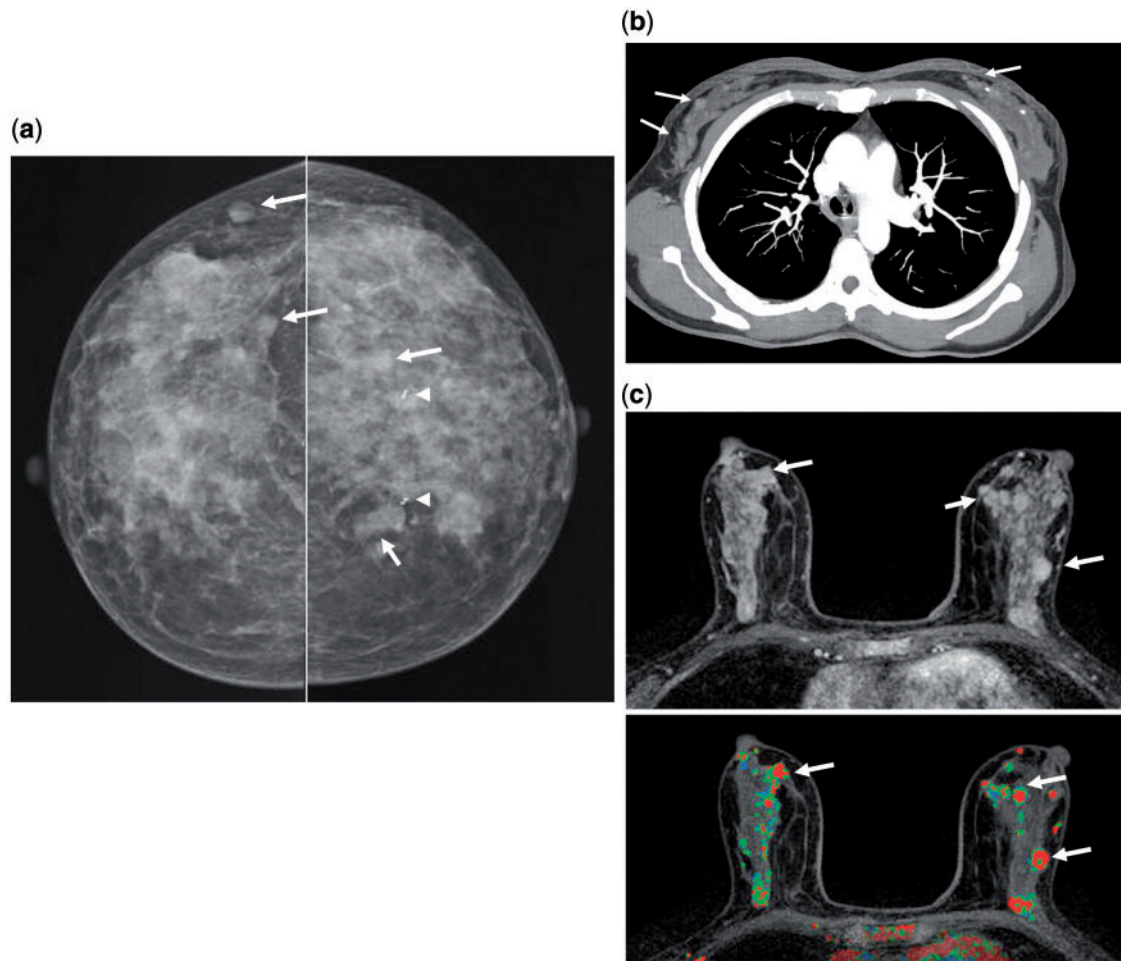
carcinoid was discovered after the pathologic diagnosis of carcinoid metastatic to the breast. Other gastrointestinal tract locations were the small bowel ( $n = 7$ ) and the colon ( $n = 1$ ). Five patients had symptoms of carcinoid syndrome (diarrhea and flushing). The primary carcinoid was diagnosed at an average of 13 years (range, 0–26 years) before the breast lesions were identified.

Six patients presented with palpable masses. Two patients had masses identified with screening mammography. One patient had an area of increased tracer activity identified within the breast during a screening octreotide scan; the mass was palpated at a subsequent physical examination. One patient had her metastatic carcinoid tumor identified incidentally during a stereotactic biopsy for calcifications (she had extremely dense breast tissue that obscured any masses).

### *Imaging characteristics*

#### Mammography

Mammograms were available for all 10 patients. Abnormalities were identified in 6: a circumscribed mass ( $n = 3$ ) (Fig. 1a) or multiple masses ( $n = 3$ ) (Fig. 2a). Some had



**Figure 2** A 45-year-old woman with colonic carcinoid diagnosed in 2003. She presented with palpable masses in the left breast in 2007; 2 were biopsied with ultrasonographic guidance and were shown to be metastatic carcinoid tumors. She presented with bilateral palpable masses in 2010. (a) Bilateral, craniocaudal, digital, diagnostic mammograms show multiple circumscribed masses in both breasts; some are partially obscured by dense breast parenchyma (arrows). Localization clips are noted in the left breast from prior ultrasonographically guided biopsies (arrowheads). (b) Axial, maximum-intensity projection, contrast-enhanced CT image of the chest shows multiple enhancing masses in both breasts (arrows). (c) Upper figure part is an axial, immediate post-gadolinium, T1-weighted, fat-saturated magnetic resonance image of both breasts with CADstream detection. Lower figure part is an axial subtraction magnetic resonance image showing multiple, rapidly enhancing masses with plateau (green color overlay) and washout (red color mapping) kinetics in both breasts (arrows).

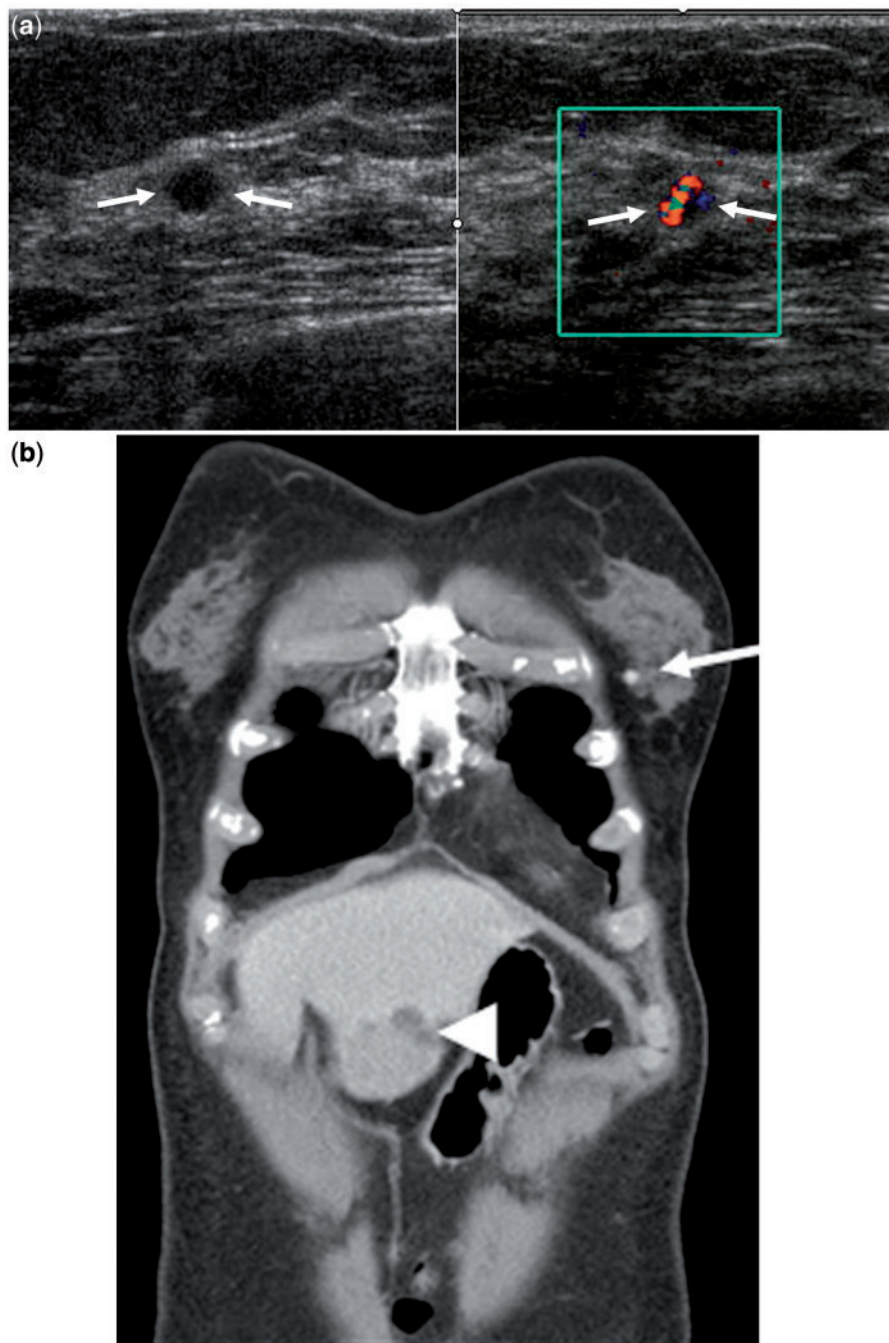
indistinct margins. No masses contained calcifications. One patient with dense breast tissue (Breast Imaging Reporting and Data System category D4) had new, indeterminate calcifications. A stereotactic biopsy showed they were benign, but a metastatic carcinoid tumor was noted incidentally within the biopsy specimen. For 3 patients, mammographic findings were negative because the lesions were obscured by dense breast tissue.

### Ultrasonography

Lesions were identified sonographically for all 10 patients. Solitary masses ( $n=4$ ) and multiple masses ( $n=6$ ) were identified. Size ranged from 3 to 18 mm

(mean, 7 mm). More masses were found sonographically than were identified mammographically (20 vs 10 lesions). Fourteen tumors presented as hypoechoic, irregular masses; 6 masses were isoechoic to surrounding fat, with a thin echogenic halo (Fig. 1b). In 2 cases, lesions with increased through transmission of sound were thought to represent possible complex cysts. No cases had posterior shadowing. Color Doppler evaluation was performed for 5 patients; of these, markedly increased vascularity was seen in 3 (Fig. 3). No flow was seen on one case examined with power Doppler ultrasonography. Elastography was performed for 1 patient. A 5-mm mass, detected through B-mode imaging, was larger on the elastogram, suggesting malignancy (Fig. 4a).





**Figure 3** A 55-year-old woman with a palpable mass in the left breast presented 10 years after the diagnosis of an ileal carcinoid tumor. (a) Left figure part is a sonogram showing an irregular hypoechoic mass. Right figure part is a color Doppler image showing marked vascularity that corresponded to the palpable mass. (b) Coronal, contrast-enhanced CT scan of the lower chest and abdomen shows a rapidly enhancing mass in the left breast (arrow) and the metastasis in the liver (arrowhead).

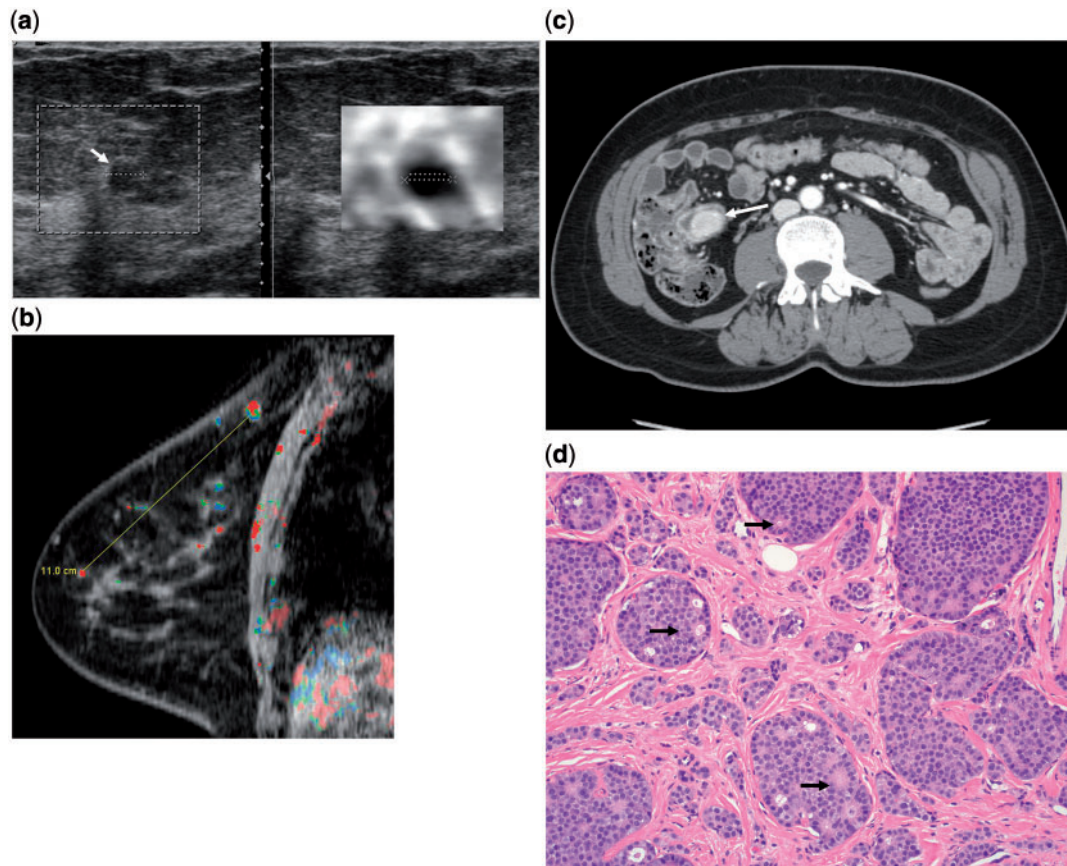
### Computed tomography

Six patients underwent evaluation with computed tomography (CT). Three patients had scans without contrast. Circumscribed nodules were identified in each patient. Arterial phase, contrast-enhanced CT was performed in 3 patients. Small, rapidly enhancing nodules were

identified; these corresponded to biopsy-proven metastases (Figs. 2b and 3b).

### Ocreotide scan

[<sup>111</sup>In]Diethylenetriamine-pentaacetic acid pentetreotide radionuclide was used as a staging tool in 5 patients.



**Figure 4** A 53-year-old woman with a palpable mass in the right breast. She initially was seen at another institution. Two lesions were found sonographically and biopsied. Histologic findings were interpreted as invasive ductal carcinoma, and a mastectomy was recommended. A review of pathologic specimens at our institution characterized both lesions as metastatic carcinoid tumors. (a) Left figure part is a sonogram of a nonpalpable mass in the right breast that shows an ill-defined isoechoic mass (arrow). Right figure part is an elastogram that shows a larger lesion (relative to the B-mode image), suggestive of malignancy. (b) Sagittal, CADstream, subtraction, post-gadolinium magnetic resonance image of the right breast shows 2 lesions with washout kinetics (red color map) that are 11 cm apart. (c) Axial, contrast-enhanced CT scan of the abdomen was subsequently performed. An occult, enhancing, carcinoid tumor in the ileum was identified (arrow). (d) Photomicrograph of the histopathologic specimen shows variable-sized nests of tumor cells with a uniform cytologic appearance, infiltrating the stroma. Tumor cells have stippled nuclear chromatin with granular eosinophilic cytoplasm. Micro-acinar structures (arrows) are seen within the solid proliferation, mimicking solid-type ductal carcinoma in situ (hematoxylin-eosin, original magnification  $\times 200$ ).

This radionuclide is a somatostatin analog that binds to somatostatin receptors in carcinoid tumors. Breast activity was identified prospectively in 4 of the 5 scans (Fig. 5a). In 1 patient, a follow-up octreotide scan showed an additional metastasis in the contralateral breast 2 years after surgical resection of the initial breast metastasis. Single photon emission CT imaging improved the conspicuity of the breast metastasis, especially with CT fusion (Fig. 5b).

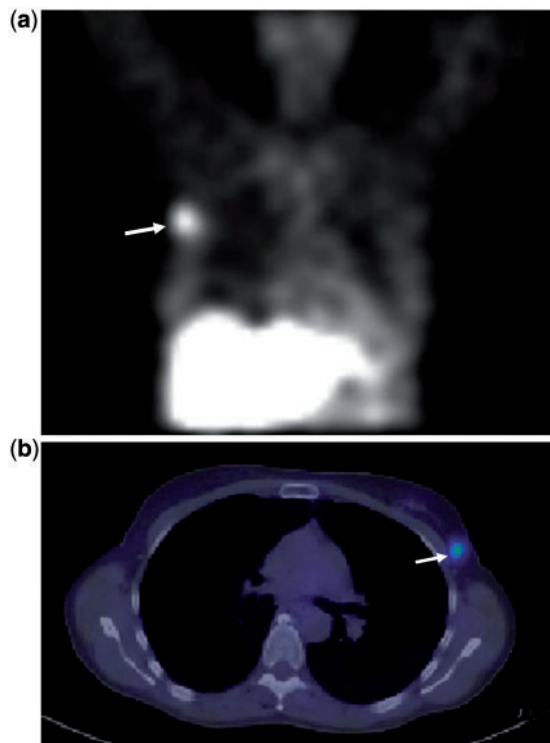
### Magnetic resonance imaging

Magnetic resonance imaging was performed in 5 patients. Rapidly enhancing, circumscribed masses were identified in all 5 cases (Fig. 1c): 4 showed washout

kinetics (Figs. 2c and 4b) and 1 showed progressive enhancement. The masses were not identified with T1 or T2 imaging because they were obscured by the surrounding dense breast tissue.

### Biopsy, treatment, and follow-up

Eleven masses from 7 patients were biopsied with sonographic guidance; biopsies were performed with a 14-gauge core biopsy device in 6 patients and an 18-gauge biopsy device in 1 patient (for the latter, the mass was adjacent to a subglandular breast implant). One patient with indeterminate calcifications underwent biopsy with stereotactic guidance and an 11-gauge, vacuum-assisted device. No complications were



**Figure 5** A 51-year-old woman with a palpable mass in the right breast presented 3 years after the diagnosis of a gastrointestinal carcinoid tumor. (a) Coronal image from an octreotide scan of the chest (performed in 2006) shows intense uptake in the right upper breast (arrow). This lesion was resected. (b) Follow-up axial CT–octreotide fusion image through the chest shows focal uptake in a mass in the upper, outer region of the left breast (arrow), consistent with a carcinoid metastasis.

noted at the time of biopsies, and no patients had carcinoid crisis (flushing, shortness of breath, wheezing, edema, or palpitation).

Two patients had ultrasonographically guided biopsies performed at other institutions, and each received a diagnosis of invasive ductal carcinoma. They presented to our institution for definitive breast cancer treatment. Metastatic carcinoid tumor was diagnosed on review of the pathologic specimens; the patients thus avoided breast cancer surgery. One patient had a history of ileal carcinoid, diagnosed 17 years before presentation. The other had an occult carcinoid tumor that was subsequently identified in the ileum (Fig. 4c,d).

Two patients underwent surgical excision after receiving a diagnosis of presumed metastatic carcinoid tumors. Three patients underwent wide local excision for disease containment of biopsy-proven metastatic carcinoid tumors. Four patients did not have breast surgery because of widespread metastases. One patient had resection of the newly diagnosed occult ileal carcinoid tumor and deferred breast surgery. No patients had axillary lymph node dissections or sentinel node biopsies.

Follow-up information was available in 8 patients for a period ranging from 1 to 8 years. Two patients died of progression of abdominal disease, 1 and 3 years after the breast biopsy. Two patients were disease free in the breast for 2 and 7 years after excisional surgery. One patient had a new area of tracer uptake observed during a screening octreotide scan, 2 years after wide local excision of the contralateral breast. No biopsy or surgical treatment has been performed for this patient with presumed further carcinoid metastasis. One patient had a new circumscribed mass detected in the same breast during a screening mammography, 6 years after the initial surgical excision. A biopsy showed this to be another carcinoid metastasis. This was followed without treatment for 1 year, but the patient had pain in the region and underwent another surgical excision. One patient showed stability of the biopsy-proven metastasis during a follow-up mammogram 1 year after diagnosis. One patient had new palpable masses in her breasts, 3 years after the initial biopsy diagnosis of multiple breast metastases; a magnetic resonance image showed innumerable masses in both breasts, consistent with extensive metastatic disease.

## Discussion

Carcinoids are slow-growing tumors that originate from enterochromaffin or Kulchitsky cells, predominantly of the gastrointestinal and urogenital tracts or bronchial epithelium<sup>[1]</sup>. Carcinoid tumors can show variable growth patterns. The tumor can grow in solid or irregular nests, cords, or trabeculae. The tumor cells have round nuclei with stippled chromatin and granular eosinophilic cytoplasm. The intervening stroma can be hyalinized or fibrous, and it lacks the typical desmoplastic reaction seen in invasive carcinomas; however, the infiltrating growth pattern can mimic invasive mammary carcinoma. Immunohistochemical staining is needed to distinguish these 2 entities. The tumor cells stain positively for 1 or more immunohistochemical markers of neuroendocrine differentiation: chromogranin A, neuron-specific enolase, synaptophysin, and serotonin. Although most primary breast malignancies strongly express cytokeratin 7 and not cytokeratin 20, these 2 markers are usually absent in carcinoid tumors<sup>[1]</sup>. Metastatic carcinoid tumors are also negative for estrogen and progesterone receptors<sup>[1]</sup>, whereas 75–80% of primary mammary carcinomas express estrogen receptors and 55–60% express progesterone receptors<sup>[6]</sup>.

Although metastases to the breast from any primary malignancy have been reported, they are uncommon, accounting for 1–2% of all breast tumors<sup>[3,4]</sup>. Sites of primary malignancies with metastases to the breast include the contralateral breast, skin (melanoma), lung, lymph nodes (lymphoma), bone marrow (leukemia), and gynecologic organs<sup>[4]</sup>. All carcinoid tumors are potentially malignant; they have an unpredictable course and



may metastasize widely<sup>[1]</sup>. Common sites of metastases for carcinoid tumors are the lungs, liver, peritoneum, and regional lymph nodes. Mammographically and sonographically, breast metastases are usually well-circumscribed masses. Carcinoid metastases mammographically have been described as well-circumscribed, round or oval masses without calcification<sup>[4]</sup>. Less commonly, they can present as spiculated masses<sup>[1,5]</sup>. Sonographically, they present as well-circumscribed, solid, hypoechoic masses that may show increased vascularity<sup>[3]</sup>. One case report described an irregular, poorly defined hypoechoic mass sonographically<sup>[1]</sup>. Little has been published about the appearance of carcinoid metastases with magnetic resonance imaging. One case report describes the metastasis as an irregular, rapidly enhancing mass with washout kinetics suggestive of malignancy<sup>[1]</sup>. With an octreotide scan, breast metastases may show tracer accumulation, although small lesions generally are beyond the resolution of the scan, particularly if single photon emission CT is not performed.

Approximately 5–7% of carcinoid tumors secrete biochemical agents, particularly serotonin, adrenocorticotrophic hormone, histamine, dopamine, substance P, neurotensin, prostaglandins, and kallikrein, which may produce symptoms of carcinoid syndrome, including facial flushing and diarrhea<sup>[7]</sup>. Classically, this is due to ileal carcinoid with hepatic metastases. If the tumor is extra-intestinal, carcinoid syndrome may be produced without hepatic metastases.

A few reports have described carcinoid crises provoked by surgical handling of the tumor, fine-needle aspirations of hepatic metastases, bronchoscopy of bronchial carcinoid<sup>[7,8]</sup>, and mammography in a patient with a carcinoid metastasis to the breast<sup>[7]</sup>. All patients had carcinoid syndrome. Fine-needle aspiration of breast lesions without sequelae has been reported in patients with carcinoid syndrome, but this method may be inadequate for the histologic diagnosis of carcinoid, making core needle biopsy necessary. Core needle biopsies of breast lesions in patients without carcinoid syndrome have been performed safely. Five patients in our series had carcinoid syndrome (flushing, diarrhea, abdominal pain) and 5 did not have symptoms. No complications occurred in any patient after core needle biopsy. Recognition of the potential risk, including access to resuscitation equipment and potential need for octreotide administration, is suggested in the literature<sup>[1]</sup>.

Approximately 23 cases of carcinoid tumor metastatic to the breast have been reported<sup>[3,5,9]</sup>: 14 had a known history of carcinoid tumor, and breast metastasis was the first manifestation of an occult carcinoid tumor for 9. Of the patients with known carcinoid, the primary tumor was diagnosed in the gastrointestinal tract, pancreas, kidney, ovary, or lung. These tumors were diagnosed 1–28 years before breast metastasis was discovered (mean, 6 years). Seventeen of the 23 patients had solitary lesions, and the remainder had multiple lesions. For the 9

patients first presenting with breast metastases, the primary tumor was in the ileocecum ( $n=6$ ), appendix ( $n=1$ ), ovary ( $n=1$ ), and an unknown location ( $n=1$ ). More than two-thirds of the patients had carcinoid syndrome. In the literature, most metastatic carcinoid tumors are surgically excised without axillary clearance. Thirteen of the 23 patients, however, had preliminary diagnoses of primary breast malignancy and underwent breast cancer surgery (mastectomies), including 5 with a known history of carcinoid tumor<sup>[10]</sup>. As it was for 2 of our patients, the pathologic diagnosis of metastatic carcinoid is difficult to establish; the lesion can be misdiagnosed as primary invasive ductal carcinoma, leading to unnecessary surgery or chemotherapy. Systemic therapy with somatostatin analogues, chemotherapy, or octreotide-targeted therapy may be more appropriate for women with widely disseminated disease.

## Conclusion

Carcinoid tumor metastatic to the breast is rare. A breast mass may be the presenting finding of an occult carcinoid tumor. The breast lesion may present as long as 28 years after the initial diagnosis of a carcinoid tumor. Lesions may mimic primary breast carcinoma on imaging studies and histologically. Recognition of this entity is important to prevent unnecessary treatment for primary breast cancer.

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