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Case series

Breast metastases: A rare manifestation of advanced uterine serous carcinoma

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ABSTRACT

Metastasis of non-mammary tumors to the breast are uncommon, representing < 1% of all breast tumors. Breast metastasis are associated with advanced disease and poor prognosis regardless of the origin of the primary tumor. Uterine cancer metastasis to the breast is an extremely rare finding and has not been reported in the case of serous histology. Here, we review two cases of uterine serous carcinoma metastatic to the breast. Both patients presented with breast-specific complaints including pain and palpable mass and were found to have widely metastatic disease. Tissue biopsy and immunohistochemistry consistent with primary uterine serous carcinoma confirmed the diagnosis of metastasis in both cases. Our findings suggest hematogenous metastasis to the breast is a late phenomenon in the course of endometrial carcinoma and associated with the development of disease at multiple sites. This emphasizes the importance of complete evaluation in patients presenting with breast complaints and known history of malignancy, as this may be the only presenting symptoms in patients with widely metastatic disease.

1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy, affecting 63,230 patients in 2018. It is projected to account for 12,160 deaths this year in the United States alone (National Institutes of Health, 2018). Endometrioid adenocarcinoma accounts for the majority of cases and typically presents at early stage with overall good prognosis. In contrast, uterine serous carcinoma (USC) is an aggressive variant that accounts for only 15% of cases of EC yet is responsible for over half of all deaths. USC tends to present at an advanced stage and extrauterine spread is present in 60% of cases at the time of diagnosis (Del Carmen et al., 2012). Despite surgery and adjuvant therapy, USC frequently recurs and many ultimately succumb to their disease. Most commonly, EC metastasizes by direct extension and lymphatic spread, and as a result, the majority of recurrences occur locally within the pelvis or abdomen (Uccella et al., 2013; Mariani et al., 2001). Metastasis at extra-abdominopelvic sites is uncommon, but has been reported in the lung, bone, cutaneous lesions, axillary lymph nodes and the neck (Keheo et al., 2010; Baydar et al., 2005). Secondary breast malignancies are rare and represent < 1% of all breast tumors, yet are important in determining a differential diagnosis in patients with a known malignancy presenting with a breast mass (Georgiannos et al., 2001). The most common malignancies to metastasize to the breast include melanoma, lung, gastrointestinal and ovarian cancer (Williams et al., 2007; DeLair et al., 2013; Recine et al., 2004). Metastasis of primary uterine cancer to the breast has been reported but is extremely rare (DeLair et al., 2013; Günhan-Bilgen et al., 2002). To our knowledge, USC has not been reported to metastasize to the breast. Here, we discuss the presentation and management of two cases of USC with breast metastases and review the existing literature.

Case 1:

A 73-year-old African-American female presented to our oncology clinic with a new diagnosis of USC on endometrial biopsy obtained during evaluation for postmenopausal bleeding. Preoperative computed tomography (CT) of the chest, abdomen and pelvis was performed, which demonstrated an enlarged uterus but no evidence of metastasis. She underwent a robotic total hysterectomy, bilateral salpingoophorectomy, and bilateral pelvic and paraaortic lymph node dissection. Final pathology confirmed FIGO stage IIIC2 USC. She then received adjuvant therapy consisting of combination chemotherapy and radiation delivered in a “sandwich” sequence. Specifically, carboplatin AUC 6 and paclitaxel 175 mg/m2 every 3 weeks for 3 cycles, followed by external beam radiation to the whole pelvis with a paraaortic extension to 4500 cGy and brachytherapy to 1800 cGy. Following completion of

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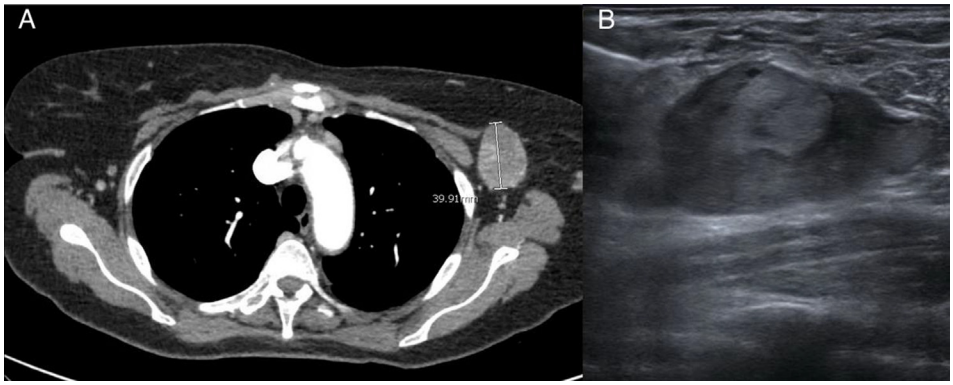

Fig. 1. *Case 1:* A. Contrast CT imaging shows a 4 cm well-circumscribed solid heterogeneous mass with areas of calcification. B. Ultrasound imaging demonstrates a round partially solid mass.

radiation, she received two additional cycles of chemotherapy, but then experienced prolonged grade 3 thrombocytopenia (CTCAE 4.03), and the last planned cycle was held. Exam and CT imaging at the completion of adjuvant therapy showed no evidence of disease.

Three months later, at her first surveillance visit, she complained of a painful left sided breast mass. Physical exam revealed a 3 cm left axillary lymph node and bilateral inguinal lymphadenopathy up to 1 cm in size. Ultrasound (US) of the breast demonstrated a solid round, well-circumscribed mass. A CT scan demonstrated a high-density mass in the left breast in the same location as the mass identified on US (Fig. 1). Additionally, a 4 × 3.1 cm left axillary mass, multiple sub-centimeter axillary lymph nodes and breast soft tissue nodules with skin thickening were identified. Multiple liver masses measuring up to 4.7 cm, an anterior abdominal wall nodule measuring 1.7 cm, multiple pulmonary nodules up to 1.1 cm, and mediastinal adenopathy up to 2.1 cm were also noted. Of note, the patient had undergone routine screening mammography 2 months prior to her initial diagnosis of USC which resulted as BI-RADs 2; no evidence of malignancy. Core needle biopsy of the breast mass confirmed a recurrence of her primary uterine tumor. IHC demonstrated strong positivity for Mullerian markers p53, p16 and PAX8 and negative for GATA 3 and mammaglobin, both typically positive in breast carcinoma. Comparison of tissue from the primary tumor and the breast lesion confirmed the diagnosis of metastatic uterine cancer (Fig. 2). The patient was started on pegylated liposomal doxorubicin 40 mg/m2 on day 1 and bevacizumab 10 mg/kg on day 1 and 15 of a 28-day cycle. She completed 5 cycles before being admitted to the hospital with acute delirium and failure to thrive. Imaging was performed which demonstrated persistent disease. At this time, she opted for no further therapy and died of disease 1 month later.

Case 2:

A 60-year-old African-American female presented with post-menopausal bleeding of 4 months duration, and USC was confirmed by endometrial biopsy. During her physical examination, she was found to have a right breast mass. She reported pain had been present in this breast for the past several months. Mammography and ultrasound showed a 3.3 cm lesion in the breast and a 1 cm lymph node in the right axilla (Fig. 3). CT imaging showed a 1.3 cm hepatic mass, left paraaortic lymph nodes up to 1.3 cm, and right inguinal lymph nodes up to 1.1 cm. Core needle biopsy of the breast mass confirmed metastatic serous carcinoma with PAX8, p16, p53 positivity and negative gross cystic fluid protein 15, GATA3 and mammaglobin. Again, comparison of tissue from the primary tumor and breast lesion confirmed the diagnosis (Fig. 4).

She underwent a laparoscopic hysterectomy and bilateral salpingoophorectomy due to persistent vaginal bleeding leading to symptomatic anemia requiring multiple blood transfusions. Postoperatively, chemotherapy was recommended due to systemic nature of disease and resection of breast mass with adjuvant radiation were recommended due to worsening breast pain. However, despite symptoms she refused any further treatment. Three months later, she presented with increasing breast pain and agreed to chemotherapy. She received carboplatin AUC 6 and paclitaxel 175 mg/m2 every 21 days for 6 cycles. A completion CT scan demonstrated a complete response in both the breast and liver masses. She then completed external beam radiation to the pelvis, a total of 4500 cGy, and vaginal brachytherapy, a total of 1800 cGy for pelvic sterilization. Four months after completion of therapy, she presented with a new palpable 2 cm right breast mass. Positron emission tomography (PET)/CT showed a 1.7 × 1.3 cm right breast mass and bilateral inguinal lymphadenopathy up to 1.1 cm with hypermetabolic activity, SUV 15.6 and 12.2 respectively. She received external beam radiation to the breast and inguinal lymph nodes, 4700 cGy and 5000 cGy respectively, and had a complete response in all lesions. She is currently without evidence of disease at 34 months of follow up.

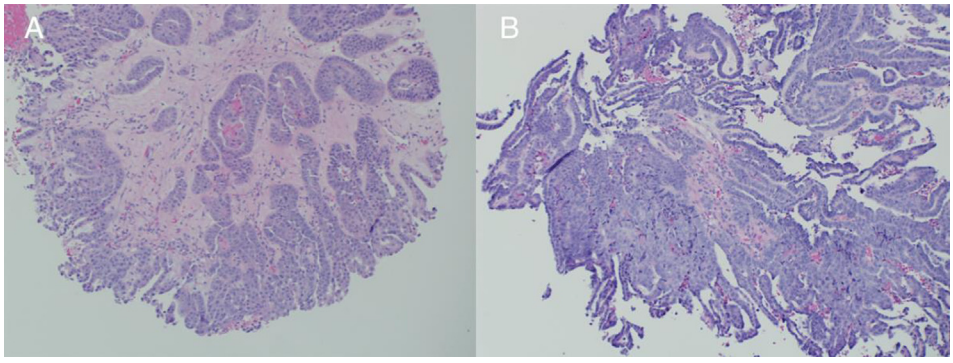

Fig. 2. *Case 1:* A. Breast mass biopsy B. Primary tumor. Both sections demonstrate numerous hyperchromatic complex papillary glandular structures lined with highly pleomorphic and atypical neoplastic cells, with numerous mitoses.

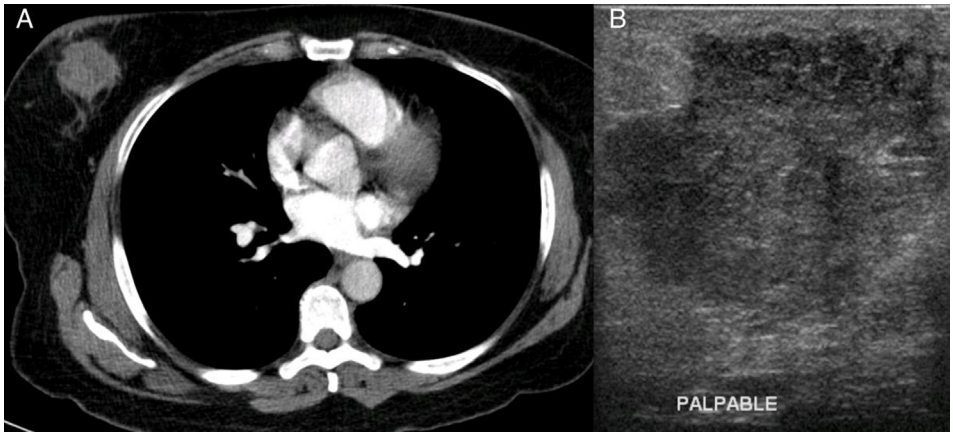

Fig. 3. *Case 2:* A. Contrast CT imaging showed 3.5 cm solid mass in the right breast with overlying skin thickening and calcification. B. Ultrasound imaging of this tumor showed irregular borders with mixed echogenicity.

2. Discussion

Metastases to the breast from a solid tumor make up only 1% of all breast tumors (Georgiannos et al., 2001). The most common malignancies to metastasize to the breast include melanoma, lung, gastrointestinal and ovarian cancer (Williams et al., 2007; DeLair et al., 2013; Recine et al., 2004). Metastasis from uterine primaries have also been reported, but are overall extremely rare. To our knowledge, only 10 cases have been reported in the literature including five leiomyosarcomas, three endometrioid, one endometrial stromal sarcoma and one undifferentiated carcinoma (DeLair et al., 2013; Günhan-Bilgen et al., 2002; Moore et al., 1998). Given the rarity of breast metastasis, combined with the high prevalence of primary breast cancer, a new breast mass is much more likely to represent a new primary breast tumor even in a patient with history of extramammary malignancy. Distinguishing between these two entities is key, as it dictates different treatment plans and prognoses.

The presentation of metastatic disease often mimics that of primary breast cancer, including pain and a palpable mass located in the upper outer quadrant (DeLair et al., 2013). However, unlike primary breast cancer, up to one-third of patients with metastatic disease will present with multiple lesions as opposed to a single solitary tumor. Imaging can aid in differentiating between primary and secondary breast tumors. Typically, primary breast tumors present as a hypoechoic mass with calcifications and speculated margins or as a diffuse lesion with significant surrounding desmoplastic reaction. Conversely, metastatic lesions tend to be well-circumscribed with clearly defined borders and lack surrounding inflammatory changes and may often mimic benign breast lesions (Williams et al., 2007; Mun et al., 2014). Interestingly, calcifications have rarely been reported in breast metastases, with the exception of metastatic high-grade serous ovarian carcinoma (HGSOC) (Bohman et al., 1982). Falling in-line with this observation, both of our patients with USC demonstrated calcifications on imaging. Often, USC behaves in a similar fashion to HGSOC.

The key to accurate diagnosis is histologic examination of the breast mass, aided by immunohistochemistry (IHC). Primary breast cancers frequently harbor invasive ductal components and regions of carcinoma in situ in conjunction with overt invasive disease. These findings are rarely observed in the case of metastatic disease. A combination of invasive ductal components with regions of carcinoma in situ will almost always confirm primary breast cancer (Williams et al., 2007). IHC is an extremely valuable tool to differentiate primary from secondary breast tumors. IHC markers utilized in the confirmation of primary breast cancer include Ki-67 cell proliferation marker, estrogen and progesterone receptor status, HER-2/neu oncoprotein, GATA 3, gross cystic fluid protein 15 and mammaglobin (Williams et al., 2007; Greco et al., 2013; Oien, 2009). IHC analysis of high-grade serous tumors of the gynecologic tract most commonly display a pattern of positivity for PAX-8, p53, p16, CK7, WT-1 and variable estrogen receptor and Ki-67 expression (Greco et al., 2013; Chiesa-Vottero et al., 2007). Although some overlap in IHC analysis may exist between primary breast and gynecologic malignancies, PAX-8 positivity will definitely confirm non-mammary origin of primary tumor, as it has not been reported to stain positive in primary breast cancer (DeLair et al., 2013; Nonaka et al., 2008). As demonstrated by our series, IHC analysis was consistent with the primary uterine tumor. Additionally, in a patient with a history of cancer, histology slides from the primary tumor should be compared to that of the breast lesion and will confirm diagnosis.

Metastasis of extramammary tumor to the breast most commonly occurs by hematogenous spread, manifesting as disease in the

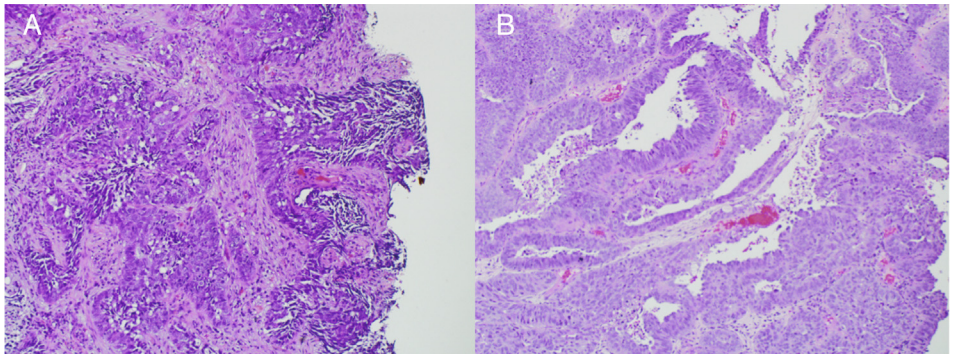

Fig. 4. *Case 2:* A. Breast mass biopsy B. Primary tumor. Both sections demonstrate numerous hyperchromatic complex glandular structures lined with highly pleomorphic and atypical neoplastic cells, with numerous mitoses.

superficial upper-outer quadrant, at the location of greatest vascularity within the breast (Williams et al., 2007). Conversely, EC most commonly metastasizes by direct extension and lymphatic spread, leading to abdominopelvic recurrences. Although uncommon in adenocarcinoma of the endometrium, USC has a propensity to metastasizes hematogenously, manifesting most frequently as liver and lung metastases (Mariani et al., 2001). Hematogenous dissemination to bone and cutaneous sites have also been reported, but are extremely rare, affecting < 1.0% of all patients (Keheo et al., 2010; Baydar et al., 2005). Though bone metastases are rarely observed in clinical practice, it has been identified in up to 25% of patients with advanced EC on autopsy (Keheo et al., 2010). In these cases, it is almost always found concurrently with advanced metastatic disease at multiple sites, implying that hematogenous dissemination is a late event in the metastasis of EC. Our series supports this theory, as both patients presented with breast metastasis as well as metastatic disease at multiple sites of hematogenous dissemination such as the liver, lung and skin.

The prognosis of patients with metastasis to the breast is poor, with a reported median survival of only 10–15 months from the time of diagnosis. Over 70% of these patients will present with widely metastatic disease, which is likely the main contributing factor leading to poor survival (Williams et al., 2007; DeLair et al., 2013). Treatment is based on traditional paradigms for the primary tumor. Surgical resection of the breast tumor remains controversial. Limited retrospective data demonstrates an improved survival with resection of the breast tumor plus systemic therapy versus systemic therapy alone. However, this data is confounded by the fact that most patients undergoing surgical resection of the breast tumor had limited sites of metastatic disease and were overall healthier than those who did not undergo surgery (Williams et al., 2007). In regards to uterine cancer specifically, a large body of retrospective literature demonstrates improved survival with complete cytoreduction in patients with extrapelvic disease (Bristow et al., 2001). Based on available data, we believe treatment should be individualized and geared towards existing standard treatment regimens for the primary tumor. Surgery should be considered in the case of palliation for symptoms, in select circumstances of isolated breast metastasis and when complete cytoreduction can be achieved.

3. Conclusion

Breast metastases from solid non-breast tumors are uncommon occurrences and extremely rare in the case of primary uterine malignancy. Metastatic disease to the breast carries a grim prognosis regardless of the origin of the primary tumor and most often will require different therapeutic strategies compared to those used to treat primary breast cancer. A new mass or breast pain in patient with known malignancy should prompt further evaluation and tissue diagnosis should be undertaken to confirm the diagnosis and triage the patient to appropriate adjuvant therapy.

Author contributions

JM: Medical record review, data acquisition, manuscript writing and review
RM: Medical record review, data acquisition
YL: Study concept development, manuscript review
MJK: Study concept development, manuscript review

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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