Case Report

Metastatic breast neuroendocrine tumor from the rectum

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ABSTRACT

يعد ورم الثدي النقيلي العصبي الصماوي من الأمراض النادرة للغاية، وهذا المرض عادة ما يشخص تشخيصاً خاطئاً في البداية. يتعرض المرضى كثيراً لعمليات استئصال الثدي مع تشريح إبطي للعقد اللمفاوية. ويعد التشخيص الصحيح لهذا الورم حاسماً وذلك نظراً إلى اختلاف طرق العلاج السريرية لورم الثدي الرئيسي. نستعرض في هذا المقال حالة مصابة بورم الثدي النقيلي العصبي الصماوي من المستقيم كما أنه منتشر إلى الثدي وفشل في الاستجابة للعلاج الكيماوي.

Metastatic breast neuroendocrine tumor is an exceedingly rare entity. They are commonly initially misdiagnosed as primary breast carcinoma. Correct diagnosis of this tumor is crucial owing to the different clinical management from primary breast tumor. We report an additional case of metastatic breast neuroendocrine tumor from the rectum that behaved in an aggressive fashion and failed to respond to chemotherapy treatment.

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Breast metastases from non-mammary malignant neoplasms are rare, accounting for less than 2% of all breast tumors.[1-4] Common tumors that metastasize to the breast include those from the lung, melanomas, thyroid, kidney, hematopoietic system and gastrointestinal system.[3,4] Only a few cases of metastatic breast neuroendocrine tumor (carcinoid) have been reported in the literature, and more than half of these cases were initially misdiagnosed as primary breast carcinoma causing serious consequences for the patients with unnecessary surgical treatment. Clinically, radiologically, and pathologically metastatic breast neuroendocrine tumor can be easily mistaken for primary breast carcinoma. The proper recognition of such tumors is very important owing to the different clinical management of these patients. In this report, we describe a case of metastatic breast neuroendocrine tumor originating from a primary rectal tumor. The use of immunohistochemistry, together with a careful review of the patient's medical history helped in diagnosing this tumor.

Case Report. A 51-year-old woman presented with a palpable right breast lump. The mammogram revealed a well-circumscribed mass that measured 2 x 1.5 cm. She refused fine needle aspiration (FNA). A lumpectomy was performed and microscopic evaluation showed that the tumor was composed of sheets of small uniform cells divided into lobules by delicate vascular septa. The tumor cells revealed uniform round nuclei with inconspicuous nucleoli and a moderate degree of eosinophilic cytoplasm (**Figures 1a & 1b**). No evidence of ductal carcinoma in situ could be identified. Immunohistochemical analysis showed that the tumor cells were strongly positive for the neuroendocrine markers, including neuron-specific enolase, chromogranin A, and synaptophysin (**Figures 1c & 1d**). The tumor cells were negative to cytokeratins 7 and 20, estrogen, and progesterone receptors, c-Erb-B2 antibodies, and carcinoembryonic antigen. P63 and CD10 revealed the absence of the myoepithelial layer. The tumor involved the surgical margin. A review of her history demonstrated that she had a rectal neuroendocrine tumor that was resected

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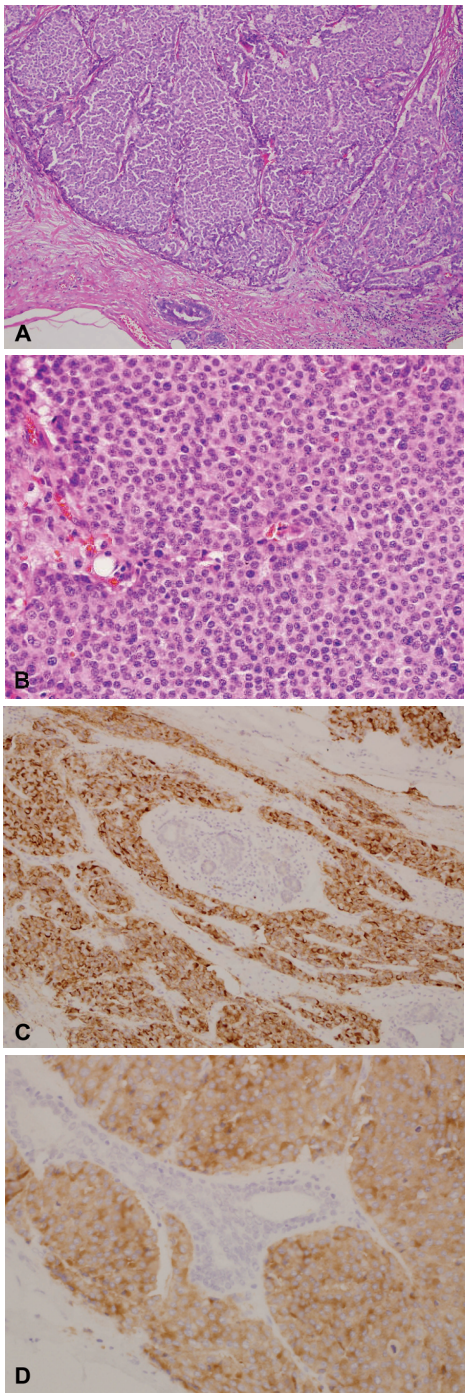

Figure 1 - Histopathological findings showing **A)** Section from the tumor composed of sheets and lobules surrounded by delicate vascular septa (hematoxylin-eosin, original magnification X100) **B)** Higher power reveals uniform cells with inconspicuous nucleoli and a moderate degree of eosinophilic cytoplasm (hematoxylin-eosin, original magnification X400). **C)** Immunohistochemistry stain for chromogranin reveals positive staining in the tumor cells (original magnification X200). **D)** Immunohistochemistry stain for synaptophysin reveals positive staining in the tumor cells (original magnification X400).

in another hospital by proctocolectomy 2 years ago. Only the pathology report was available from the outside institution, and no histopathology material from the rectal tumor could be retrieved. A CT scan showed multiple liver metastases. The diagnosis of breast metastatic neuroendocrine tumor from a primary rectal tumor was made. She did not show symptoms of carcinoid syndrome. She was treated with standard cytotoxic chemotherapy using a combination of 5-fluorouracil (5-FU), dacarbazine, and epirubicin; however, this did not result in any radiological response. The metastatic disease continued to progress slowly over the next one year.

Mammography performed one year later revealed 2 well-circumscribed masses behind the nipple of the right breast; each measuring 1.7 cm (**Figure 2**). Both of these were felt to represent metastases. The rest of the breast showed no evidence of microcalcification. By ultrasound, these 2 lesions were solid. Abdominal and pelvic CT revealed a heterogeneously enhancing lobulated pre-sacral mass measuring 6.2 x 3.1 cm, which was inseparable from the adjacent bowel loop, and associated with multiple regional para-aortic lymph nodes enlargement with evidence of necrosis. The known liver lesions increased in size and number. There was also a right adrenal mass that measured 3.3 x 2.5 cm. Fine needle aspiration of the pre-sacral mass confirmed a neuroendocrine tumour consistent with tumor recurrence. Her general condition continued to deteriorate and she was managed with supportive care.

Discussion. A palpable breast mass is usually suggestive of a primary breast tumor. However, the

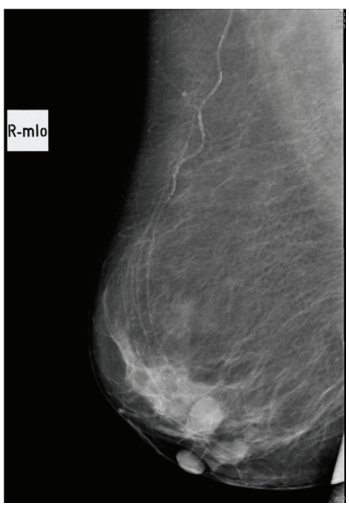

Figure 2 - Mammogram image showing recurrence of 2 well-circumscribed masses behind the nipple of the right breast.

possibility of a non-mammary secondary neoplasm should be kept in mind. Reviewing the literature through searches of Medline and PubMed revealed that fewer than 40 cases of metastatic breast neuroendocrine tumors have been described to date. The most common site of origin is the small bowel.[3] A metastatic breast neuroendocrine tumor can be easily mistaken for primary carcinoma of the breast. This may potentially be detrimental for the patient, especially if the primary surgery is a mastectomy with dissection of axillary lymph nodes. We report an additional case of metastatic breast neuroendocrine tumor that behaved in an aggressive fashion, and failed chemotherapy treatment.

Neuroendocrine tumors are slow growing tumors derived from enterochromaffin cells, and are, thus, neuroendocrine in nature. Metastatic breast neuroendocrine tumors may present clinically as single or multiple well-circumscribed lumps, with a firm consistency. Radiologically, they can appear as a spiculated lesion detected on mammography and indistinguishable from primary invasive breast carcinoma,[3] or as well-circumscribed lesions that can mimic and be interpreted as fibroadenomas, mucinous carcinoma, or medullary carcinoma.[2,5]

Morphologic distinction from primary ductal carcinomas is sometimes difficult, both on cytological and histological levels. However, features such as plasmacytoid appearance, salt-and-pepper stippled chromatin, and inconspicuous nucleoli on fine needle aspiration should raise the possibility of neuroendocrine origin.[1,2] In a review by Fishman et al,[6] 8 of 13 (61.5%) patients with metastatic breast neuroendocrine tumors were initially misdiagnosed as primary breast carcinoma and were subjected to mastectomies. Misdiagnosis of breast neuroendocrine tumor as primary breast carcinoma has also been reported even with a prior history of carcinoid tumor at a different site in the patient.[2] Most patients misdiagnosed with primary breast carcinoma have been treated with a modified radical mastectomy. Lumpectomy has been performed in only a few cases.[1,2] Indeed, in our case the tumor recurred in the same breast despite primary lumpectomy. Metastatic breast carcinoid can show estrogen receptor positivity, creating additional problems in the differential diagnosis with a primary breast carcinoma of the breast.[2]

Primary breast carcinoid tumors have been described in the literature; however, no neuroendocrine granules were detected in normal human breast tissue by immunohistochemistry or electron microscopy; therefore, the concept of primary breast carcinoid has now largely been discredited and no longer accepted.[1,2,5] The term breast carcinoma with endocrine features is favoured.[1,2,5] In the current WHO classification of breast tumors, neuroendocrine tumors included; solid neuroendocrine carcinoma (carcinoids-like), small cell/oat cell carcinoma, and large cell neuroendocrine carcinoma.[2,7] When certain microscopic histologic features are seen, the diagnosis of metastatic breast neuroendocrine tumor should be considered. Such features include a well-circumscribed lesion, the absence of an intraductal component, and the frequent presence of many lymphatic emboli.[1,2,5] Confirmation of the mammary origin of those carcinomas can be only made in the presence of ductal carcinoma in situ (DCIS) with neuroendocrine expression.[2,7] The use of smooth muscle actin, p63 or CD10 can be helpful, since in any DCIS the basal layer of myoepithelial cells still persists, while such a layer is absent in the case of metastatic carcinoid. Carcinomas of mammary origin characteristically strongly express CK7 and will not express CK20, whereas in metastatic carcinoid, both CK7 and CK20 will be negative. A large series of such tumors are lacking in the literature, with no clear recommended guidelines for management; however, mastectomy axillary lymph node dissections are not necessary. In the last few years, there have been significant developments in drug therapy of advanced neuroendocrine tumor. Long acting octreotide, m-TOR inhibitors (everolimus), and VEGF tyrosine kinase inhibitors (sunitinib) have shown anti-tumor effects and are becoming standard treatments for patients with advanced neuroendocrine tumors. For this reason, the accurate diagnosis of metastatic neuroendocrine tumor is of paramount importance. Tumor management guidelines have to be established for such a rare tumor.

In conclusion, a case of metastatic breast neuroendocrine tumor from the rectum is reported in a patient with a known history of rectal neuroendocrine tumor. Recognition of this tumor is important, as the treatment for a neuroendocrine tumor metastatic to the breast is different than a primary breast neuroendocrine tumor.

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