Metaplastic Breast Carcinoma: A Report of Two Cases

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Abstract

Breast cancers are the commonest female malignancy worldwide with attendant diversity in its clinico-pathological presentation. The diagnosis of this disease entity has witnessed innovations over the decades and many novel therapies have been discovered with respect to the molecular and biological characteristics. There are different variants of breast cancer and this study presents a report of 2 cases of metaplastic breast carcinomas; (a rare variant) diagnosed in our centre. The diagnosis of this entity was corroborated by immunohistochemical analysis. Metaplastic breast carcinomas are a group of rare breast pathologies that demonstrate unpredictable and aggressive clinical course with poor prognostic outcome. Detailed pathological analysis is essential for diagnosis to achieve satisfactory oncological management.

Introduction

Breast cancer is the most common female malignancy and a significant cause of mortality and morbidity worldwide.[1,2] The incidence has been on the rise in the sub-Saharan Africa where hitherto, it was rare.[3] Over the years, there has been a heightened level of awareness about the disease entity among the general populace especially women. Clinical researches have also unraveled information about the diversity of this tumour with respect to the clinical behaviour, cytogenetics and diagnostic investigations [4] Based on the current available clinical information, breast cancers are classified according to their histopathological pattern, molecular characteristics and biological behavior. These various classifications are used by clinicians to stratify the patients with respect to their treatment protocol. Metaplastic breast carcinoma (MBC) is one of the breast cancer variants characterized by intimate admixture of glandular and non-glandular cellular components (and this may entail the presence of either epithelial and /or mesenchymal components). [4,5]

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MBC accounts for < 1% of all breast cancers and constitute a rare variant of invasive breast carcinoma with the potential of spread to other regions of the breast and other parts of the body. [5] In this report, we describe the presentation of two women who presented to the breast clinic with features of breast cancer; had mastectomy with subsequent histopathological diagnosis of metaplastic breast cancer associated with triple negative receptor status.

Case Presentations:

Patient 1

PN, a 26-year old lady who presented with features ulcerating left breast mass of 9 months duration, with associated matted ipsilateral axillary fullness. There was associated bloody nipple discharge but no cough and jaundice. Clinical examination revealed a young lady who was pale, anicteric, emaciated with ulcerating left breast mass and ipsilateral matted axillary lymph nodes. Chest and abdominal examinations were essentially normal on clinical examination. Radiological investigations done (chest x-ray, abdominal ultrasound) and liver function test were essentially normal. A diagnosis of locally advanced left breast cancer was made (T3aN1Mx). An incisional biopsy of the ulcerating breast mass was taken for histopathological and immunohistochemical analysis.

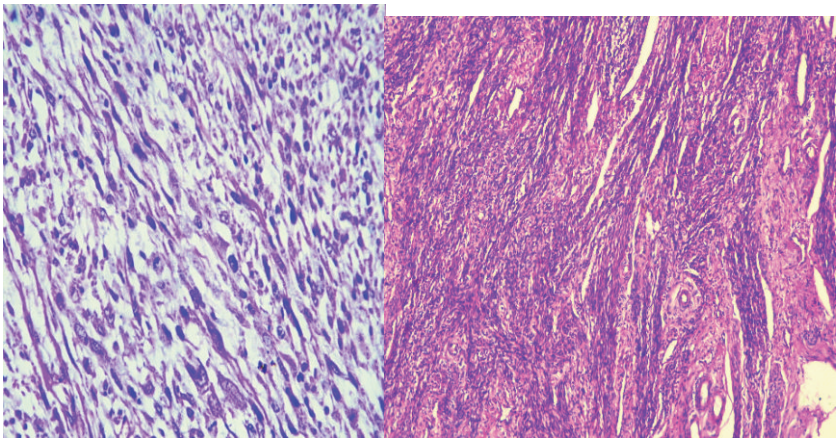
Histopathology specimen

Macroscopic: Received is a mastectomy specimen measuring 20x20x12cm weighing 2.5kg. There is a central area of ulceration measuring 10cm x 10cm with attached everted skin. Serial sections show multiple cystic spaces with areas of necrosis.

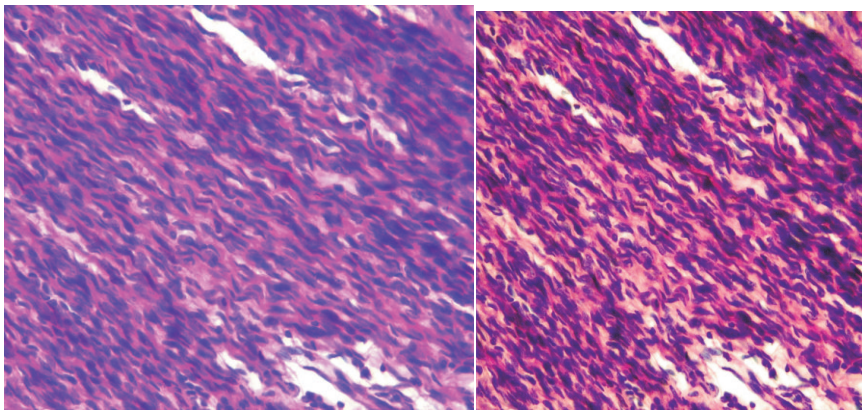
Microscopic: Histologic sections of the breast tissue show a mixture of proliferation of malignant epithelial and mesenchymal cells. The malignant epithelial cells are few and have hyperchromatic vesicular nuclei. The predominant neoplastic cells are malignant spindle-shaped cells with pleomorphic, hyperchromatic nuclei and increased nucleo-cytoplasmic ratio.

A diagnosis of metaplastic breast carcinoma was made and immunohistochemistry analysis revealed triple negative receptor status. She had 3 courses of neo-adjuvant chemotherapy (docetaxel/capecitabine) with subsequent total mastectomy with axillary dissection. Adjuvant chemotherapy was thereafter given.

Illustrations:

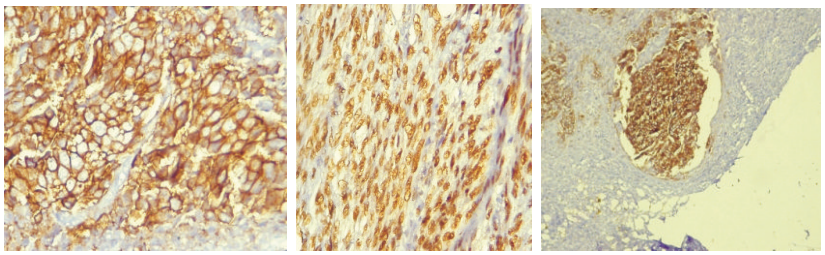


Patient 1 microphotographs

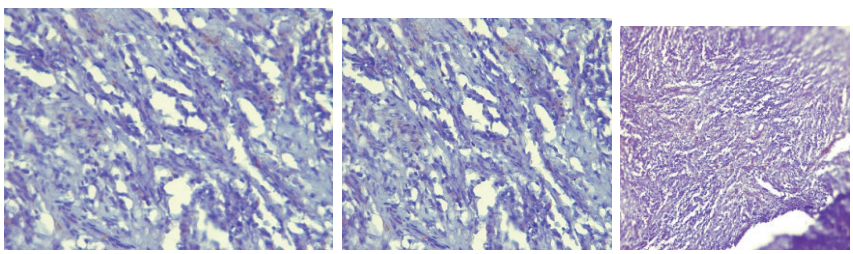


Patient 2 microphotographs (s-367)

Immunohistochemical details:



ER positive (control) **PR positive (control)** **HER- 2/neu positive (control)**



S-367 ER negative **S-367 PR negative** **S-367 Her-2/ neu negative**

Patient 2

AH, a 26-year old lady who presented with left breast mass of 5 months duration with associated pain, axillary swellings, weakness, weight loss and yellowness of the eyes. Clinical examination revealed ulcerating left breast mass, with peau d'orange, nipple retraction, multiple, matted ipsilateral axillary lymph nodes with left upper limb lymphedema.

Chest x-ray revealed multiple opacities in both lung fields with some pleural effusion. Liver function tests showed marginal elevation of serum alkaline phosphatase enzyme. Incisional biopsy of the breast mass was carried out for histopathology and immunohistochemistry.

Histopathology specimen:

Macroscopic: Mastectomy specimen measuring 20x14x20cm and weighed 2.0kg. Cut section shows a tumour mass, measuring 13 x 4cmat widest diameter.

Microscopy: Histological sections of breast tissue shows dual picture of proliferating neoplastic atypical spindle shaped cells in a fibrocollagenous stroma. These cells are in sheets have spindle shaped pleomorphic, hyperchromatic nuclei. (see photomicrographs)

A diagnosis of metaplastic left breast carcinoma (triple negative receptor status) was made (advanced stage-T4cN1M1). She had thoracostomy tube inserted and pleurodesis done for the pleural effusion and thereafter optimized. She had 3 cycles of neo-adjuvant chemotherapy with docetaxel/capecitabine regimen followed by total mastectomy with axillary dissection. Adjuvant chemotherapy was administered after the surgery.

Discussion

The clinical presentation of MBC has been observed to slightly vary from the typical invasive ductal carcinoma. The median age at presentation of MBC has been

reported to be 48-59 years which is a bit higher compared to invasive ductal carcinoma.[4] Features of loco-regional invasion (such as fixity to pectoralis muscle and fascia with infiltration of the overlying skin) has been reported in > 20% of patients (while axillary node involvement) has been found to be present in up to 30% of women presenting with MBC.[4,5] These clinical features are quite different from that observed in patients presenting with IDC in whom axillary node involvement is usually present in over 50% of patients as at the time of diagnosis. [4,6]

The pathology of MBC is described by the heterogenous nature of the disease in which different neoplastic epithelial cells are present consisting of glandular and non- glandular patterns with epithelial and/ or mesenchymal components.[6,7] The spindle cell variant is the most common type with poorly cohesive sheets of atypical spindle cells. Metaplastic carcinomas are usually characterized by the presence of immature mesenchymal and epithelial elements.[8,9] The immature mesenchymal components include fibrosarcoma, leiomyosarcoma, osteogenic sarcoma. The immature glandular epithelial cells have been found to transform into the non-glandular mesenchymal cells. These cell lines tend to exhibit aggressive behavior and more often than not demonstrate triple negative receptor status hence; their non-response to either hormonal or targeted therapies.

There are limited molecular studies on pathology of metaplastic carcinomas. However, Hayes *et al* concluded that activation of Wnt signaling pathway is common in this subtype of breast cancer. CTNNB1(beta-catenin), APC,WISP3 gene mutations have also been found to be implicated.[10] About 70% of metaplastic carcinomas show epithelial growth factor receptor (EGFR) gene amplification and over expression**.** The biphasic nature of MBC (the presence of both carcinomatous and heterogenous sarcomatous cell lines) has been attributed to certain factors that are related to the biclonal origin of the metaplastic cells, metaplastic mechanism of cells from a monoclonal origin and presence of transitional areas around epithelial tight junctions. These areas pertaining to the cytogenetic behaviour of MBC still remain largely controversial. However, certain biomarkers that are useful in the prognostication of MBC have been identified and these include S-100 and cytokeratin 5 and 6 (CK 5/6) [epithelial markers], vimentin (mesenchymal marker), P53, vascular endothelial growth factor (VEGF) and matrix metalloprotenases.[11] MBC tends to present at a more advanced stage at diagnosis with high propensity for local recurrence. This tumour has been found to occur *de-novo* but the possibility of it arising from a previous lesion like sclerosing lesions, nipple adenomas and papillomas has been earlier reported.[12] MBC have also been found to demonstrate multiple molecular subtypes of breast cancer e.g luminal, basal-like, normal breast-like, HER-2 positive and these molecular markers are quite useful in determining the outcome of such a tumour.

In making the diagnosis of MBC, histopathological evaluation is an invaluable tool that stands as the final arbiter. Modalities that can be employed include fine needle aspiration cytology (FNAC), core-cut biopsy or excisional biopsy. In the hands of the expert, FNAC remains an acceptable means of obtaining specimen. This modality picks discrete carcinomatous epithelial components anywhere in the tumour. Either FNAC or core-cut biopsies could be done with image guidance to improve the yield. Excision biopsy is however advocated in huge lesions.

Pathological samples afford the opportunity of carrying out receptor studies through special staining techniques. The prevalence of triple negative status (ER-, PR-, HER 2/neu-) in MBC specimen has been reported and the presence of such in our index patients was not surprising. [13]. Histopathological diagnosis of metaplastic carcinoma of the breast can be challenging as they often demonstrate triple negative receptor status.

Conclusion

Metaplastic breast carcinoma being a rare variant of invasive ductal carcinoma may often be confused with other breast lesions because of its diverse and non-specific features. The hallmark of diagnosis therefore depends on the experience of the pathologist to characterize the microscopic features of this entity as well as its biological behavior. Both cases reported in this series were spindle cell variant and were both triple negative and cytokeratin 5/6 negative.

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