



Case Report

Metastatic ovarian carcinoma in breast cancer patients during risk-reducing salpingo-oophorectomy: Report of two cases

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ABSTRACT

Introduction and importance: Metastatic ovarian cancer of breast carcinoma is rare and accounts for only 0.68%–2% of all ovarian tumors, the majority of which are diagnosed incidentally during follow-up or therapeutic oophorectomy. Risk-reducing salpingo-oophorectomy (RRSO) is a highly recommended prophylactic surgery associated with a significant decrease in ovarian cancer risk in both *BRCA1* and *BRCA2* mutation carriers, and in those with and without prior breast cancer.

Case presentation: We present two cases who presented with a lump in the right axilla and left breast respectively and were subsequently diagnosed as invasive mammary carcinoma but later, diagnosed with metastatic ovarian carcinoma with breast primary after RRSO. The patients were treated with cycles of chemo-radiation.

Discussion: Invasive lobular carcinoma, larger tumor size, advanced breast cancer increases the risk of developing ovarian metastases. Thorough macroscopic, microscopic, immunohistochemical, and molecular tests are considered the cornerstone in the diagnosis of metastatic breast cancer to the ovaries. Bilateral salpingo-oophorectomy, a risk-reducing surgery for the *BRCA* gene mutation, has been shown to reduce the risk of death from ovarian cancer.

Conclusions: Metastatic ovarian cancer in breast cancer is a rare possibility among patients undergoing RRSO for breast cancer. The importance of continued surveillance of ovaries rather than the delayed diagnosis of ovarian metastasis for patients with newly diagnosed breast cancer cannot be less emphasized.

1. Introduction

Ovarian metastasis of breast carcinoma is uncommon. A study in the Netherlands with 2648 patients aged <41 years and diagnosed with primary invasive breast cancer (BC) who underwent a unilateral/bilateral oophorectomy as a prophylactic or therapeutic purpose, showed that only 63 patients (2.4%) had histologically proven ovarian metastasis [1]. Similarly, another study with 10,944 new cases of ovarian cancer showed that only 75 cases (0.68%) were diagnosed as metastatic breast cancer [2,3].

In the majority of cases, the patients are asymptomatic and diagnosis is made incidentally during follow-up breast cancer examination or therapeutic oophorectomy/castration surgery [4].

Among patients with *BRCA1* and *BRCA2* mutations, risk-reducing salpingo-oophorectomy (RRSO) can significantly reduce the risk of ovarian cancer from 85% to 95% and is thus strongly advised once childbearing is complete [5]. In addition, patients with prior breast cancer have a significant decrease in ovarian cancer after RRSO [6]. In addition to decreasing this risk, RRSO also helps to detect occult early-stage ovarian or fallopian tube cancer (2–10% of cases) along with metastatic breast cancer if any (1–2%), after the procedure [7].

Herein, we report two case reports of diagnosed invasive carcinoma of the breast in whom ovarian metastasis was found after RRSO along with a review of the literature. The cases have been reported in line with SCARE criteria [8].

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2. Presentation of case

2.1. Case 1

A 37-year P₁L₁, regularly menstruating, presented with a complaint of a single, progressive lump over the right axilla for a year. There was no complaint of pain, overlying skin changes, change in lump size during menstruation and nipple discharge, and no complaint of the contralateral breast. She had no family/personal history of breast and ovarian cancer.

She presented to our center a diagnosed case of invasive mammary carcinoma with liver and bone metastasis. She had received seven cycles of cyclophosphamide-based neoadjuvant chemotherapy.

On follow-up CT scan, liver lesions were static. Additionally, lungs and bone metastasis were detected. MRI of the breast revealed locally aggressive primary neoplasm of the right breast with skin involvement. The bone scan also showed bony metastasis in C₇/D₁, D₄₋₅. In addition, her CA-15.3 was raised to 52.8 U/ml. No lesions were detected in the ovaries on the CT scan and the USG of the abdomen and pelvis.

After metastatic work-up, the patient underwent a right-modified radical mastectomy (MRM) along with bilateral RRSO by the team of breast oncosurgeon and gynecologists owing to the hormone status (ER+, PR+) of the breast tumor. Histopathological examination of the excised specimen from the right breast showed invasive carcinoma of no special type and the examination of the left ovary revealed a metastatic breast carcinoma with ER/PR+. Immunohistochemistry studies showed ovarian tumor cells positive for CK7, GATA3, mammoglobin, ER and PR while negative for CK20, WT1, and PAX8 (Fig. 1).

However, gross and microscopic examination of the right ovary was unremarkable. Because of ER and PR positive status, the patient was prescribed letrozole and zoledronic acid four weekly.

She received 10 cycles of radiation therapy on the lower cervical

spine with margin (C₅-D₂) over two weeks because of severe back pain due to bone metastasis. Currently, the patient is on letrozole, Palbociclib, and zoledronic acid and is on regular follow-up.

2.2. Case two

A 33-year P₁L₁, regularly menstruating, presented with a gradually increasing painless lump in the left breast for three weeks. There was no history of any skin changes, ipsilateral axillary lumps, contralateral breast complaints or family history of breast/ovarian malignancy.

On examination, an approximately 3 cm × 3 cm non-tender, hard palpable lump in the left lower quadrant of the breast was present which was fixed to the overlying skin and had well-defined margins. Ultrasound of the left breast showed an ill-defined lobulated hypoechoic mass and the right breast was normal. Mammography showed irregular hypoechoic subcutaneous lesion at 4–5 o'clock zone B/C of the left lower outer quadrant measuring 2.2cm × 1.8cm. Multiple enlarged lymph nodes were noted in the left axilla. No significant enlarged lymph nodes were noted in the left supra/infraclavicular region or internal mammary chain. Fine needle aspiration cytology of the breast mass was suggestive of invasive ductal carcinoma of the breast.

The patient underwent a left MRM. Histopathological examination showed invasive carcinoma of no special type, Grade II, pT₂N_{2a}. She received irradiation on the left chest wall after the completion of three cycles of chemotherapy. Evaluation after radiation therapy showed complete remission and the patient was under regular follow-up with complete remission for three years with hormonal therapy.

However, three years after remission, during regular evaluation, MRI whole body showed minimal pleural effusion with multiple pleural-based nodules with foci of restricted diffusion in left pleural space, suspicious of metastasis, and bilateral small ovarian cyst with a small hemorrhagic cyst in left ovary. Biopsy of pleural mass revealed

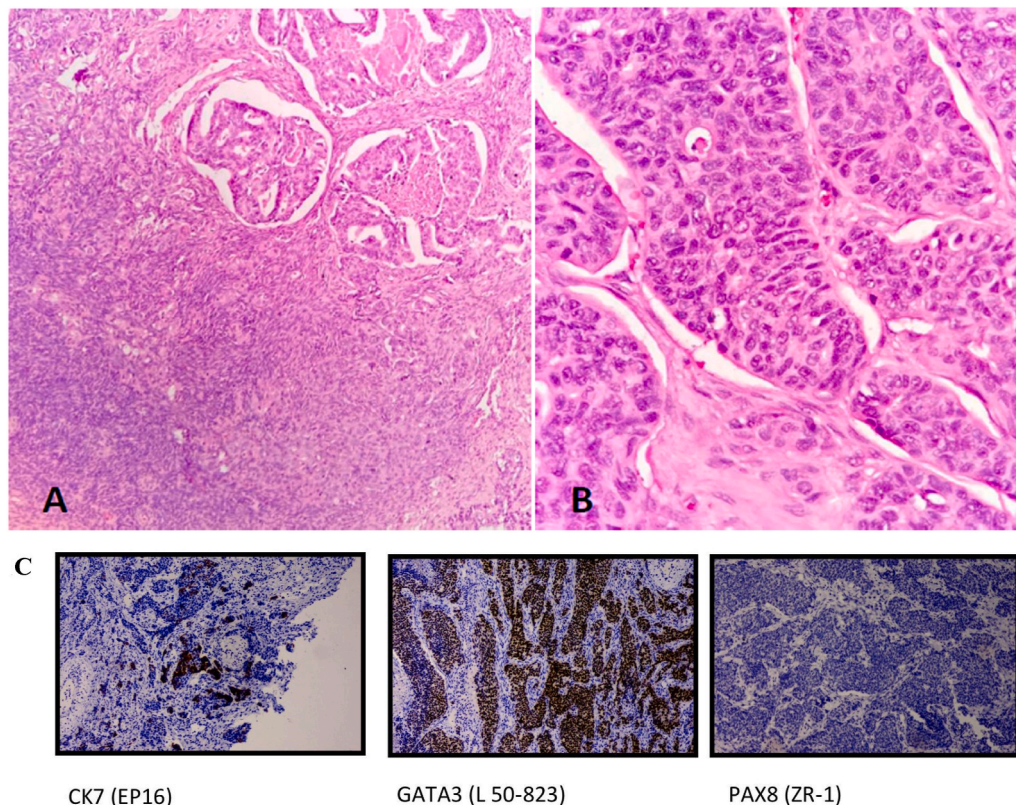


Fig. 1. A) Section shows tumor cells infiltrating the ovarian parenchyma. B) The tumor shows pleomorphism and has enlarged nuclei, irregular nuclear contours, visible nucleoli, and a scant to moderate amount of cytoplasm. Mitosis noted. (Case 1)

Fig. 1C: Immunohistochemistry analysis from the ovary showing tumor cells positive for CK7, GATA3, and negative for PAX8. (Case 1).

metastatic poorly differentiated carcinoma. CA-15.3 was elevated to 98.8 U/mL. In the view of relapsed breast carcinoma, she was planned for goserelin, oral palbociclib, and letrozole. After 6 months of chemotherapy, the patient underwent laparoscopic bilateral salpingo-oophorectomy for persistent complex ovarian cyst (Fig. 2). Histopathology of the left ovary showed metastatic ovarian carcinoma with breast primary (Fig. 3). As per the consensus of the expert panel, a second-line chemotherapy fulvestrant was started and the patient is under regular follow-up.

3. Discussion

Ovarian metastasis as compared to primary ovarian tumors is difficult to diagnose, manage and has a worse prognosis [9]. History of breast cancer, ovarian cancer in the family, BRCA1/2 gene mutation, advanced breast cancer, and premenopausal state which tend to activate cancer cells increase the risk of metastatic ovarian cancer [10,11]. Both of our patients were premenopausal with no family history of malignancy but metastatic lesions were present in the first case. The risk of ovarian metastasis in breast cancer depends on the morphological subtypes of breast cancer. Though, ovarian metastasis is often seen in patients with invasive ductal carcinoma owing to a higher frequency of invasive ductal carcinoma. However, the metastatic tendency of invasive lobular carcinoma to the ovaries is three times greater [4]. On the contrary, Peters et al. found that there are no significant differences in histological subtype between the cases and matched controls among young breast cancer patients [1]. Additionally, larger tumor size (i.e. >5 cm), the presence of inflammatory breast cancer, and the presence of other organ-system metastasis are associated with an increased risk of developing ovarian metastasis [1,12]. Both of our cases had invasive ductal carcinoma with a tumor size of less than 5cm. However, the first patient had metastasis to the liver and bone at the time of presentation and thus RRSO was performed as a palliative procedure.

Ovarian metastasis of breast cancer is usually bilateral, and often seen in premenopausal hormone receptor-positive young women [13]. However, metastatic and early primary ovarian carcinoma cannot be differentiated based on laterality [14]. Interestingly our case had a unilateral finding of metastasis in the left ovary. No clinically detectable

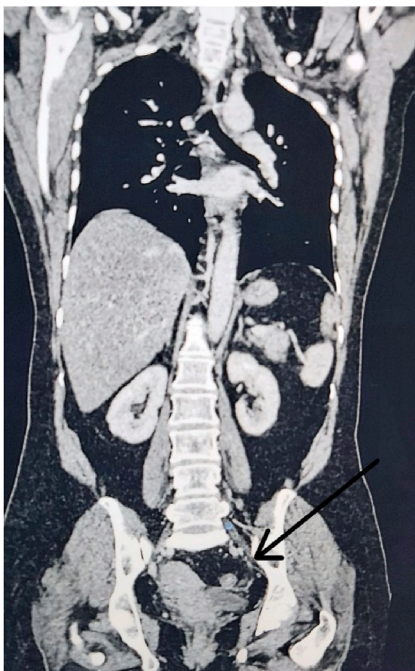


Fig. 2. CT scan (coronal section) shows left ovarian cyst with internal septations. (Case 2).

lesion suggestive of malignancy was present in our case and a prophylactic bilateral salpingo-oophorectomy was done for persistent complex cyst in the second case. However, both the cases of breast cancer were ER and PR positive.

As it is difficult to diagnose ovarian metastasis from breast cancer, a high level of suspicion along with macroscopic, microscopic, immunohistochemical, and molecular tests are the gold standard in the diagnosis of metastatic breast cancer to the ovaries [15]. Positive mammaglobin aids in determining breast as the origin for metastasis [14].

The most important step in the management of ovarian metastasis from breast cancer is surgery as it also helps in further diagnosis and staging. For a suspicious ovarian mass in breast cancer patients, a simple laparoscopic oophorectomy can help pathological diagnosis, metastatic tumor removal, and therapeutic castration [4]. However, high-risk women should be offered prophylactic oophorectomy and the need to possibly undergo a staging procedure if indicated should be well explained to those patients [16]. Additional systemic therapies (chemotherapy, endocrine therapy, and anti-HER2 therapy) should be considered if there are other organ metastasis [4].

As ovarian metastasis of breast cancer often has a poor prognosis, patients should be carefully monitored after treatment of primary breast cancer including a proper gynecological assessment. At present, women with a family history of breast cancer and ovarian cancer with high suspicion should be offered appropriate genetic testing and counseling for BRCA1/2 mutations. Though RRSO offers an enormous benefit in preventing primary ovarian cancer among women with BRCA mutation, Genetic screening for BRCA1/2 mutation is highly expensive and not easily available in developing countries like Nepal. We had advised both of the patients to undergo the mutation analysis but they refused owing to the costliness of the test. Hence, we need to rely on meticulous history, clinical examination, and investigations such as sonography and tumor markers. However, we do counsel all patients on germline tests as standard practice and on hereditary breast/ovarian cancer.

4. Conclusion

Ovarian metastasis in breast cancer is rare. RRSO done as prophylactic surgery reduces ovarian cancer risk in patients with primary breast cancer. Regular follow-up of women with breast cancer is necessary; clinical assessment should not neglect gynecological examination. Finally, we emphasize the importance of continued surveillance of ovaries for patients with newly diagnosed breast cancer.

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Ethical approval

Not Applicable.

Consent

Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Prafulla Shakya- Study concept, data collection and analysis and surgical treatment of the patient. Anu Shakya- Study concept, data

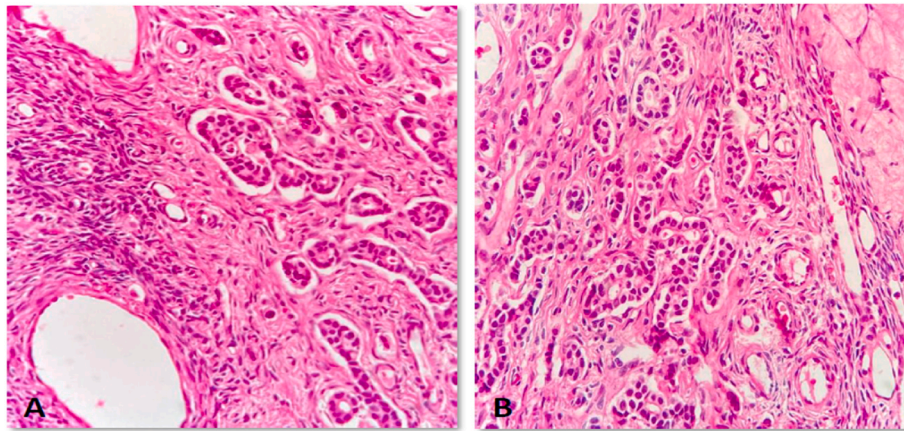


Fig. 3. A & B) Section from the ovary shows features of metastatic carcinoma, likely from the breast. These tumors show atypical cells infiltrating the ovarian parenchyma. They are arranged in tubules and clusters. (Case 2).

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Registration of research studies

Name of the registry:
 Unique Identifying number or registration ID:
 Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

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Declaration of competing interest

None to declare.

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