Metastatic carcinoid presenting as a breast lesion

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ABSTRACT

Metastasis to the breast is a rare occurrence, constituting fewer than 2% of all breast tumours. Of all metastatic tumours in the breast, most arise from contralateral breast primaries. Other reported primary solid tumour sites include melanoma; lung, gastric, and renal cancers; and approximately 29 cases of carcinoid tumour.

Ambiguous presentations and an absence of carcinoid syndrome features make accurate radiographic and histologic assessment of breast carcinoids challenging. Here, we report the case of a 52-year-old woman who presented with a mammographic abnormality in the left breast. Excisional biopsy revealed histopathology consistent with carcinoid. After an exhaustive work-up, carcinoid within the terminal ileum was ultimately identified, and the woman was diagnosed with metastatic breast carcinoid, an exceedingly rare entity. This paper describes the common mammographic, cytologic, and immunohistochemical features typical of metastatic breast carcinoid tumours, together with their common clinical features, prognosis, and treatment options.

KEY WORDS

Breast cancer, carcinoid, metastasis, neuroendocrine

1. CASE DESCRIPTION

In January 2006, a 52-year-old woman underwent routine screening mammography and was found to have a small abnormality in the upper outer quadrant of the left breast at the two o'clock position. The mass was nonpalpable, and the patient deferred follow-up of the abnormality until September, when she presented for a repeat mammogram. At this time, repeat left mammography showed a nodule in the upper outer quadrant, which was estimated at 12×9 mm (Figure 1). A core needle biopsy of the left breast was performed and revealed a low-grade tumour suggestive of neuroendocrine origin.

Approximately 1 month later, the patient underwent radiolabelled octreotide imaging which was negative for increased uptake within the left breast. There was, however, a linear focus of increased uptake in the mid-left and distal left femur, which persisted on both the initial 4-hour and the 48-hour images (Figure 2). Follow-up plain radiography of the left femur showed mild degenerative changes, but no abnormalities suggestive of osseous pathology.

Urine free and fractionated metanephrines, normetanephrine panel, complete blood count, and chemistry panel were all within normal range. Upper endoscopy with small-bowel follow-through examination was unremarkable. The breast lump was nonpalpable, and the patient had not experienced any clinical signs or symptoms suggestive of carcinoid syndrome.

The patient's past medical history was significant for type 2 diabetes mellitus and diverticulitis. Her family history included a mother with lymphoma, a brother with prostate cancer, and multiple first-degree relatives with type 2 diabetes mellitus.
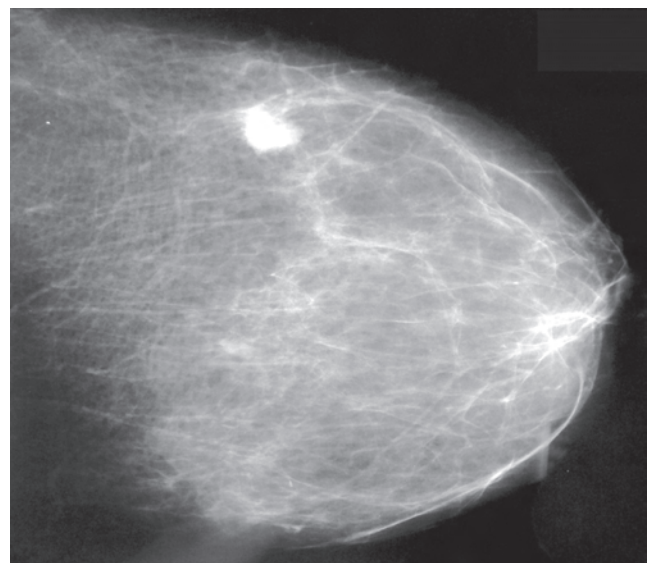

FIGURE 1   Follow-up left cranial–caudal mammogram showing a nodule detected at the two o'clock position.
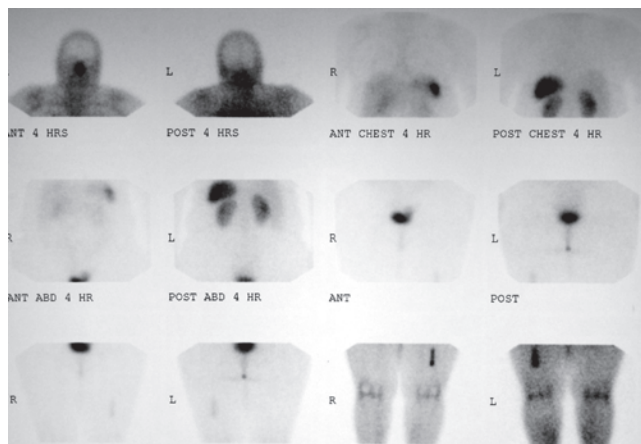
FIGURE 2   Radiolabelled octreotide imaging, September 2006. No uptake in the region of the left breast tumour is seen. Additional uptake appreciated within the mid-left and distal left femur.

The patient underwent an elective wire localization lumpectomy with sentinel lymph node sampling. The final pathology report was congruent with her earlier diagnosis, revealing a low-grade neuroendocrine tumour approximately 0.9 cm in greatest dimension with areas of focal hemorrhage, fibrosis, and hemosiderin-laden macrophages. The sentinel lymph node was negative.

Postoperatively, the woman underwent whole-breast radiation therapy. Repeat octreotide imaging subsequently revealed an ileal mass, omental and liver deposits, and a metastatic lesion in the femur. The patient underwent intra-abdominal debulking, radiation treatment to the femur, and octreotide therapy. Two years postoperatively, she remained on octreotide with no evidence of intra-abdominal disease progression. Mammograms remained negative.

1.1 Cytologic Findings

The initial core needle biopsy revealed an organoid tumour composed of cords and sheets of cells without nuclear enlargement. Cells varied in both size and shape, ranging from round to oval. There was evidence of stippled chromatin and inconspicuous nucleoli. All cells had a low mitotic index and eosinophilic to amphophilic cytoplasm. The adjacent stroma consisted of dense eosinophilic collagen. The surrounding breast tissue was composed of normal fibroadipose tissue with ducts and lobules. Initial estrogen and progesterone receptor staining was negative. Chromogranin and synaptophysin stains were weakly positive.

Histology findings from the lumpectomy were similar to those from the core needle biopsy and included well-approximated breast tissue surrounding an organoid tumour. Grossly, the tumour was firm, fibrotic, and septated by a delicate fibrovascular network (Figures 3 and 4). Focal areas of hemorrhage without evidence of necrosis were noted. Microscopic examination revealed cells arranged in

FIGURE 3   Gross specimen of wire localization biopsy. Tumour approximately 0.9 cm at greatest diameter. Fibrosis noted throughout the specimen with focal areas of hemorrhage. Specimen surrounded by normal breast tissue.
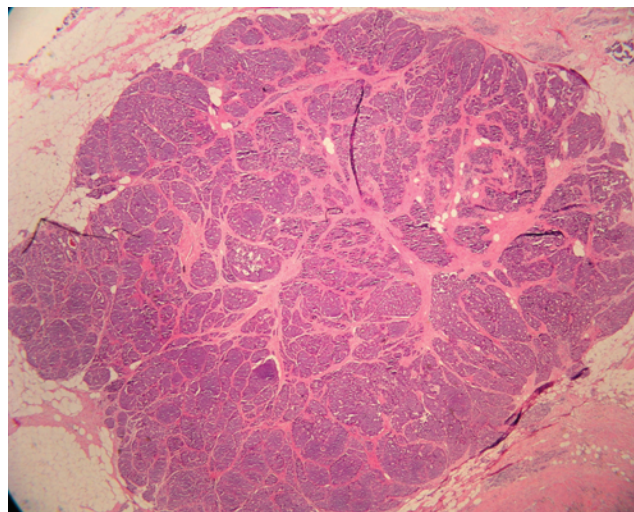

FIGURE 4   Delicate stromal network of dense eosinophilic collagen septating carcinoid tumour cells. Hematoxylin and eosin stain, 20× magnification.

cords and sheets and showing nuclear enlargement with stippled chromatin and inconspicuous nucleoli (Figure 5). Cellular cytoplasm was expressed as both eosinophilic and amphophilic (Figure 6).

No lobular or ductal differentiation of the tumour was noted. The tumour was septated by a delicate stromal network consisting of dense eosinophilic collagen. Surrounding the tumour were areas of cystic change and the occasional hemosiderin-laden macrophage, consistent with the previous biopsy site. The tissue surrounding the tumour was composed of mammary ducts and lobules with intervening fibroadipose tissue. The lymph node contained sinus histocytosis with primary and secondary lymphoid follicles and germinal centers.
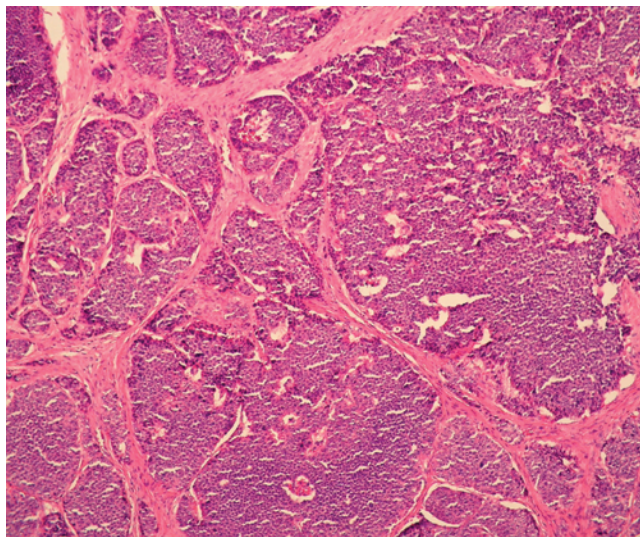
FIGURE 5   Aggregates of carcinoid tumour cells arranged in sheets and cords with intervening fibrovascular tissue. Ductal and lobular mammary cells are absent. Hematoxylin and eosin stain, 200× magnification.
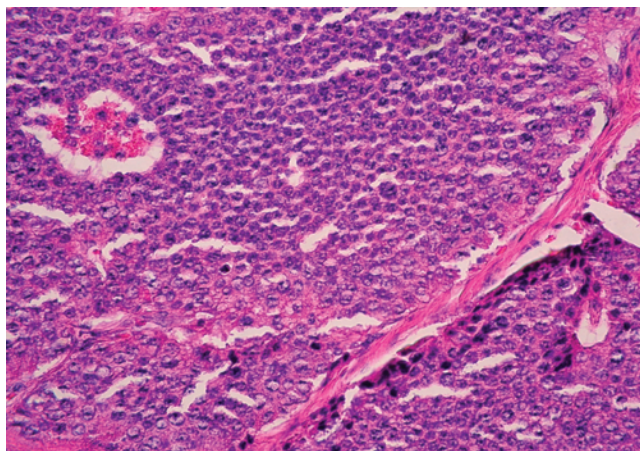

FIGURE 6   Cytoplasm ranges from eosinophilic to amphophilic. Occasional hemosiderin-laden macrophages present. Carcinoid cells showing nuclear enlargement with stippled chromatin and inconspicuous nucleoli. Cells are markedly variable in size and shape, ranging from round to oval. Mitotic activity is low. Hematoxylin and eosin stain, 400× magnification.

1.2   Immunohistochemical Findings

Formalin-fixed, paraffin-embedded immunostaining revealed that the tumour cells were strongly positive for chromogranin, synaptophysin, and cytokeratin, and weakly positive for CD56 (Figures 7 and 8). Tests for estrogen, progesterone, and HER2/*neu* were negative. Sentinel lymph node cells were negative for pankeratin.

2.   DISCUSSION

Carcinoid tumours represent a class of slow-growing neuroendocrine malignancies with a limited but
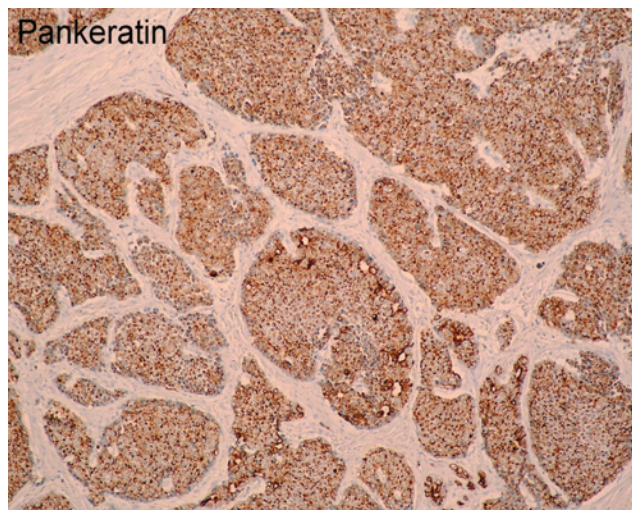

FIGURE 7   Immunohistochemical stain positive for pankeratin, with diffuse uptake among tumour cells. 200× magnification.
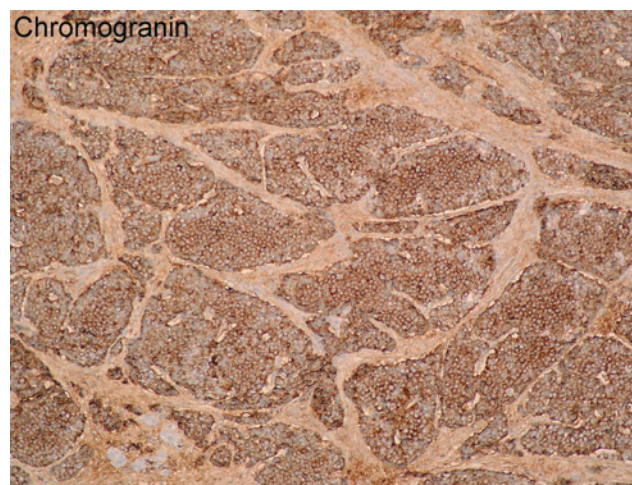

FIGURE 8   Immunohistochemical stain positive for chromogranin A. Diaminobenzidine chromogen, 200× magnification.

well-recognized predisposition for metastasis. Derived from enterochromaffin cells, carcinoid tumours may manifest in a variety of locations, including the gastrointestinal system, trachea, bronchus, and kidneys, among others. In 1982, Kashlan et al. [1] described the first case of carcinoid metastatic to the breast. Metastatic carcinoid to the breast remains a rare entity that is difficult to diagnose and is often mistaken for more common breast conditions.

Breast carcinoid is typically detected because of a palpable breast lump or an abnormal mammogram. Most patients do not present with pain or nipple discharge, symptoms that can be representative of primary ductal or lobular breast carcinoma [2]. Carcinoid syndrome is rare with breast carcinoid and, if present, indicates metastatic involvement of the liver. The high rate of bilateral breast occurrence should prompt a contralateral breast work-up in each presentation [3–5]. Men presenting with symptoms of mammary malignancy

should also be screened for carcinoid, given its heightened prevalence in that population [5–7].

Mammography is frequently used to detect these unusual neoplasms. However, their typical presentation as sharply circumscribed masses can lead to misinterpretation as a fibroadenoma, medullary carcinoma, mucinous carcinoma, or cyst [8]. Thus, early follow-up with core biopsy remains an essential first step in the evaluation process. Pathology suggesting neuroendocrine features should prompt a complete lumpectomy, because morphologic distinction on core biopsy may be misinterpreted as an infiltrating ductal carcinoma [9]. A complete work-up should include a thorough gastrointestinal evaluation, including esophagogastroduodenoscopy and colonoscopy, chest radiography, and radiolabelled octreotide imaging to evaluate for extramammary origin. In our case, a work-up of this sort led to the correct diagnosis of metastatic breast carcinoid.

Histology examination is the most useful method of diagnosing a carcinoid tumour, but the morphologic distinction between breast adenocarcinoma with neuroendocrine features and metastatic carcinoid is challenging. In both conditions, cellular patterns range from nests (as seen in ductal cell carcinoma) to cords (as seen in lobular cell carcinoma) [10]. To date, there is no convincing evidence to suggest that the presence of these patterns is predictive or prognostic. The histology manifested in our patient contained both of the foregoing structural designs (Figure 6). Cellular aggregates are separated by a delicate fibrovascular stroma. Cases of unique cellular arrangements, including rosette-like structures and features of nuclear palisading have been reported [11].

Another feature common to carcinoid tumours is the unique stippled chromatin patterns described as a "salt and pepper" appearance (as seen in Figure 7). The chromatin is typically situated in a background of eosinophilic cytoplasm. Cells are well differentiated with slight variation in size and shape ranging from oval to round. Nucleolar appearance may vary and thus is not recommended as a diagnostic indicator.

One of the most prominent features of carcinoid tumour cells is the presence of dense core neurosecretory granules. The granules can be detected with stains such as chromogranin, synaptophysin, and neurone-specific enolase. Positive chromogranin staining can be found in granule-containing endocrine cells, central and peripheral nerves, and most neuroendocrine tumours. Synaptophysin will label most neoplasms of neuroendocrine origin, including neuroblastomas, ganglioneuroblastomas, ganglioneuromas, pheochromocytomas, chromaffin paragangliomas, and non-chromaffin paragangliomas. Epithelial neuroendocrine neoplasms of the lung and gastrointestinal tract and skin will also be reactive. The positive staining for both chromogranin and synaptophysin in this patient's specimen strongly suggests that the tumour was of neuroendocrine origin.

In an attempt to evaluate for invasive ductal and lobular carcinoma, the specimen was sampled for estrogen and progesterone receptors, with negative results. Recent reports have suggested that testing for such receptors provides little information, because a high percentage of carcinoid tumours, mammary and extramammary alike, can display positive staining for both receptors [11,12]. The differential diagnosis for primary mammary carcinoid includes mammary non-Hodgkin lymphoma, lobular and ductal adenocarcinoma, and metastatic carcinoid tumour [11]. An accurate diagnosis is essential to develop an optimal treatment plan.

The prognosis for mammary carcinoid is similar to that for other primary breast carcinomas, correlating with stage, size, and lymph node status. To date, no studies comparing the prognosis of primary and metastatic breast carcinoid have been performed. In general, localized spread in primary breast carcinoid has been reported to have favourable outcomes. Roughly 18% of all mammary carcinoid cases have involved nodal or distant metastases, which occurred only after the tumour had achieved a size of 2.5 cm or greater with 10 or more mitoses per high-power field [13]. The most common locations for metastasis have been bone, liver, brain, and lung [14]. Metastatic breast carcinoid appears to carry with it a prognosis similar to that of carcinoid metastatic to other locations.

Treatment for primary mammary carcinoid is also similar to that for other primary breast carcinomas and includes lumpectomy for small lesions or modified radical mastectomy for greater disease spread. Adjuvant radiation therapy may be used in doses similar to those applied to ductal and lobular cell carcinomas. Chemotherapeutic agents such as cisplatin and etoposide have been proven efficacious.

3. CONCLUSIONS

We present an interesting case of metastatic carcinoid, initially presenting as a breast lesion. The patient was evaluated appropriately and was ultimately found to have carcinoid metastatic to the breast. Although rare, this disease is attracting increased interest as more physicians become aware of its existence. Continued research is needed in the areas of immunochemical tumour staining techniques for, and possible genetic predispositions to, this entity. We hope that research efforts will continue in the attempt to improve prevention, treatment, and long-term quality of life.

4. REFERENCES

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