

## Immunohistochemistry markers in diagnosing high-grade serous carcinoma of ovary with breast metastasis: a rare case report

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Ovarian cancer patients presenting with breast metastasis are a rare phenomenon. Very few cases have been documented so far in the literature and have shown that long-term prognosis of these patients is poor despite intense chemotherapy schedules. This report discusses a case of high-grade serous carcinoma of the ovary with metastases to the right breast and axilla in a 49-year-old female as the first case in the authors' centre in South India. Additional immunohistochemistry markers were checked to confirm the diagnosis. The patient was on the third line of chemotherapy in December 2015. It is strongly emphasised that breast examination should be routine in all cases of ovarian malignant tumours. IHC markers may differentiate between second primary versus metastatic secondaries in the breast. Further clinical trials using novel chemotherapy and systematic review of all case reports may help to form uniform consensus guidelines for these rare entities.

**Keywords:** breast mass, metastases to breast, ovarian cancers, rare ovarian presentation, relapse in breast

### Introduction

Ovarian cancer is the leading cause of death from gynaecological cancers worldwide.<sup>1</sup> Often branded as one of the most clinically challenging malignancies due to its non-specific symptoms and late diagnosis, it presents at an advanced stage in most cases. The common sites of distant metastases are liver, lung, brain and bone. Metastasis to the breast from a primary ovarian cancer is rare and very few cases have been reported in the literature so far. A long-term study of 4051 patients with breast cancer reported an incidence of 0.07% of breast metastasis.<sup>2</sup> In this short report, the authors wish to discuss the case of a woman diagnosed with primary high-grade serous carcinoma of the ovary with metastasis to the breast. The authors would also like to emphasise the importance of immunohistochemistry (IHC) studies in the differentiation of primary breast cancers versus metastatic spread to the breast.

### Case report

#### Initial presentation

A 48-year-old pre-menopausal woman presented with vague symptoms of abdominal pain and bloating in January 2011 for which she was evaluated and found to have a large right-sided adnexal mass with solid and cystic components and a focal lesion in the right lobe of the liver. Her CA125 was > 600 U/ml. Fine needle aspiration cytology (FNAC) from the adnexal mass reported a malignant surface epithelial ovarian tumour.

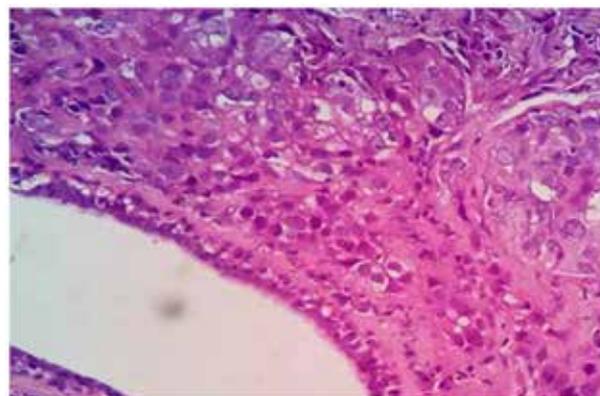
#### Treatment, follow-up and relapse

The patient was reviewed by our multidisciplinary tumour board, and it was decided to proceed with three cycles of neo-adjuvant chemotherapy with paclitaxel and carboplatin followed by interval de-bulking surgery. Surgery was carried out in April 2011 and she was given three further cycles of adjuvant chemotherapy with carboplatin and paclitaxel. On her first follow-up visit after six weeks, contrast-enhanced computerised tomography (CECT) scan of the chest, abdomen and pelvis was done and was reported as normal. She was on regular follow-up until February 2012, when repeat CECT showed an enhancing nodular lesion in

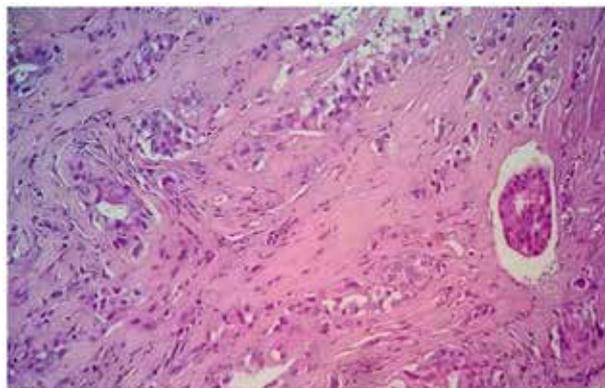
the vault region suggestive of a local recurrence and repeat CA125 level was 81.2 U/ml. The patient was again re-challenged with six cycles of paclitaxel and carboplatin. Her follow-up period was uneventful with serum CA125 showing normal values. In December 2013, the CA125 level started rising (> 253.6 U/ml) and the patient was advised to undergo repeat imaging with CECT of the thorax and abdomen. She was found to have multiple para-aortic, para-tracheal and supra-clavicular (SCF) nodes with short axis diameter (SAD) of more than 1.5 cm. She was started on platinum-based chemotherapy as the time interval of recurrence was more than six months. She was started on paclitaxel-carboplatin in February 2014, but developed hyper-sensitivity to carboplatin, which then was changed to cisplatin. The patient had completed six cycles by June 2014. Her follow-up CA125 values and thorax and abdomen imaging were normal.

#### Metastasis to breast

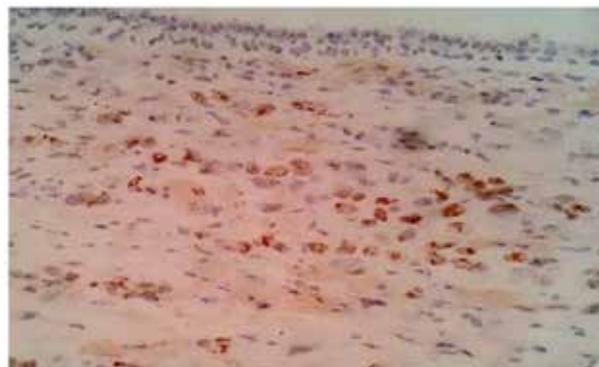
In March 2015, the patient presented with a 6 × 5 cm hard, tender mass in the upper outer quadrant of the right breast. The histopathological evaluation of a core biopsy from the tumour showed many solid areas with a focal papillary pattern along with the tumour



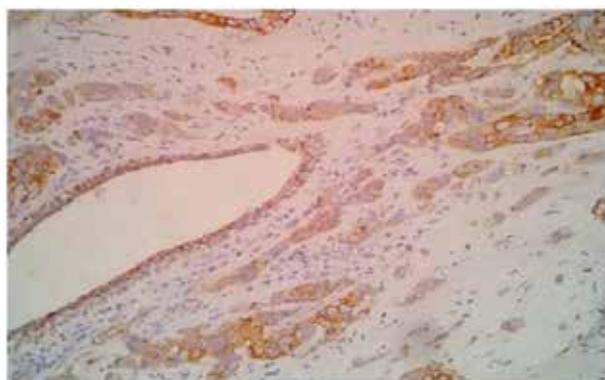
**Figure 1:** Hematoxylin and eosin stained section (400X) shows normal benign breast epithelium along with tumour cells.



**Figure 2:** Hematoxylin and eosin stained section (200X) shows tumour cells with glandular differentiation along with tumour emboli.



**Figure 4:** Immunohistochemistry stain for WT1 (200X) shows diffuse nuclear positivity in the tumour cells and negativity in the benign breast epithelium.



**Figure 3:** Immunohistochemistry stain for CK7 (200X) shows diffuse cytoplasmic positivity in the benign breast epithelium as well as the tumour cells.



**Figure 5:** CECT of thorax showing the enhancing lesion in the right breast.

emboli. The tumour cells showed high-grade nuclear features and frequent mitosis (Figures 1 and 2). On immunohistochemistry these tumour cells were negative for hormone receptors — oestrogen and progesterone — in addition to primary breast tumour marker gross cystic disease fluid protein-15 (GCDFP-15) and mammaglobin. Given the history of ovarian malignancy additional markers like Wilm's tumor 1 (WT1), cytokeratin 7 (CK7) and cancer antigen (CA125) were performed. The tumour cells showed diffuse strong nuclear and cytoplasmic positivity for WT1 and CK 7 respectively (Figures 3 and 4). CA125 staining was focally positive. CK7 staining can be seen in primary breast as well as in the majority of ovarian tumours; however, strong positivity of WT1 (positive in all serous tumours of the ovary) and negativity of the GCDFP stain confirmed the tumour to be a metastatic deposit from an ovarian serous adenocarcinoma. A CECT of the thorax and abdomen was done, which reported multiple paratracheal, mediastinal and retroperitoneal nodes with an enhancing lesion in the right breast (Figure 5). She was started on the second line of chemotherapy with doxorubicin and cyclophosphamide followed by docetaxel and received seven cycles (3 x AC + 4 x docetaxel) until July 2015. Her follow-up CECT showed a good response for the mediastinal and retroperitoneal nodal regions but the breast mass, which had been quiescent during chemotherapy, now showed disease progression with the appearance of axillary and supraclavicular nodes, the largest of which measured 1.5 cm. The patient was on the third line of chemotherapy with gemcitabine in December 2015.

## Discussion

The most common route of spread from a malignant epithelial ovarian tumour is intraperitoneal and through the lymphatics. Distant metastasis via haematogenous spread is not uncommon and develops in 38% of patients; this may be present at initial presentation or during the disease history.<sup>3</sup> Theoretically, metastasis can occur anywhere in the body, but the skin, pleura, lungs, bone, spleen, breast are, in that order, the most commonly involved sites. The effects of these rare metastases are devastating, and survival is usually very poor.<sup>4</sup> The frequency of reported breast metastasis is very rare, in the frequency of 0.4–1.3%.<sup>5</sup> While reviewing 14 000 breast cancer cases for over 90 years only 0.43% was reported to be a metastatic lesion to the breast.<sup>5</sup> The most common sources of metastasis to the breast are malignancies involving the lung, haematological malignancies, kidney, malignant melanoma, ovary, and rectum.<sup>8</sup>

Primary breast cancer in the context of ovarian malignancy has been reported and is common among those with hereditary breast and ovarian syndrome because of mutation in BRCA1 and BRCA2. Hadju and Urban *et al.* reported an incidence rate of primary gynaecological malignancies with breast metastasis as 0.17%, whereas the incidence rate of ovarian cancer with breast metastasis is still lower (0.07%).<sup>9</sup>

In contrast to primary breast cancer, the metastatic lesion is well circumscribed and multi-nodular. Also, the lesion is superficial, not fixed to the chest wall and underlying muscles, with overlying

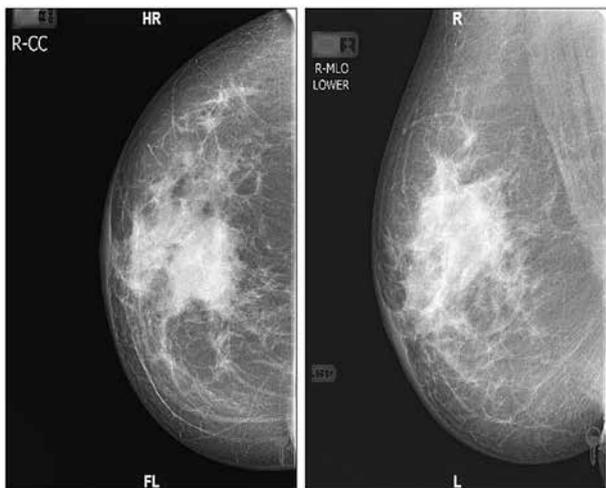


Figure 6: Mammogram images of right breast showing micro-calcifications.

skin maintaining its consistency. Radiologically, mammographic findings could provide additional details. Metastatic lesions lack spiculations and architectural distortions; however, micro-calcifications can be seen (Figure 6a and 6b). Because of difficulty in morphological differentiation between primary breast pathology and metastasis and delay in treatment, additional immunohistochemistry markers specific to ovarian cancer are warranted. Nearly 96% of ovarian adenocarcinomas were positive for CK7. In our case also, both CK7 and WT1 markers were positive. ER is usually expressed in 80% and GCDFP-15 in 45–53% of breast carcinomas whereas both proved negative in our sample.<sup>10–13</sup> Newer markers such as PAX-8 and GATA-3 would be of high value in differentiating these tumours. Metastatic cancer to the breast carries a poor prognosis with median

survival of less than one year.<sup>9</sup> Clinical and histopathological differentiation between primary breast versus metastatic lesion is shown in Table 1.

Oncologists should anticipate unusual sites of distant metastasis because of the improvement in the management of ovarian primary tumours. Breast metastasis from the ovary should be considered as a systemic disease and be treated in the same line of management as ovarian cancer. Further IHC markers may prevent unnecessary radical breast surgery and radiotherapy. Mastectomy should be reserved for palliation and tumours unresponsive to chemotherapy. A systematic review of all case reports and series could help to form a uniform consensus for managing such rare cases.

**Conclusion**

Although ovarian metastasis to the breast is rare, it should be considered as a differential diagnosis in ovarian malignancy patients. Breast examination should be considered in all cases of ovary malignant tumours. IHC markers may differentiate between second primary and secondaries in the breast. A thorough review of the literature is warranted to form uniform consensus guidelines.

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Table 1: Differences between primary breast cancers and metastases to breast

Metastasis to breast	Primary breast cancer
Clinically:	
Circumscribed mobile mass	Irregular diffuse mass
Uncommon location with rapid growth	Situated mostly in upper outer quadrant of breast
Nipple retraction, skin involvement uncommon	Skin involvement, nipple retraction are common findings
Histopathology:	
Micro-calcifications are not common	Usually seen
Margins are well circumscribed	Commonly seen
Carcinoma in situ absent	Infiltrating margin
Immunohistochemistry	
Ovary	Primary breast cancer
CK7 strongly positive	Positive or negative
WT1 strongly positive	Negative
CEA positive	
CA125 positive	
ER not strongly positive	Strongly positive
PR negative	Positive

Received: 29-03-2016 Accepted: 19-09-2016