



# Treatment conundrums in osteosarcoma of the breast: Two clinical cases from a tertiary care cancer center in India

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## ABSTRACT

Extrasosseous sarcoma of the breast occurs infrequently and is a harbinger of poor prognosis. The histogenesis of this tumor is ambiguous, and it can arise both in de novo and metastatic settings. Morphologically, it is indistinguishable from its skeletal counterpart, and clinically, it presents similarly to any other subtype of breast cancer. Tumor recurrence with a propensity for hematogenous rather than lymphatic spread plagues this malicious disease. The treatment guidelines are mainly derived from the those of other extraskeletal sarcomas as the literature is limited in this context. We hereby present 2 clinical cases with similar clinical profiles and different treatment outcomes. The intent of this case report is to contribute to the limited database available for the management of this rare disease.

**Keywords:** Breast carcinoma, chemotherapy, extrasosseous, mesenchymal, osteosarcoma, sarcomas

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## Cite this paper as:

Doval DC, Tayal J, Choudhary KD, Goyal P, Gupta G, Pasricha S. Treatment conundrums in osteosarcoma of the breast: Two clinical cases from a tertiary care cancer center in India. Turk J Surg 2018; 10.5152/turkjsurg.2018.4075.

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Received: 04.01.2018

Accepted: 09.04.2018

Available Online Date: 13.09.2018

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Available online at  
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## INTRODUCTION

Mammary osteosarcoma represents less than 0.1% of all breast tumors and 12% of all breast sarcomas (1). It is subcategorized as the group of mesenchymal tumors as per the World Health Organization classification of breast tumors (1). Breast osteosarcomas arise primarily in the breast or rarely as metastasis from a primary bone sarcoma. They occur almost exclusively in women with a reported median age of 64.5 years, unlike bone sarcomas, which occur at a much younger age. A literature search revealed that these cases are infrequently reported as case reports, except one detailed retrospective clinicopathologic analysis of 50 cases (2). Diagnostic dilemmas and a lack of treatment guidelines surround this rare disease and justify the reporting of these cases.

## CASE PRESENTATIONS

### Clinical Case 1

A 55-year-old female patient presented to our hospital in her post-operative period in November 2012. She provided a history of lumpectomy in her left breast. She had first noticed the mass 2 months before. Her medical and family history were unremarkable. She was evaluated at an outside oncology facility and had undergone a lumpectomy for the breast lump. The histopathological report gave the differentials of metaplastic carcinoma versus osteogenic sarcoma. She came to our center for further management. A mammographic rereview revealed a BIRADS IV lesion (Figure 1). A confirmation of the histopathological diagnosis was obtained through an immunohistochemistry (IHC) with pan-cytokeratin (CK) and epithelial membrane antigen (EMA) on the submitted blocks. A definitive diagnosis of osteosarcoma was made as both these markers failed to be highlighted. The hormone profile and human epidermal growth factor receptor-2 (HER2) testing revealed the disease to be triple negative breast cancer (TNBC). After due discussions, both with the family and in the multidisciplinary tumor board, it was decided to do a simple mastectomy keeping in view the unclear margin status and also keep the patient in a close follow-up (6 monthly). Adjuvant therapy was deemed unnecessary in the presence of an adequate local control and the absence of metastatic disease. Interim metastatic evaluations using positron emission tomography-computed tomography (PET-CT) has shown the patient to be well without any tumor recurrence at 52 months.

### Clinical Case 2

Another 54-year-old diabetic and hypertensive female patient presented to our center in August 2015 with complaints of a lump in the left breast that had been present for 1.5 months. She had an unremarkable family history and gynecologic history. There was no history of radiation exposure, birth control, or hormone replacement therapy. On clinical examination, the patient had a hard, palpable 3x2 cm lump in the upper quadrant of the left breast with no palpable axillary nodes. Mammography revealed the mass to be the BIRADS IV disease (Figure 2). The fine-needle aspiration cytology from the lesion was inconclusive. An ultrasound-guided biopsy from the left breast confirmed the lesion to be malignant with the suggested differentials of metaplastic carcinoma and osteosarcoma. She underwent a conser-

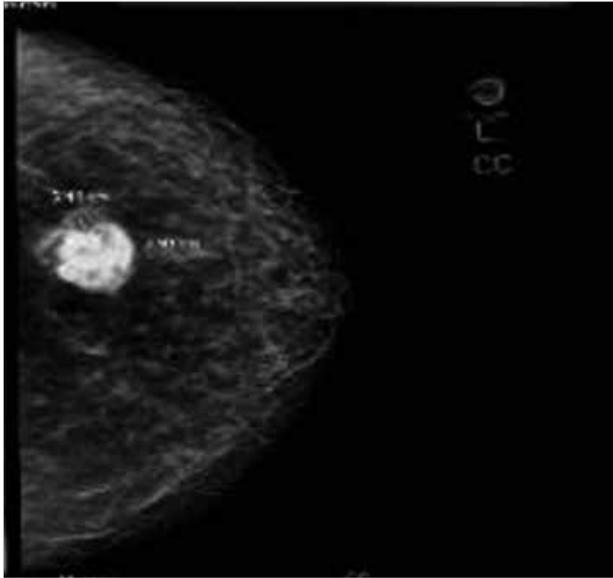


Figure 1. (Case 1) Mammogram of the left breast showing a well-circumscribed mass with prominent calcifications

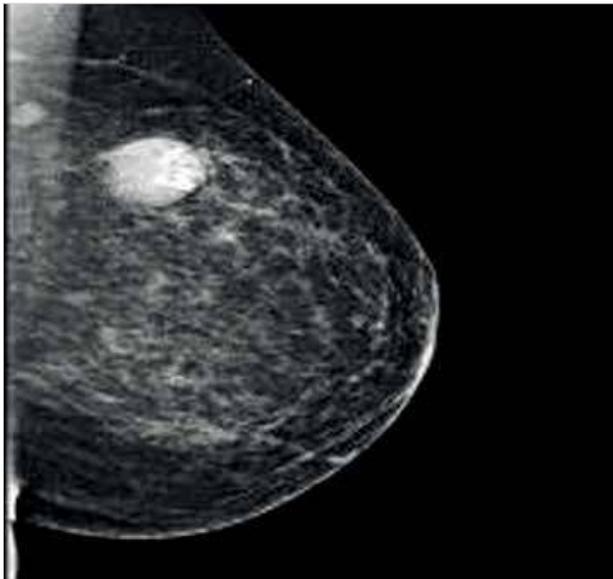


Figure 2. (Case 2) Mammogram of the left breast showing a well-defined oval mass in the upper outer quadrant with indistinct margins and foci of calcification

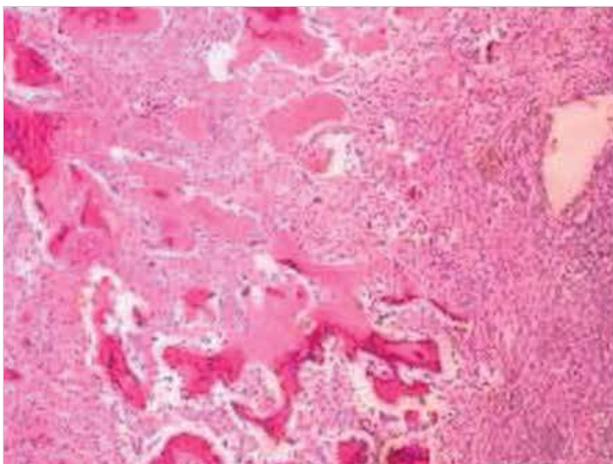


Figure 3. Proliferation of neoplastic spindle cells with extensive osteoid (arrow) deposition (H&E; x10 magnification)

vative breast surgery with the left axillary nodal dissection. A histopathological examination showed a marked proliferation of neoplastic spindle cells with extensive osteoid deposition (Figure 3). Other notable features included high-grade nuclear atypia, mitosis, and tumor giant cells (Figure 4). Extensive sampling was done for the evidence of ductal carcinoma in-situ, which was absent and confirmed later by ancillary testing with CK and EMA (Figure 5). The hormone receptor and HER2 testing showed the disease to be TNBC. After explaining the nature of disease and the intent of treatment, the patient was started on ifosfamide-, adriamycin-, and paclitaxel-based chemotherapy (CT). The chemoplan was changed after two cycles to ifosfamide and adriamycin due to gastrointestinal intolerance. She completed six CT cycles in January 2016. Both the interim and post treatment PET-CT showed the patient to be disease free (Figure 6). A follow-up evaluation in February 2017 showed progressive disease in the right lower lobe of the lung (Figure 7). She was further offered metastasectomy and palliative CT with six cycles of ifosfamide and paclitaxel. The patient completed treatment and achieved a complete response in July 2017, and she is now on a six monthly follow-up. A telephone update in March 2018 revealed the patient to be alive with no evidence of disease at 8 months.

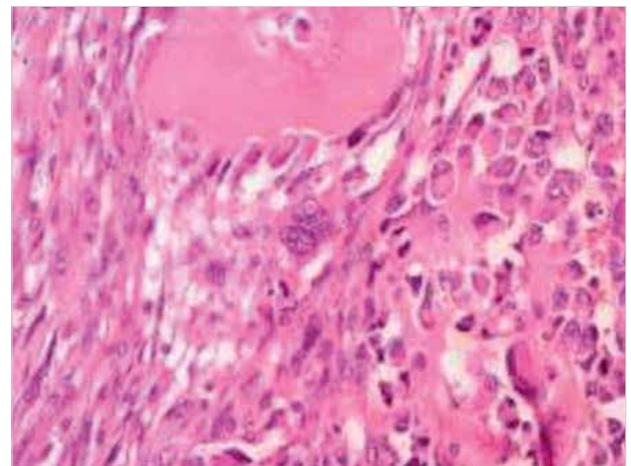


Figure 4. Plump spindle-to-epithelioid neoplastic cells with high-grade nuclear atypia, mitosis (thin arrow), and tumor giant cell (thick arrow) (H&E; x40 magnification)

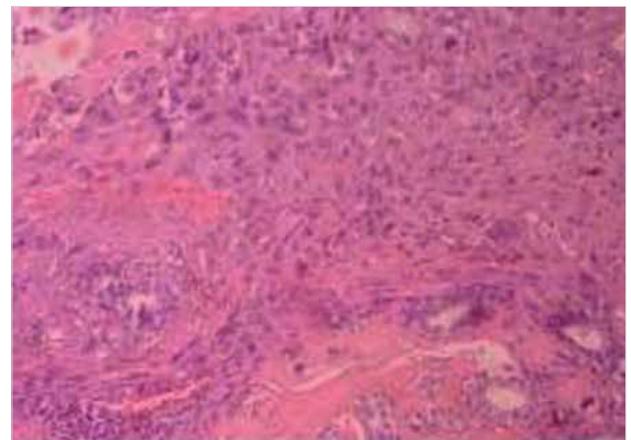


Figure 5. Cytokeratin (CK) highlights the entrapped normal duct, while the tumor cells are negative (IHC stain; x20 magnification)

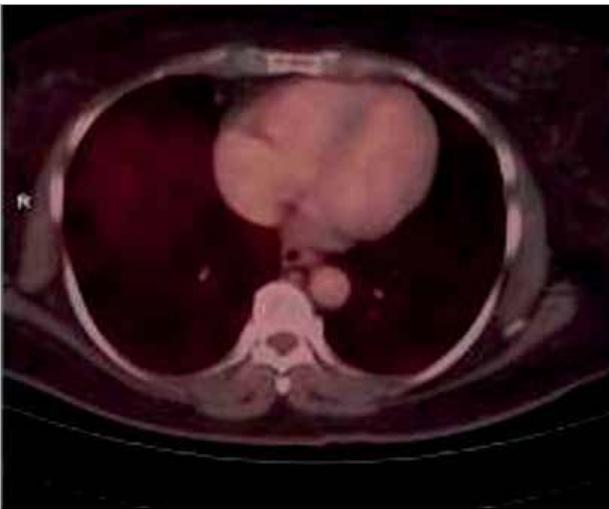


Figure 6. (Case 2) Baseline PET-CT: Transaxial view of the lung showing no metabolically active lesions

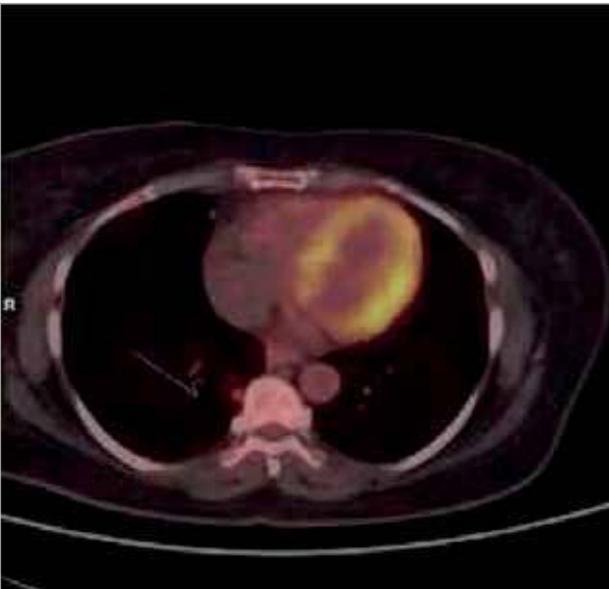


Figure 7. (Case 2) PET-CT at follow up: Transaxial view of the lung showing metabolically active lesion (0.7cm x0.7cm) in the right lower lobe lung

## DISCUSSION

Mammary osteosarcomas are highly aggressive lesions, and there is an uncertainty regarding their histogenesis and optimal therapy. Clinical presentation, although not specific for this subtype, presents as a hard, palpable mass without axillary lymphadenopathy (3). Although most cases arise *de novo*, radiation has been elucidated as a possible predisposing factor.

Mammography at diagnosis may or may not show microcalcifications, and a radiological presentation, as a well circumscribed lesion, can mimic a fibroadenoma (4). Preoperative diagnosis is difficult, and a complete histomorphological confirmation after a surgical resection remains the main approach. The most common differential diagnosis includes metaplastic carcinoma, phyllodes tumor with osteosarcomatous differentiation. The IHC using CK will help establish the epithelial differentiation in the spindle cells and will rule out the possibility of primary osteosarcoma (5). Other noteworthy

histological findings include spindle-to-epithelioid neoplastic cells with high-grade nuclear atypia, mitosis (Figure 2), tumor giant cells, and extensive osteoid.

Long-term prognosis is difficult to ascertain as the literature is limited. The literature shows an overall 5-year survival of 38%, with 28% of patients developing local recurrence and 41% metastasis (2). There is a higher propensity for hematogenous dissemination to the lungs, bones, and liver (6). To date, there are no validated treatment guidelines, but the best approach documented for localized disease is a wide local excision or mastectomy with negative resection margins, as the margin involvement is a major factor in local recurrence (6). Axillary lymph node removal is optional as these tumors do not spread through lymphatics. It has been observed that specific data on the role of adjuvant chemotherapy and radiotherapy are absent, so extrapolation of the treatment data from skeletal osteosarcomas and other extraosseous sarcomas can be done. Polychemotherapy using methotrexate, cisplatin, ifosfamide, adriamycin, and paclitaxel has been shown to improve the survival in the osteosarcoma bone, and similar observations have been documented in short reports on breast osteosarcoma. Post-operative radiotherapy is advisable in cases where the tumor-free margins are not obtained (7, 8).

## CONCLUSION

We report two cases of breast osteosarcoma that although being matched for age, stage, and hormone receptor status responded very differently to therapy. The patient who received a single modality of treatment, that is surgery, is alive without any evidence of disease at 52 months in contrast to the patient who received a multimodality treatment including surgery and adjuvant therapy and presented with distant metastasis at 12 months. Our cases highlight the treatment conundrums surrounding the treatment of breast osteosarcoma. Further research is needed to understand the biology of this disease and explain the arising controversies. Due to its rarity, we have started pooling tissues in our tissue bank to conduct further molecular research.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - D.C.C., T.J.; Design - J.T., K.D.C., P.G., G.G., S.P.; Supervision - D.C.C.; Resource - D.C.C.; Materials - K.D.C., P.G., G.G., S.P.; Data Collection and/or Processing - J.T., G.G., S.P.; Analysis and/or Interpretation - D.C.C., J.T.; Literature Search - J.T., K.D.C., P.G.; Writing Manuscript - D.C.C., J.T.; Critical Reviews - D.D.C., K.D.C.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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