

## Case Report :

### Carcinosarcoma of Breast: A report of triple positive variant

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#### Abstract:

Carcinosarcoma of the breast is an exceedingly rare and aggressive tumour with exiguous prognosis. This tumour has the epithelial and mesenchymal components derived from two diverse cell lines. They are arduous to diagnose both preoperatively and postoperatively. Differential staining with cytokeratin, vimentin and lack of transition between the two components of the tumour aids in clinching the diagnosis. Attaining negative surgical margins either by radical or breast conserving procedures remain the gold standard in management. Carcinosarcoma of the breast with triple receptor positive phenotype are inimitable. Adjuvant therapy should be tailored to the immuno-histochemical signature of the individual tumours. A careful periodic follow-up is vital to detect metastasis and recurrence early and to minimize mortality. We hereby report a case of carcinosarcoma of the breast with triple positive phenotype because of its rarity and prognostic importance.

**Key words:** Breast; Carcinosarcoma; Triple positive breast cancer

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#### Introduction:

Carcinosarcoma of the breast is a rare form of breast malignancy; the behaviour and the treatment plans of this heterogeneous tumour are distinct from other breast malignancies. Hence, arriving at a precise diagnosis is of paramount significance in the management of carcinosarcoma.

These tumours are unique because of their aggressiveness, immunohistochemistry, histology, and moreover, ominous prognosis. Herein we report a rare triple receptor positive variant of carcinosarcoma of the breast [1].

#### Case report:

A 65 years postmenopausal female presented with a lump in her right breast for 6 months, which had precipitously enlarged and ulcerated in the last fortnight. Physical examination

unveiled a grossly enlarged right breast with a hard mass of 15x12cm size, encompassing upper and lower outer quadrants with ill-defined margins (Fig 1a) and 6x5x3 cm ulcer in the lower outer quadrant (Fig 1b) with two enlarged axillary lymph nodes. Left breast and systemic examination were unremarkable.

A mammogram showed a dense lesion with irregular spiculated margins associated with architectural distortion of surrounding breast tissue. Core needle biopsy was suggestive of malignant phyllodes tumour with marked stromal cellularity and a high mitotic count. No metastasis was found in the systemic radiological examination. In view of the size of the lesion, the patient underwent right modified radical mastectomy (Fig 1c) and the gross examination of the specimen showed a

20x16x12 cm greyish brown tumour mass. Microscopically, it showed extensive areas of malignant phyllodes tumour with regions of poorly differentiated carcinoma and none of the fields showed the transition between the two elements (Fig 1d). Two of the 24 nodes were positive for metastatic carcinomatous elements and there was no evidence of perinodal tumour extension. The deep resected margins were free from the tumour mass. The immunohistochemical staining exhibited keratin and vimentin positivity of epithelial and sarcomatous components correspondingly. Estrogen and progesterone receptor status and HER-2neu oncogene were positive (Fig 1e, f). Post operatively the patient received six cycles of anthracycline and taxane centered chemotherapy. She is now on systematic follow up and hormonal therapy (anti estrogens) for last 18 months and is doing well.

#### **Discussion:**

Carcinosarcoma of the breast is a tumour of the malignant epithelial tissue mixed with malignant cells of mesenchymal origin [2]. These rare, aggressive tumours account for less than 0.2% of all malignant breast lesions [3]. In the year 2000, the WHO acknowledged carcinosarcoma as a distinct pathological entity and classified them into the mixed mesenchymal variant of metaplastic breast carcinoma. The representative age of presentation ranges from 32 to 77 years. Clinically patients commonly present with rapidly growing swelling or a palpable mass in the breast [4]. Most of which are quite large with features of skin ulceration and nipple retraction. About 20% of these tumours are fixed to the skin and deep tissues. These tumours have high hematogenous metastatic potential, especially

disseminating to the lungs and the bones [5]. Though the tumours are of large size, the axillary lymph nodal involvement is less frequent when compared to other breast cancers [6].

The incidence of axillary lymph nodal involvement is stated to be between 6% and 26%. The other clinical features of carcinosarcoma of the breast are not different from those of other breast carcinoma.

The aetiology of this peculiar tumour is yet to be identified and the origin of the breast carcinosarcoma is controversial and the debate on the issue dates back to the 1950s. The historical collision theory suggested that the tumour cells were derived from two distinct cells of origin, which joined together at some point during oncogenesis. In contrary to this, modern day molecular advances have clearly established clonal relationship between morphologically distinct components of the same tumour and further alterations leading to the transdifferentiation in selected tumours [7].

The recommendations for diagnostic imaging are the same as that of any palpable mass in the breast. All the patients should be investigated with diagnostic mammography and/or with focussed ultrasound. On a mammogram, carcinosarcoma are depicted by high density lesions with circumscribed, obscured, irregular or spiculated margins [6]. They are associated with a high degree of architectural distortion. The sonographic appearance of this bellicosetumour is described as a heterogenous or hypoechoic solid or mixed cystic and solid mass with posterior acoustic enhancement, which is in contrary to the posterior shadowing commonly visualised with invasive ductal

carcinoma<sup>[7]</sup>. The carcinosarcoma appears in Magnetic Resonance Imaging as isointense to hypointense mass on T1 weighted images and with often increased signal intensity in T2 weighted images. The increased signal intensity in T2 weighted images is consistent with the pathological findings of cystic degeneration and necrosis associated with the tumour. Moreover, Velasco et.al observed that 91% of the patients with carcinosarcoma had increased signal intensity in T2 weighted images<sup>[8]</sup>. As with other malignant breast tumour, X-ray/ CT chest, USG/CT abdomen, radionuclide bone scan and/or PET/ CT fusion scan forms a part of the metastatic work-up.

Though Fine needle biopsy or core needle biopsy of the mass is frequently used in the preoperative diagnosis, interpreting the specimen is often challenging. The sampled tissue in these techniques may clinch the diagnosis; but the trifling quantity of the specimen may not be ample to represent the overall pre-surgical profile of the tumour<sup>[9]</sup>. On pathological examination, these tumours exhibit both epithelial and mesenchymal components; though the composition and quantity may vary from case to case. The essential finding which differentiates the carcinosarcoma from other metaplastic carcinomas is the absence of region of transition between the two components<sup>[10]</sup>. Hence a thorough search of the specimen for the transition regions is of supreme importance. Most of these tumours are composed of poorly differentiated, high grade, mitotically active and highly cellular pleomorphic spindle cells. The epithelial component of the tumour may be composed of undifferentiated carcinoma, adenocarcinoma, insitu carcinoma, infiltrative ductal carcinoma or squamous carcinoma. The

mesenchymal component may vary from undifferentiated mesenchymal areas to fibroblastic, chondroblastic or osteoblastic areas. Although diagnosing the carcinosarcoma in an epithelial tumour with sarcomatous component is fairly undemanding, diagnosing the same in the background of malignant phyllodes tumour with poorly differentiated carcinomatous component is often tricky<sup>[10]</sup>. Such presentations are quite common and are frequently misdiagnosed as sarcoma by the pathologist, especially if sampling is insufficient or the microscopic examination is inadequate.

Immunohistochemical analysis aids in pathological diagnosis and treatment plan of the patient. Majority of the Carcinosarcoma of the breast is estrogen and progesterone receptor negative and HER- neu negative by immunohistochemical analysis<sup>[6]</sup>. But in cases where estrogen, progesterone receptors and HER- neu status are positive, adjuvant hormonal therapy and therapy with Trastuzumab (Herceptin) will offer survival benefit. This subset of receptor positive tumours tend to be less aggressive and behave more like invasive ductal carcinoma, offering a better prognosis when compared to triple negative carcinosarcomas. Carcinomatous component and sarcomatous components stain positive for cytokeratin and vimentin respectively. Though p53, S-100, EGFR and newer marker analysis are being studied currently, their exact role in diagnosis and overall impact on the outcome of the patient has not been concretely proven so as to be applied universally<sup>[11]</sup>.

Defining a treatment strategy for patients with carcinosarcoma is often difficult because of the paucity of literature regarding the management protocols. Hence a multidisciplinary approach is

the choice of treatment. The aim of the surgery should be to attain negative margins. Modified radical mastectomy is the practical surgery of choice in cases of Carcinosarcoma [10]. Nevertheless, wide local excision and partial mastectomy with potential for breast conservation should be individualised to the case [12]. Anti estrogens and other hormonal therapies are of little importance in view of negative estrogen, progesterone and HER-2/neu receptor status. But whenever the receptor status is positive, offering anti estrogens and other hormonal therapies will improve the prognosis and survival rates. The results of adjuvant chemotherapy are also sub optimal when compared to other malignant breast lesions. As with other breast cancers, Cyclophosphamide, Methotrexate, 5-Fluorouracil (CMF) and anthracycline/ taxane based regimen is commonly prescribed. However, existing literature suggests that CMF regimen is less effective than anthracycline/ taxane based combination regimen [13]. Hence anthracycline/ taxane based combination regimen are more suitable for cases of the breast carcinosarcoma [10]. Most commonly, tumour cells spread into the perivascular tissues and beyond the capsule leading to increased incidence of local recurrences. Adjuvant radiotherapy reduces the local recurrences in such cases and also in cases where negative margins post surgery could not be attained [14]. Still, due to aggressive nature the tumour recurrences are quite common in practice. In cases of recurrences, if recurrent tumour is resectable, the prognosis is better.

The prognosis of the breast carcinosarcoma is dismal. The cumulative five year survival rate is around 49% [10]. According to Hennessy et al.

the overall survival rate for stage I, II, III, and IV are 73%, 59%, 44% and 0% respectively [6]. A careful periodic follow-up is essential in detecting metastasis and recurrences early and in combatting them efficiently, thereby improving the overall outcome of the patient and reducing the mortality. The future targeted therapies hold the key in managing cases of carcinosarcoma. Targeted therapies to EGFR especially cetuximab and gefitinib are being evaluated in clinical trials and have shown promising results [11]; however, further research needs to be performed in order to completely evaluate its potential in treating patients with carcinosarcoma of the breast.

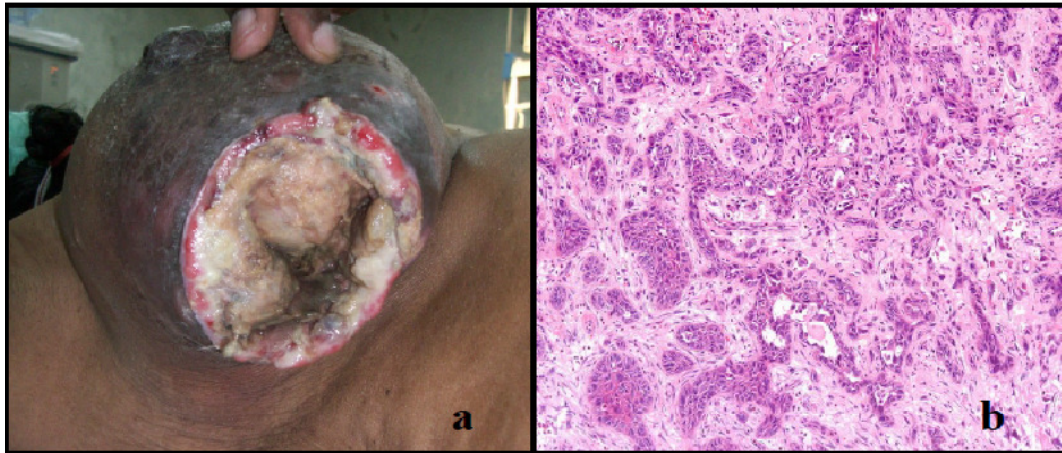
#### **Conclusion:**

Due to the rarity and heterogeneity of carcinosarcoma of the breast, there are no defined standard therapies to these tumours. Although radical surgery is the preferred option, Breast conservative procedures achieving negative surgical margins yield comparable results in a selected subset of patients. Obtaining a precise diagnosis of carcinosarcoma is essential in order to optimally tailor the adjuvant therapy towards this aggressive breast cancer subtype. Traditional chemo and hormonal therapies for invasive ductal carcinoma are ineffective against carcinosarcoma and are often associated with poorer survival. But whenever the receptor status is positive, offering anti estrogens and other hormonal therapies will improve the prognosis and survival rates. A careful periodic follow-up is paramount to detect metastasis and recurrence early and minimize mortality.

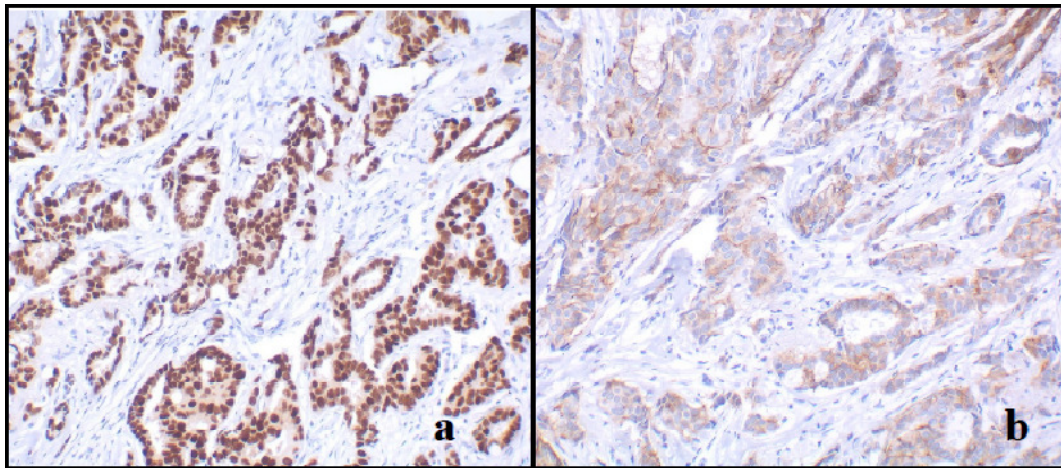
In order to gain insight into the similarities and different characterizing aspects of

carcinosarcoma, all diagnosed cases should be reported especially the receptor positive variants. Although in future, targeted therapies

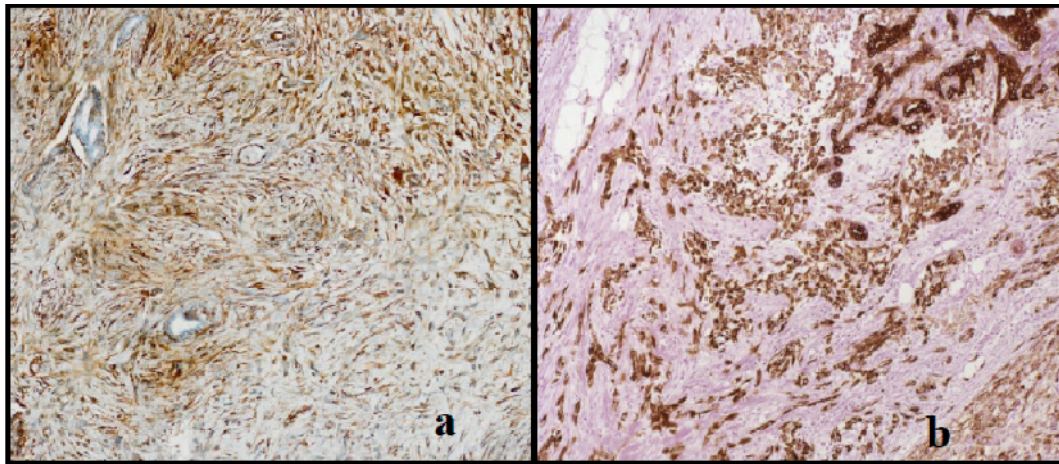
hold promise in treating these rare tumours; more research is warranted before adapting them.



- **Fig 1(a)**Preoperative photograph showing an irregular 6x5x3 cm ulcer in the lower outer quadrant of the right breast **(b)**Low power microscopic field showing biphasic lesion composed of sheets of spindle cells exhibiting moderate nuclear pleomorphism, eosinophilic cytoplasm and indistinct cell border and interspersed neoplastic glands lined by cuboidal cells with vesicular nuclei, prominent nucleoli and moderate amount of eosinophilic cytoplasm



- **Fig 2 (a)**Low power microscopic field showing estrogen receptor positivity **(b)**Low power microscopic field showing HER-2/neu oncogene positivity



- **Fig 3 (a)** Low power microscopic field showing sarcomatous stroma showing vimentin positivity **(b)** Low power microscopic field showing epithelial component showing cyokeratin positivity

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