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CASE REPORT

A case of renal cell carcinoma metastasizing to invasive ductal breast carcinoma

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Tumor-to-tumor metastasis is an uncommon but well-documented phenomenon. We present a case of a clear cell renal cell carcinoma (RCC) metastasizing to an invasive ductal carcinoma (IDC) of the breast. A 74-year-old woman with a past history of clear cell RCC status after radical nephrectomy underwent right modified radical mastectomy for an enlarging breast mass 3 years after nephrectomy. Histological examination revealed a small focus with distinct morphological features similar to clear cell RCC encased in the otherwise typical IDC. Immunohistochemical studies showed that this focus was positive for CD10 and vimentin, in contrast to the surrounding IDC, which was negative for both markers and positive for Her2/neu. Based on the histological and immunohistochemical features, the patient was diagnosed with metastasis of clear cell RCC to the breast IDC. To the best of our knowledge, this is the first reported case of a breast neoplasm as the recipient tumor in tumor-to-tumor metastasis.

Introduction

The phenomenon of tumor-to-tumor metastasis was first documented in 1902 by Berent.[1] Although not as rare as previously believed, tumor-to-tumor metastasis is still an uncommon occurrence. Only 165 cases have been reported in the English-language literature. The most common recipient tumor is renal cell carcinoma (RCC, 38.8%), followed by meningioma (25.4%), and the most frequent donor tumor is lung cancer (55.8%). Breast neoplasms have been reported as the tumor donor in 21 (12.7%) cases, but they never had been reported as a recipient site of tumor-to-tumor metastasis. Here, we report a case of clear cell RCC metastasizing to invasive ductal carcinoma (IDC) of the breast.

Case report

A 74-year-old woman presented to our outpatient department with a progressively enlarging nontender right breast mass. She had a past history of stage III (pT3pN0cM0) grade 2 clear cell RCC after right radical

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nephrectomy in 2006. No additional intervention was given after the nephrectomy, and there was no evidence of recurrence or metastasis after 1 year follow-up. At this time, breast sonography revealed a solid mass measuring 3.75 cm × 3.72 cm × 3.22 cm with an irregular margin at 9 o'clock, 4 cm from the right nipple. Core needle biopsy revealed ductal carcinoma *in situ*. At the same time, a small nodular lesion measuring 2.2 cm in greatest dimension was found in the right upper lobe of her lung, which was shown to be metastatic clear cell RCC after computed tomography-guided biopsy and immunohistochemical confirmation [CD10(+), vimentin(+), estrogen receptor (ER)(−), progesterone receptor (PR) (−), and thyroid transcription factor-1(−)]. No local recurrence at the previous nephrectomy site was found by imaging. The patient then underwent modified radical mastectomy for the breast tumor.

On gross examination, the removed breast tissue measured 23.0 cm × 17.5 cm × 4.0 cm. On sectioning, a single solid and circumscribed mass lesion measuring 3.5 cm × 3.5 cm × 2.0 cm with a hemorrhagic area was noted; this lesion had a firm consistency and brown−tan appearance. Microscopically, the tumor was composed of solid sheets of malignant cells with stromal invasion. More than 75% of the tumor cells throughout the tumor had ductal differentiation (score 1). Multiple areas of hemorrhage were found, but there was no evidence of necrosis or calcification. The tumor cells were moderately atypical (score 2) with a low mitotic rate (score 1). These features were consistent with a score 4 (1 + 2 + 1) grade I IDC. There was no lymph node metastasis and no evidence of distant metastasis. A combined pathological and clinical stage IIA, pT2pN0cM0 tumor was diagnosed.

However, there was a small distinct focus measuring 2 mm × 2 mm in dimensions found mostly circumscribed by the IDC (Fig. 1A). The cells composing the focus were arranged in a small nest pattern with delicate fibrovascular septa. The cells exhibited clear cytoplasm with moderate nuclear atypia and conspicuous nucleoli. When encountering a clear cell tumor in the breast, differential diagnoses from primary breast tumors to metastasis from nonmammary malignant neoplasms should be considered (Table 1). Of all these differentials, clear cell RCC was first considered according to the patient's history and the striking morphological similarities upon hematoxylin and eosin staining (Fig. 2A). Immunohistochemistry showed that this distinct focus was positive for CD10 and vimentin but negative for ER, PR and Her2/neu. In contrast, tumor cells within the IDC region were negative for CD10, vimentin and ER, but they were focally positive for PR and equivocally positive (2+) for Her2/neu (Fig. 2B−D). Primary breast tumors of ductal differentiation were generally excluded based on the triple negative for ER, PR and Her2/neu, and with positive staining for CD10 and vimentin. The possibilities of adenomyoepithelioma and metastatic malignant lymphoma were further eliminated by negative staining for myoepithelial markers (calponin and smooth muscle actin), and melanocytic marker (HMB-45). It is worth noting that although S-100 protein is a sensitive marker for detecting melanoma, it is also positive in 69% and 70% of primary and metastatic clear cell RCC, respectively.[2] Thus, S-100 protein positivity alone, without other supportive evidence, has no benefit in differential metastatic clear cell RCC and metastatic melanoma. Based on the histological and immunohistochemical results noted above, the patient was diagnosed with metastatic clear cell RCC to IDC of the breast.

Discussion

The diagnosis of tumor-to-tumor metastasis requires the fulfillment of criteria originally described in 1968 by Campbell et al.[3] First, the patient must have at least two different tumors, and the recipient tumor must be a true neoplasm. Second, the metastatic neoplasm must be a true metastasis, not a contiguous growth such as a "collision tumor" or an embolism. Third, cases should be excluded if tumors metastasize to the lymphatic system that had contained a primary lymphatic malignancy. In 1984, Pamphlett[4] established three additional criteria: (1) the metastatic nidus must be at least partially enclosed by a rim of histologically distinct primary tumor tissue; (2) the existence of the primary carcinoma must be proven; and (3) the metastatic tumor must be compatible with the primary carcinoma by morphological or immunohistochemical

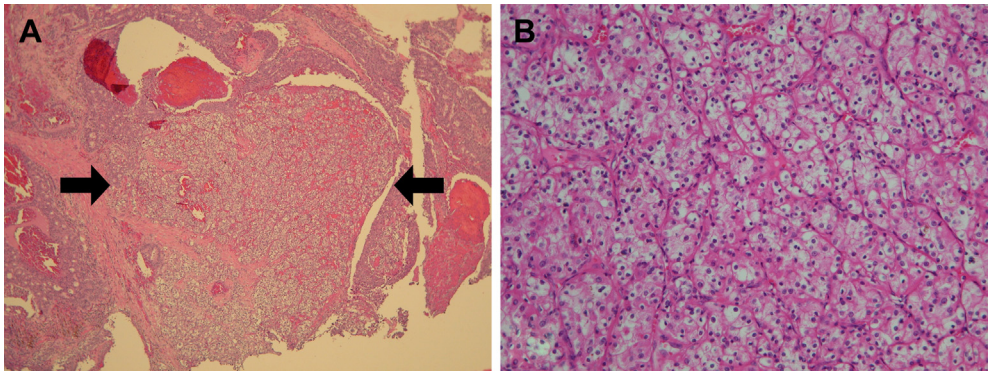

Figure 1 (A) A low-power view of the breast tumor showing a focus morphologically similar to clear cell RCC (arrow) almost entirely encased by the typical invasive ductal carcinoma. Original magnification 20×, H&E. (B) Comparing Fig. 2A with the grade II clear cell RCC in 2006 in the same patient shown in this figure, striking morphological similarity is evident. Original magnification 200×, H&E. H&E = hematoxylin and eosin; RCC = renal cell carcinoma.

Table 1 Differential diagnoses of clear cell tumors of the breast.

Primary breast tumor
Breast tumors of ductal differentiation
Glycogen-rich clear cell carcinoma
Lipid-rich carcinoma
Histiocytoid lobular carcinoma
Apocrine carcinoma
Secretory carcinoma
Breast tumors of myoepithelial differentiation
Adenomyoepithelioma
Nonmammary malignant neoplasms
Metastatic clear cell renal cell carcinoma
Metastatic malignant melanoma
Metastatic prostatic carcinoma

means. Our case met all of the above criteria; thus, it can be considered a true tumor-to-tumor metastasis.

Two theories are proposed to explain the pathophysiology of tumor-to-tumor metastasis.[5] Based on the ideas first described by Sir Steven Paget in 1889, the "seed and soil" theory proposes that metastatic tumor cells (seeds) attain successful growth and propagation in a hospitable environment (soil), such as tumors with a low metabolic rate and high collagen and lipid content. The "mechanical" theory suggested by Ewing in 1928 proposes that the recipient tumors may be particularly susceptible to metastases because of high blood flow, highly vascular architecture, and anatomical location. In these two models, RCC would be a preferential site of tumor-to-tumor metastasis, and clinical findings suggest that RCC accounts for about half of the cases.[6] Meningioma as a usually slowly growing benign neoplasm located in the fertile central nervous system, providing longer time for seeding and a nourish environment, is the second most common recipient site of tumor-to-tumor metastasis.[6] We used the keyword "tumor-to-tumor metastatsis" in PubMed to perform a literature review of English-language publications and their references. Table 2 shows the current numbers of cases and distribution of donor/recipient in tumor-to-tumor metastasis.

The breast, however, is neither an anatomical location with rich blood flow nor a fertile "soil" with good nutritional supplies. These characteristics might explain why the breast is an uncommon site of tumor metastasis. Metastasis to the breast accounts for only 0.5—1.3% of all malignant mammary tumors in clinical reports.[7] Although metastases are present in approximately 30% of all patients diagnosed with RCC,[8] only 18 cases of breast metastases of primary renal tumors have been reported,[7–14] which represent only 3% of all extramammary tumors metastasizing to the breast.[9] There are no reports of a breast neoplasm serving as a recipient in tumor-to-tumor metastasis.

Although the present patient's history of clear cell RCC and the striking dimorphic features prompted accurate

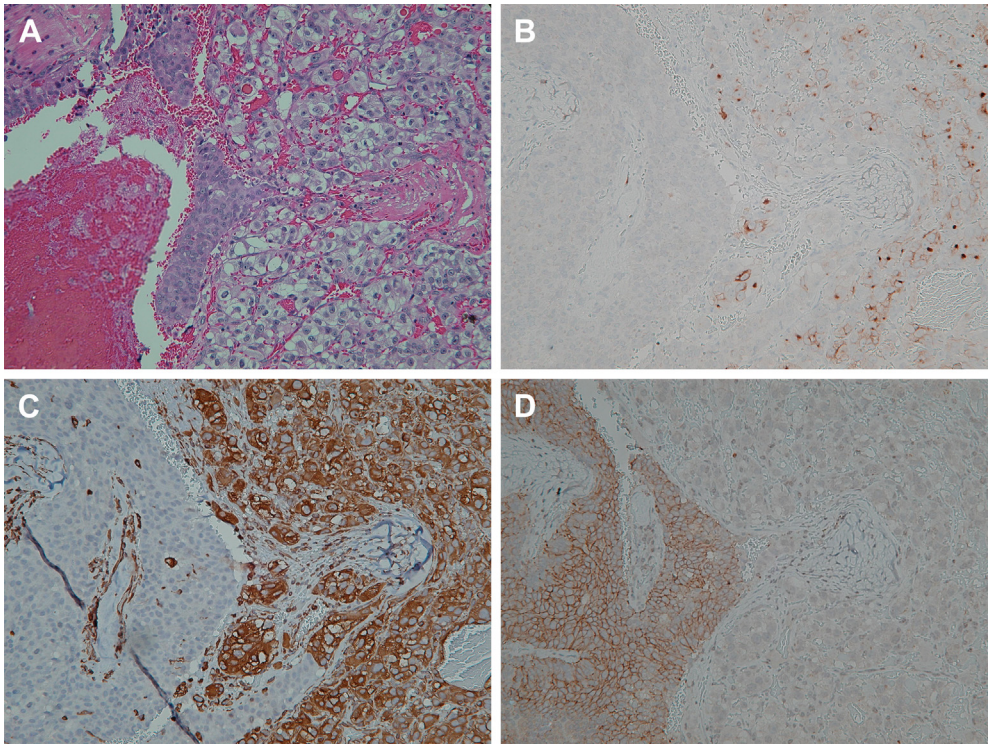

Figure 2 (A) A high-power view showing the distinct focus on the right composed by cells with clear cytoplasm and nuclear atypia arranged in nests with delicate fibrovascular septa. (B—D) Immunohistochemistry of the renal cell carcinoma-like focus showed CD10(+), vimentin(+), and Her2/neu(−). In contrast, invasive ductal carcinoma showed CD10(−), vimentin(−), and Her2/neu(2+). Original magnification 200×, hematoxylin and eosin (A), CD10 (B), vimentin (C), Her2/neu (D).

Table 2 Recipient and donor proportions in tumor-to-tumor metastases.

Recipient tumor	No. of cases	%	Donor tumor	No. of cases	%
Renal cell carcinoma	64/165	38.8	Lung cancer	92/165	55.8
Meningioma	42/165	25.4	Breast cancer	21/165	12.7
Thyroid neoplasms	14/165	8.5	Renal cell carcinoma	15/165	9.1
Others	45/165	27.3	Others	37/165	22.4

diagnosis in our case, diagnostic problems do exist in metastatic neoplasms involving otherwise normal breast tissue. There have been several reported cases initially diagnosed as primary breast tumors that were later shown to be metastatic neoplasms from extramammary origins such as clear cell RCC,[10] papillary RCC, and ovarian serous adenocarcinoma.[11] No reliable clinical features distinguish a metastatic breast lesion from primary breast cancer.[8] A history of other primary malignancies may be an important clue. However, one must keep in mind that in 20—40% of cases, breast metastases are the initial presentation of extramammary malignancies metastasizing to the breast.[11] In suspicious or difficult cases, ancillary testing such as immunohistochemical studies should be performed in addition to routine histological examination. It is important to differentiate metastatic tumors from primary breast cancer because the metastatic tumors can represent the first presentation of a previously unrevealed malignancy. The subsequent treatment and/or clinical course may be different from that for a primary breast neoplasm.[12] The presence of metastatic carcinoma to the breast is an indication of advanced disease and has a poor prognosis.[11] Over half of the patients presented with additional systemic metastases, and the median survival was 10 months.[15] Three factors determine the survival: patients who were in otherwise disease-free status, patient who had undergone mastectomy as part of the treatment, and patients with neuroendocrine primary tumors have better prognosis.[15] For our patient, mastectomy provided not only the treatment of her primary breast cancer but also might have aided her chance of survival. She is currently alive 12 months after discovery of the metastasis with the use of tamoxifen and interferon therapy.

In summary, extramammary neoplasm metastasizing to the otherwise normal breast is uncommon, and neoplasm of breast as a recipient of tumor-to-tumor metastasis has not been described previously. We report a case of IDC of the breast as the host of a clear cell RCC. Although tumor-to-tumor metastasis is an infrequent event, the incidence of this phenomenon may increase because cancer patients have improved prognoses and survival times. Identifying this phenomenon is crucial because it may significantly affect further evaluation, treatment, and prognosis.

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