Metastatic Neuroendocrine Tumor Found on Screening Mammogram

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ABSTRACT

Background: Tumor metastatic to the breast is uncommon, and a neuroendocrine tumor metastatic to the breast is even more unusual. The breast lesion can be the first manifestation of a nonmammary malignancy.

Methods: Metastatic neuroendocrine tumors to the breast have been described in the literature in case reports or very small case series. Because of the small number, current treatment recommendations are not well defined. We present a case report of a metastatic neuroendocrine tumor that first presented as a breast lesion on screening mammography.

Conclusion: Accurate diagnosis is important for appropriate management, as the treatment for a breast primary neuroendocrine tumor is different than a neuroendocrine tumor metastatic to the breast.

INTRODUCTION

Neuroendocrine tumors comprise a diverse group of neoplasms including carcinoid tumors, islet cell tumors, neuroblastomas, and small-cell carcinoma of the lung. They vary widely in clinical characteristics, but the presence of neurosecretory granules, detected with immunochemical staining, is diagnostic. Primary neuroendocrine tumors in the breast are rare, first described by Cubilla and Woodruff in 1977, and account for <0.1% of all breast cancers and <1% of all neuroendocrine tumors.[1] Metastatic tumors to the breast also are uncommon and represent approximately 1% to 2% of all breast tumors.[1] Melanoma is the most common malignancy to metastasize to the breast in adults, followed by lung, stomach, ovary, kidney, and lymphoma. In children, rhabdomyosarcoma is the most common primary tumor to metastasize to the breast.[2]

CASE REPORT

A 69-year-old asymptomatic woman presented to the Clinical Cancer Center at the Medical College of Wisconsin in May 2010 with a screening mammogram that demonstrated a new 6-mm round nodular density in the left breast. She had undergone yearly screening mammograms prior to this finding, which all were unremarkable. This density was further imaged with diagnostic mammogram (Figure 1); ultrasound, which demonstrated a 4-mm hyperechoic oval mass with a smooth margin; and, because of suspicion of malignancy, ultrasound-guided biopsy. The pathology of the lesion was neuroendocrine carcinoma, large-cell type, grade II, triple negative for (Estrogen receptor) ER, (progesterone Receptor) PR, and HER2/*neu*. It stained positive for chromogranin and synaptophysin on immunohistochemistry. Because primary breast neuroendocrine tumors are exceedingly rare, a metastatic workup was performed. A routine screening colonoscopy performed prior to mammography demonstrated several tubular adenomas in the cecum, but no evidence of a primary neuroendocrine tumor.

On the computed tomography scan of the abdomen and pelvis, the patient had extensive hepatic metastases (Figure 2) as well as masses in the head and proximal body of the pancreas and a soft-tissue mass in the root of the mesentery near the duodenum and adjacent to the ascending colon (Figure 3). Octreotide scan demonstrated increased activity in the liver consistent with metastatic neuroendocrine lesions, but no increased activity in the pancreas. Ultrasound-guided biopsy of 1 of the liver lesions also was positive for metastatic neuroendocrine tumor. Her serum chromogranin A level was significantly elevated at

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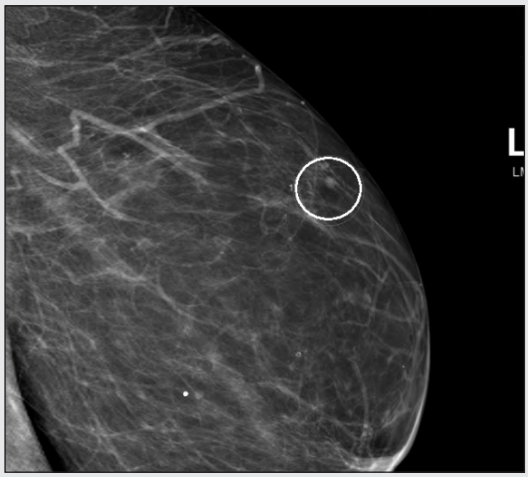

Figure 1. Diagnostic mammogram of the left breast. New 6-mm lesion at 12 o'clock within the circle.

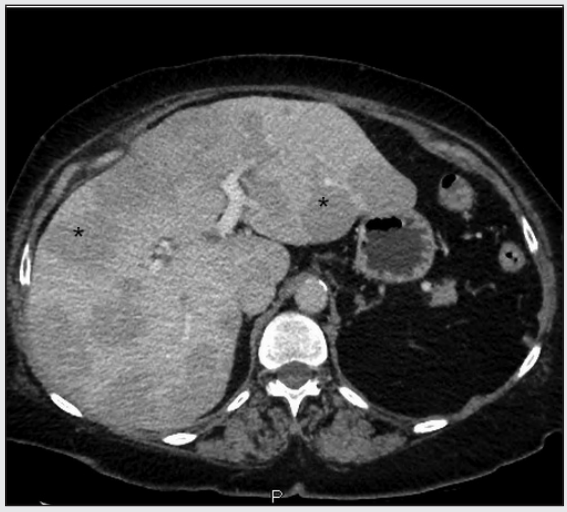

Figure 2. Cross-sectional images from abdominal CT scan demonstrating extensive hepatic metastases. Asterisks annotate 2 of the larger lesions.

878.4 ng/mL (reference: <36.4 ng/mL) with a normal neuron specific enolase (NSE) level of 6.2 ug/L (reference: 3.7-8.9 ug/L). She was deemed a nonoperative candidate because of her extensive liver tumor burden as well as involvement of her right and middle hepatic veins. She was referred to interventional radiology, where the patient was started on a clinical trial to receive selective internal radiation therapy (SIRT) with the goal of debulking her tumor for palliation. She also was referred to medical oncology to discuss systemic chemotherapy options. Upon further questioning, the patient admitted to intermittent flushing and several loose stools per day. She was started on systemic octreotide to address these symptoms and improve her progression-free survival based on the PROMID study.[3]

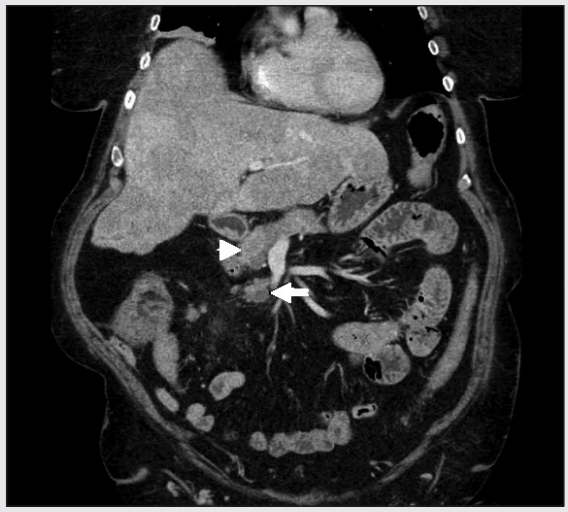

Figure 3. Coronal images from abdominal CT scan. The white arrow head points to a 2.2-cm mass in the head of the pancreas. The white arrow points to a soft-tissue mass in the mesentery adjacent to the superior mesenteric vein.

DISCUSSION

Neuroendocrine tumors are uncommon, slow-growing tumors originating from neoplastic transformation of enterochromaffin or Kulchitsky cells. They arise most commonly in the gastrointestinal tract and bronchopulmonary system, with an overall prevalence of 1 to 2 cases per 100,000 people. Carcinoid syndrome, including flushing, diarrhea and bronchospasm, occurs in about 5% to 10% of patients with neuroendocrine tumors. In 2003, the World Health Organization (WHO) classified primary neuroendocrine tumors of the breast into solid neuroendocrine carcinoma, small-cell/oat-cell carcinoma, and large cell neuroendocrine carcinoma.[4] The diagnosis of a primary neuroendocrine tumor of the breast may be made if nonmammary sites are confidently excluded or if there is the presence of a ductal carcinoma in situ component within the specimen. Neuroendocrine tumors also can metastasize to the breast. It is important to differentiate between a primary breast neuroendocrine tumor and metastatic disease to the breast because of the differences in treatment.[5] A clinical history of a prior neuroendocrine tumor elsewhere in the body may be helpful in making this diagnosis.

Histologically, neuroendocrine tumors typically form nests or sheets consisting of a uniform population of cells with abundant eosinophilic cytoplasm and round nuclei. More than 50% of the cell population must be immunoreactive for at least 1 neuroendocrine marker, including chromogranin, synaptophysin, and neuron-specific enolase.[1] A neuroendocrine tumor will typically be negative for cytokeratin 7, whereas true breast carcinomas will strongly express cytokeratin 7.[6] Staining for estrogen and progesterone hormone receptors may not

be helpful in differentiating between a breast carcinoma and a primary neuroendocrine tumor of the breast, because the receptor status may be positive in both cases.[7] Metastatic neuroendocrine tumors to the breast typically have negative hormone receptors.[2]

The mammographic appearance of a neuroendocrine tumor of the breast is that of a round, sharply circumscribed mass. This is in contrast to a breast carcinoma, which usually has more ill-defined or spiculated edges. Microcalcifications, which often are present in a breast carcinoma, usually are absent with a neuroendocrine tumor of the breast. On breast MRI, a neuroendocrine tumor of the breast shows early enhancement, similar to a breast carcinoma. On ultrasound, the tumor may appear as a hypoechoic solid mass with increased vascularity,[8] which also may be seen with primary breast cancer. However, these imaging characteristics are not sufficient for a diagnosis, and fine-needle aspiration or core-needle biopsy examination is necessary for definitive diagnosis. Caution must be taken when biopsying a lesion in patients with a hormonally active tumor because there have been case reports of biopsy precipitating a carcinoid crisis.[6]

The data have been conflicting about the prognosis of primary neuroendocrine tumors of the breast. Some studies have suggested that patients have a better prognosis with a primary neuroendocrine tumor of the breast compared to patients with invasive ductal carcinomas. However, the reason for this finding may be that previous studies had a selection bias, with a large proportion of patients with solid papillary and/or mucinous types of neuroendocrine tumors of the breast, which tend to be well differentiated and are associated with a better prognosis.[7,9] However, there are other variants of neuroendocrine tumors of the breast, including small cell and large cell that are poorly differentiated and tend to carry a worse prognosis. Higher nuclear grade also is associated inversely with disease-free and overall survival.[7] Therefore, when considering all variants of primary neuroendocrine tumors of the breast, this disease has a higher tendency for local and distant relapse and poorer overall survival when compared to primary breast carcinoma.[7] The median survival for a patient with metastatic primary neuroendocrine tumor of the breast is 14 months.[10]

Neuroendocrine tumors found in the breast also may be metastatic from another primary source. There is a tendency for these tumors to have late metastases, which may be focal or widespread and diffuse, as in our patient. The ileum is the most common primary site for metastatic breast carcinoids tumor, followed by the appendix, duodenum, pancreas, lung, and ovary.[11] The first case of a carcinoid tumor metastatic to the breast was found on autopsy and was reported in the literature in 1957.[11] In a review of the literature, Upalakalin found that 59 cases of carcinoid tumors in the breast had been reported, 9 of which were metastatic lesions with an occult primary carcinoid tumor.[5] The mean age of presentation was 56.[5] Patients with metastatic neuroendocrine tumors to the breast appear to present on average 10 years younger than patients with primary neuroendocrine tumors of the breast, which typically occur in patients in their 6th and 7th decade of life.[9]

There is a lack of clear recommendations regarding the surgical management of these uncommon tumors. It appears that primary breast neuroendocrine tumors should be treated in a similar manner to invasive ductal carcinoma appropriate for the size and stage of the lesion, including mastectomy or breast-conserving therapy with lumpectomy and negative margins, as well as axillary staging with sentinel lymph node biopsy.[5] The use of adjuvant treatment with endocrine and radiation therapy has shown a trend in survival benefit, as reported in a case-controlled study by Wei et al, though none of these reached significance because of a lack of statistical power.[7] However, they found that standard chemotherapy was associated with a poorer outcome.

Historically, patients with breast metastases from neuroendocrine tumors of another source were subjected to mastectomy because the lesion was often erroneously diagnosed as a primary carcinoma, and the diagnosis was made only after reviewing the histology of the mastectomy specimen. If patients with metastatic neuroendocrine tumors to the breast are surgical candidates, meaning they may have only a few isolated metastases that are amenable to resection, they should undergo lumpectomy alone. Mastectomy would be indicated only if there were numerous or very large metastatic neuroendocrine tumors to the breast. Multiple resections may be performed if more than 1 lesion is present and breast-conserving surgery is desired, as this aids in local control.[5,12] Axillary node dissection is not necessary in the case of metastatic disease, but may be considered if palpable adenopathy is present.[5] Complete surgical resection of both the primary tumor and metastasis is curative, but resection of metastatic disease alone may offer survival advantage over no resection.[13] Liver metastases that are too bulky for resection can be managed with arterial-based liver-directed therapies such as transarterial embolization (TAE), transarterial chemoembolization (TACE), and SIRT. These methods have been shown to reduce hormone levels, palliate symptoms, and reduce tumor burden.[14]

Systemic therapy is still the cornerstone for metastatic malignancies. However, existing options remain suboptimal for metastatic neuroendocrine tumors, and it remains to be determined what the most appropriate systemic regimen should be. Somatostatin analogs can control symptoms and stabilize certain slow-growing tumors, but they rarely result in tumor

regression.[3,15] Metastatic neuroendocrine tumors have been responsive to platinum-based combination regimens, but systemic chemotherapy overall is minimally effective.[15] A multimodality approach is typically the most appropriate method of treatment for a patient with unresectable disease.

CONCLUSION

In summary, we present a patient with a breast lesion found on screening mammography that was the first detected site of a metastatic neuroendocrine tumor. It is important to determine whether the neuroendocrine lesion of the breast is a primary tumor or a metastatic tumor when biopsy confirms this diagnosis. Finally, it is important to search for the primary tumor when it is determined that the tumor is metastatic.

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Quiz: Metastatic Neuroendocrine Tumor Found on Screening Mammogram

EDUCATIONAL OBJECTIVES

1. To understand the diagnostic approach to the patient found to have a neuroendocrine tumor of the breast and the importance of differentiating whether it is a primary or metastatic tumor.
2. To understand some of the specific characteristics of neuroendocrine tumors, particularly as they present as breast masses.
3. To understand some of the treatment options available for patients with neuroendocrine tumors of the breast.

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QUESTIONS

1. Neuroendocrine tumors include all except:
   A. Carcinoid tumors
   B. Islet cell tumors
   C. Neuroblastomas
   D. Ductal cell breast carcinoma
   E. Small cell carcinoma of the lung

Answer:

- ❑ A
- ❑ B
- ❑ C
- ❑ D
- ❑ E
- ❑ A and C
- ❑ B and D

2. Which of the following markers is not typically seen in neuroendocrine tumors:
   A. Chromogranin
   B. Cytokeratin 7
   C. Synaptophysin
   D. Neuron-specific enolase

Answer:

- ❑ A
- ❑ B
- ❑ C
- ❑ D
- ❑ All of the above
- ❑ None of the above

3. Which of the following statements is/are incorrect:
   A. Neuroendocrine tumors originate from neoplastic transformation of enterochromaffin or Kulchitsky cells.
   B. Primary neuroendocrine tumors of the breast may express estrogen (ER) and progesterone (PR) receptors while metastatic neuroendocrine tumors are generally negative for ER and PR.
   C. In general, primary neuroendocrine tumors of the breast have less tendency for local and distant relapse with a better overall survival when compared to primary breast cancer.
   D. The mean age of presentation of patients with metastatic neuroendocrine tumors to the breast is 10 years younger than patients with primary neuroendocrine tumors of the breast.

Answer:

- ❑ A
- ❑ B
- ❑ C
- ❑ D
- ❑ A and C
- ❑ B and D
- ❑ All of the Above

4. Carcinoid syndrome, which may include flushing, diarrhea, and bronchospasm, occurs in a majority of patients with neuroendocrine tumors.

Answer:

- ❑ True
- ❑ False

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