Breast Mass in a Patient with Ovarian Cancer

A Case Report

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BACKGROUND: Less than 1% of malignant breast masses represent metastases from an extramammary source. Gynecologic tumors rarely metastasize to the breast. We report 2 patients who developed a breast mass following a known diagnosis of metastatic ovarian carcinoma or primary peritoneal carcinoma.

CASE REPORTS: A 28-year-old woman receiving therapy for recurrent ovarian cancer developed a breast mass with pleomorphic calcifications that was an ovarian cancer metastasis. A 61-year-old woman with primary peritoneal carcinomatosis developed a new primary breast tumor expressing CA 125 at the end of adjuvant therapy for peritoneal cancer.

CONCLUSION: Treatment and prognosis for metastatic and primary breast lesions are different, therefore accurate differentiation using radiographic and pathologic criteria is essential. We describe unique features of primary and metastatic breast lesions in patients with ovarian cancer. (J Reprod Med 2009;54:639–644)

Keywords: breast cancer, CA 125, ovarian cancer, metastasis.

Ovarian malignancies spreading to breast represent < 0.5% of breast metastases and are a consequence of hematogenous seeding.

Malignant breast masses commonly originate in the mammary gland and <1% of cases represent metastases from extramammary sources.1,2 Tumors metastasizing to the breast include lymphoma, melanoma, lung and gynecologic malignancies.1,3 Accurate differentiation between primary breast tumors and metastases to breast is essential because treatment and prognosis vary. Clinical, radiographic and pathologic criteria are used for diagnosis. We report 2 patients with breast masses following a known diagnosis of ovarian cancer or primary peritoneal carcinomatosis. One case was ovarian cancer metastasis, and the other was a primary breast tumor.

Case Report

Case 1

A 28-year-old woman presented with recurrent papillary serous ovarian cancer. She had presented 11 years previously with a right-sided pelvic mass that was stage IIIC low-malignancy-potential tumor. The patient had tumor recurrence with...
transformation to grade 1 invasive serous carcinoma 7 years later. She underwent secondary debulking and adjuvant carboplatin and paclitaxel, followed by maintenance paclitaxel. After a short remission, recurrence was treated with single-agent carboplatin and subsequently with liposomal doxorubicin. Patient was then enrolled in a phase II trial with aflibercept. After 10 months of therapy inducing disease stabilization, she developed right breast fullness. New breast microcalcifications were seen on chest computed tomography (CT), breast ultrasound and mammography (Figure 1). Biopsy revealed papillary serous carcinoma with psammomatous calcifications, morphologically similar to the primary tumor (Figure 2). Subsequent treatment included cisplatin and gemcitabine, inducing a minor response. The patient is alive, with disease, and continuing therapy for recurrent ovarian cancer.

Case 2
A 61-year-old woman presented with a change in bowel habits and abdominal distention. She underwent exploratory laparotomy and suboptimal cytoreductive surgery for stage IIIIC, poorly differentiated grade 3 serous primary peritoneal carcinomatosis. Adjuvant chemotherapy included carboplatin, taxol and gemcitabine, leading to complete remission. Five months later, she experienced an asymptomatic rise in CA 125 to 120 U/mL and began therapy with liposomal doxorubicin. Shortly thereafter, a right breast mass was found. Mammogram revealed a spiculated mass, and biopsy findings were consistent with invasive ductal carcinoma. This carcinoma was histologically different from her prior peritoneal cancer and had a Scarff-Bloom-Richardson score of 9. The breast tumor was estrogen, progesterone receptor and Her-2/neu negative. Of interest, the breast tumor stained with CA 125 (Figure 3). Further staging revealed no evidence of metastasis, and she was treated for second primary malignancy with doxorubicin and cyclophosphamide followed by mastectomy with axillary lymph node dissection. The residual tumor measured 2.6 cm, and 3 of 15 lymph nodes were positive. Following mastectomy, CA 125 declined to 25 IU/mL. Four cycles of docetaxel and radiotherapy to the chest wall followed. At the end of breast cancer therapy, the CA 125 level was 14 IU/mL. A few months later, she experienced peritoneal carcinomatosis recurrence in the mediastinum and perihilar space. Subsequent chemotherapy failed to induce remission, and she succumbed to disease. She declined genetic testing for inherited familial cancer syndrome.

Discussion
Most common malignancies metastasizing to the breast include carcinoma of the contralateral breast,
Figure 2  (Case 1) Histologic examination of ovarian tumor metastatic to the breast. A, Serous papillary ovarian cancer with psammoma bodies. (B) Serous papillary metastasis to breast (×100). (C) Serous papillary metastasis to breast (×400).

Figure 3  (Case 2) Histologic examination of primary breast tumor staining for CA 125. (A) Hematoxylin-eosin staining of a primary breast tumor. (B) CA 125 staining of breast tumor (magnification, ×400).
melanoma and bronchogenic carcinoma. Ovarian malignancies spreading to breast represent <0.5% of breast metastases and are a consequence of hematogenous seeding. This explains their rarity because ovarian cancer disseminates primarily intraperitoneally or via lymphatics, whereas hematogenous spread is less common. The most common type of ovarian cancer metastasizing to breast is papillary serous carcinoma and rare cases include endometrioid, carcinoid, granulosa and germ cell tumors (Table I).

Because of the similarity in presentation, primary breast tumors and metastases to the breast are difficult to differentiate. Diagnosis is based on clinical, radiographic and histologic characteristics. Compared to primary tumors, metastatic breast masses

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of cases</th>
<th>Histologic type and grade</th>
<th>Survival after diagnosis of breast metastasis</th>
</tr>
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<tbody>
<tr>
<td>Sitzenfrey, 1907</td>
<td>1</td>
<td>PSC</td>
<td>NS</td>
</tr>
<tr>
<td>Abrams, 1950</td>
<td>2</td>
<td>PSC</td>
<td>NS</td>
</tr>
<tr>
<td>Charache, 1953</td>
<td>2</td>
<td>PSC</td>
<td>&gt;1 yr</td>
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<tr>
<td>Ilbach, 1964</td>
<td>1</td>
<td>Mucinous</td>
<td>6 mo</td>
</tr>
<tr>
<td>Harwood, 1971</td>
<td>1</td>
<td>Granulosa cell carcinoma</td>
<td>11 mo</td>
</tr>
<tr>
<td>Hadju, 1972</td>
<td>3</td>
<td>PSC</td>
<td>&lt;1 yr</td>
</tr>
<tr>
<td>Moncada, 1974</td>
<td>2</td>
<td>PSC, gr. 1 (1) and 3 (1)</td>
<td>&gt;2 yr</td>
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<tr>
<td>Royen, 1974</td>
<td>1</td>
<td>PSC, gr. 1</td>
<td>NS</td>
</tr>
<tr>
<td>McIntosh, 1976</td>
<td>3</td>
<td>1 Choriocarcinoma</td>
<td>2 mo</td>
</tr>
<tr>
<td>Krishnan, 1980</td>
<td>1</td>
<td>PSC, gr. 1</td>
<td>6 mo</td>
</tr>
<tr>
<td>Paulus, 1982</td>
<td>5</td>
<td>1-PSC</td>
<td>NS</td>
</tr>
<tr>
<td>Hughes, 1983</td>
<td>1</td>
<td>PSC, gr. 3</td>
<td>5 mo</td>
</tr>
<tr>
<td>Scotto, 1985</td>
<td>1</td>
<td>PSC</td>
<td>NS</td>
</tr>
<tr>
<td>Laifer, 1986</td>
<td>1</td>
<td>PSC, gr. 1</td>
<td>&gt;3.5 yr</td>
</tr>
<tr>
<td>Silverman, 1987</td>
<td>3</td>
<td>2 PSC, gr. 2 and 3</td>
<td>NS</td>
</tr>
<tr>
<td>Matseoane, 1988</td>
<td>2</td>
<td>PSC, gr. 1</td>
<td>12 and 27 mo</td>
</tr>
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<td>Loredo, 1990</td>
<td>1</td>
<td>PSC, gr. 3</td>
<td>24 mo</td>
</tr>
<tr>
<td>Duda, 1991</td>
<td>1</td>
<td>PSC, gr. 1</td>
<td>&gt;16 mo</td>
</tr>
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<td>Frauenhoffer, 1991</td>
<td>1</td>
<td>PSC, gr. 1</td>
<td>&gt;13 mo</td>
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<td>Ron, 1992</td>
<td>1</td>
<td>Endometrioid, gr. 2</td>
<td>&gt;16 mo</td>
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<tr>
<td>Kattan, 1992</td>
<td>1</td>
<td>Dysgerminoma, gr. 1</td>
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<td>Yamasaki, 1993</td>
<td>1</td>
<td>PSC, gr. 3</td>
<td>&gt;2 mo</td>
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<td>Fishman, 1995</td>
<td>1</td>
<td>Carcinoid</td>
<td>&gt;18 mo</td>
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<tr>
<td>Rapis, 1996</td>
<td>6</td>
<td>5 PSC, gr. 3</td>
<td>5–&gt; 52 mo</td>
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<tr>
<td>Hennigan, 1997</td>
<td>3</td>
<td>1 Clear cell</td>
<td>1 Clear cell</td>
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<tr>
<td>Muttarak, 1998</td>
<td>1</td>
<td>PSC</td>
<td>3, 7 and 13 mo, respectively</td>
</tr>
<tr>
<td>Manini, 1998</td>
<td>1</td>
<td>PSC</td>
<td>NS</td>
</tr>
<tr>
<td>Peterson, 1999</td>
<td>1</td>
<td>PSC</td>
<td>NS</td>
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<tr>
<td>Deshpande, 1999</td>
<td>1</td>
<td>PSC</td>
<td>NS</td>
</tr>
<tr>
<td>Ozgur, 1999</td>
<td>1</td>
<td>Mucoys cystadenocarcinoma</td>
<td>NS</td>
</tr>
<tr>
<td>Ozkan, 2000</td>
<td>1</td>
<td>PSC</td>
<td>NS</td>
</tr>
<tr>
<td>Oksuzoglu, 2001</td>
<td>1</td>
<td>PSC</td>
<td>NS</td>
</tr>
<tr>
<td>Cormier, 2001</td>
<td>1</td>
<td>PSC, gr. 2</td>
<td>&lt;12 mo</td>
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<tr>
<td>Gupta, 2001</td>
<td>1</td>
<td>PSC, gr. 3</td>
<td>NS</td>
</tr>
<tr>
<td>Kayikcioglu, 2001</td>
<td>1</td>
<td>PSC, gr. 2</td>
<td>18 mo</td>
</tr>
<tr>
<td>Oksuzoglu, 2003</td>
<td>1</td>
<td>PSC</td>
<td>3 mo</td>
</tr>
<tr>
<td>Martel, 2003</td>
<td>1</td>
<td>PSC</td>
<td>8 mo</td>
</tr>
<tr>
<td>Yeh, 2004</td>
<td>1</td>
<td>PSC</td>
<td>&lt;1 yr</td>
</tr>
<tr>
<td>Recine, 2004</td>
<td>14</td>
<td>PSC, gr. 3 (11), gr. 1 (3)</td>
<td>1–31 mo</td>
</tr>
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<td>Barai, 2004</td>
<td>1</td>
<td>PSC, gr. 1</td>
<td>NS</td>
</tr>
<tr>
<td>Gokaslan, 2005</td>
<td>1</td>
<td>PSC</td>
<td>NS</td>
</tr>
<tr>
<td>Kolwijck, 2007</td>
<td>1</td>
<td>PSC, gr. 3</td>
<td>28 mo</td>
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</tbody>
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PSC = papillary serous carcinoma, NS = not specified, gr. = histologic grade.
are more likely to be superficial and less fixed to surrounding tissue.\textsuperscript{12} Skin retraction, peau d’orange skin appearance and nipple discharge are generally absent in metastases,\textsuperscript{6,13-17} but these signs are also infrequent in primary tumors. Metastatic tumors present radiographically as round masses with well-defined or slightly irregular margins. Calcifications are rare, with the exception of ovarian cancer metastases, where calcifications may correspond to psammoma bodies. In contrast, spiculations are characteristic for primary breast tumors.

A histologic clue pointing to ovarian cancer metastasis is the papillary architecture characteristic of serous tumors.\textsuperscript{11} One entity that may be difficult to differentiate is micropapillary breast carcinoma that resembles müllerian histology.\textsuperscript{18} Metastatic lesions are rarely associated with hyperplastic or atypical ductal or lobular cells, which are common features in primary breast tumors. Presence of ductal or lobular carcinoma in situ points to a primary breast tumor.

Immunohistochemistry (IHC) for proteins distinctly expressed in breast or müllerian tissue are used for diagnosis.\textsuperscript{19} For instance, \textit{Wilms’ tumor 1} (\textit{WT1}) is characteristically expressed in nuclei of müllerian cells, \textit{WT1} staining being positive in \textasciitilde80\% of ovarian tumors.\textsuperscript{20,21} In contrast, \textit{WT1} is expressed in \textasciitilde10\% of breast cancers.\textsuperscript{11,19,22} Indeed, in both cases presented here, the primary ovarian or peritoneal tumor stained for \textit{WT1}. In contrast, the primary breast tumor was \textit{WT1} negative. \textit{GCDFP-15}, a breast marker, is expressed in apocrine ductal cells. Positive \textit{GCDFP-15} staining has 74\% sensitivity and 95\% specificity for breast cancer\textsuperscript{10,11,19,23-24} and is rarely detected in ovarian cancer. Other useful markers include CA 125 and \textit{mesothelin}, characteristic for ovarian cancer. Less than 10–45\% of breast cancers express CA 125\textsuperscript{23,25,26} and \textasciitilde15\% of breast tumors express \textit{mesothelin}.\textsuperscript{27,28}

This is the first report of breast metastasis from ovarian cancer arising during antiangiogenic treatment. Given that the rest of target metastatic lesions were stable, this event raises the question whether breast tissue may be impervious to antiangiogenic effects. We speculate that this may be attributed to breast tissue-specific milieu conducive to tumor growth or poor distribution of aflibercept in the breast fatty tissue.

Another unique feature presented here is the positive CA 125 staining and detectable serum CA 125 from a primary breast tumor, described in case 2. This highlights nonspecificity of CA 125 as a diagnostic tool and biomarker in epithelial malignancies. It is accepted that >90\% of müllerian tumors secrete CA 125. However, the glycoprotein can be expressed by other epithelial cancers.\textsuperscript{29-31} In one report, 16\% of breast tumors were also positive for CA 125.\textsuperscript{19} Higher incidence of CA 125 staining of breast tumors was reported by others\textsuperscript{18,23-25}. Thus, caution and discriminative thinking should be exercised when analyzing CA 125 expression or secretion in serum in patients with epithelial cancers.

In summary, distinction between primary breast tumors and metastases is important, because management and prognosis are distinct. The cases presented illustrate interesting dilemmas in diagnosis that should be considered when evaluating such patients.

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