A rare case of metaplastic breast carcinoma from India: Towards precision oncology

Soirindhri Banerjee[1], Ishika Mahajan[2], Aruni Ghose[3], Stergios Boussios[4], and Shivam Chakraborty[1]

[1]IPGMER
[2]Lincoln County Hospital
[3]Barts Health NHS Trust
[4]Medway NHS Foundation Trust

August 3, 2023

Abstract

Background : Metaplastic Breast Cancer (MpBC) is an exceedingly rare entity, accounting for less than 1% of all malignant breast tumours. Predominantly triple-negative, they are notorious for their chemoresistance, high rates of recurrence and decreased disease-free survival (DFS). All this contributes significantly to BC mortality and results in poor prognostic implications. Limited evidence has led to a lacuna of specific treatment guidelines for this entity and hence remains an uncharted territory for clinicians. Case : We report a case of left-sided low-grade metaplastic triple negative T3N2aM0 BC treated with neoadjuvant chemotherapy, primary surgery, and adjuvant radiotherapy, presently in remission. Conclusion : Limited experience in management of this pathological entity warrants the need for more research on it, with a special focus on targeted therapy. Discussing possibilities of a tailored approach, rather than a one-size-fits-all approach may aid in paving the path for the future of MpBC treatment.

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A rare case of metaplastic breast carcinoma from India: Towards precision oncology

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***Soirindhri Banerjee[1], Ishika Mahajan[2], Aruni Ghose[3,4,5,6,7], Stergios Boussios[5,8,9,10], Shivam Chakraborty[11]**

[1]Department of Radiation Oncology, Institute of Post Graduate Medical Education & Research and SSKM Hospital, Kolkata, India.

[2]Department of Haematology and Oncology, Lincoln County Hospital, United Lincolnshire Hospitals Trust, Lincoln LN2 5QY

[3]Department of Medical Oncology, Barts Cancer Centre, St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK

[4]Department of Medical Oncology, Mount Vernon Cancer Centre, East and North Hertfordshire NHS Trust, London, UK

[5]Department of Medical Oncology, Medway NHS Foundation Trust, Kent, UK

[6]United Kingdom and Ireland Global Cancer Network

[7]Immuno-Oncology Clinical Network, UK

[8]Faculty of Life Sciences and Medicine, School of Cancer and Pharmaceutical Sciences, King's College London, London, UK

[9]Kent and Medway Medical School, University of Kent, Canterbury, UK

[10]AELIA Organisation, 9th Km Thessaloniki – Thermi, 57001, Thessaloniki, Greece

[11]Depatment of Pathology, Institute of Post Graduate Medical Education & Research and SSKM Hospital, Kolkata, India.

***Corresponding Author**

Soirindhri Banerjee

Senior Resident

Department of Radiation Oncology, Institute of Post Graduate Medical Education & Research and SSKM Hospital.

244, A J C Bose Road, Kolkata 700020, India.

Email – soirindhribanerjee@yahoo.co.in

Abstract

Background : Metaplastic Breast Cancer (MpBC) is an exceedingly rare entity, accounting for less than 1% of all malignant breast tumours. Predominantly triple-negative, they are notorious for their chemoresistance, high rates of recurrence and decreased disease-free survival (DFS). All this contributes significantly to BC mortality and results in poor prognostic implications. Limited evidence has led to a lacuna of specific treatment guidelines for this entity and hence remains an uncharted territory for clinicians.

Case : We report a case of left-sided low-grade metaplastic triple negative T3N2aM0 BC treated with neoadjuvant chemotherapy, primary surgery, and adjuvant radiotherapy, presently in remission.

Conclusion : Limited experience in management of this pathological entity warrants the need for more research on it, with a special focus on targeted therapy. Discussing possibilities of a tailored approach, rather than a one-size-fits-all approach may aid in paving the path for the future of MpBC treatment.

Keywords

breast cancer; metaplastic; triple negative; adjuvant radiotherapy; targeted therapy

Introduction

A rare entity, constituting 0.2-5% of the global breast cancer (BC) burden, metaplastic breast cancer (MpBC) [1]. MpBC represents a significant proportion of global BC mortality.

MpBC represents a group of mostly high-grade tumours, demonstrating at least two unique cellular types-characteristically epithelial and mesenchymal elements mixed with carcinoma of the usual kind [2]. These metaplastic changes represent a conversion from glandular breast tissue to non-glandular carcinomatous (squamous) and sarcomatous (spindle cell, chondroid, osseous, and rhabdoid cells) morphologies [3].

There can be high-grade variants with high metastasis potential or low-grade variants such as fibromatosis-like carcinoma and low-grade adenosquamous carcinoma (Fig 1).

The high-grade variants have a high likelihood of metastasis and are notoriously chemoresistant and aggressive [4]. The rarer low-grade variants have a relatively favourable prognosis as compared to the commoner high-grade subtypes [5].

These tumours are typically triple-negative [3,4]. There are however proteomic and genomic differences between conventional TNBC and MpBC. Spindle-cell carcinoma commonly expresses p63 and low-grade adenosquamous carcinoma show high rates of PIK3CA. Conventional TNBC have low PIK3CA expression. Osteoid and chondroid variants show increased SNail, BCL-2-like protein and Akt-1 pathway activity. In contrast to non-MpBC TNBC tumours, MpBC showed higher upregulation of epithelial-to-mesenchymal transition (EMT) and collagen genes, but downregulation of keratinization genes. These support the hypothesis that the histological, proteomic and genomic variations may contribute to the deadliness of these BC variants [6].

MpBC has a worse prognosis as compared to non-metaplastic triple-negative BC (TNBC). There is a shorter disease-free interval and overall survival with a double chance of recurrence [7]. Spindle cell differentiation has the worst 5-year survival at about 40% [6].

Here we report the case of a lady who presented with a locally advanced disease that was found to be metaplastic cancer on histology and is now 3 years disease free.

Case

A 46-year-old premenopausal, diabetic lady with two living children presented to the outpatient clinic in September 2020 with a left-sided breast lump.

On clinical examination, the lump measured 5x6 cm, occupying the upper half of the left breast. It extended to the nipple-areolar complex (NAC) with no fixity to the skin or underlying tissue. There were no skin changes. Axillary palpation showed multiple left-sided matted lymph nodes.

Elaboration of a risk factor history revealed a 5-year history of oral contraceptive pills (OCPs) usage 20 years previously.

An Ultrasonogram of the breasts showed a large hypoechoic space-occupying lesion, measuring about 6.5x4.6cm, with irregular, mildly lobulated margins on the left upper breast at 12 o'clock position. The lesion showed no calcification or necrosis. Two oval lymph nodes measuring 1.2cm and 1.4cm in the largest diameter with noted in the left axilla. The scan was classified as BIRADS-4.

A trucut biopsy was done shortly after the presentation. The histopathology of the sample was suggestive of invasive BC. Immunohistochemistry (IHC) revealed hormone receptors (oestrogen and progesterone) and HER2-neu negative- triple negative breast cancer (TNBC).

Oncological work-up including a chest X-ray (CXR) and USS of her abdomen revealed no abnormalities. A Tc99 m bone scan was advised, but the patient was unable to get it done due to economic constraints.

The tumour was staged at T3N2aM0 and the patient was discussed in a multidisciplinary team meeting. She was planned for surgical clip (marker) placement to delineate the tumour margins followed by neoadjuvant chemotherapy (NACT), re-imaging and definitive surgery. A further plan was to be made following the histopathological examination of the surgical specimen.

She underwent 6 cycles of NACT with intravenous Docetaxol (75mg/m2), Doxorubicin (50mg/m2) and Cyclophosphamide (500mg/m2) at 3 weekly intervals. Chemotherapy was tolerated well.

An interval ultrasonogram of both breasts was done post-chemotherapy, which showed an interval increase in the size of the lesion- 9.4x6.4x5.9cm. There were internal echoes noted, likely necrotic foci within the lesion, with no significant axillary adenopathy. The right breast remained normal. The scan was classed BIRADS-6.

Following this, the option of surgery was discussed with the patient. She was keen on breast conservation. Due to a high breast: tumour ratio, she underwent a left-sided extreme oncoplasty- where the tumour and left axillary nodal tissue were removed en-mass and reconstruction was performed with a latisimus dorsi musculocutaneous flap. The nipple-areola complex was spared. The post-operative period was uneventful.

Histopathological sections of the 18x13x6cm surgical specimen showed a tumour measuring 7x6x4 cm. The tumour was composed of tubules, clusters, solid nests, and syncytial cell infiltrate. (Fig 2) A large necrotic focus was also identified. There were areas of mesenchymal differentiation with pleomorphic cells and intervening occasional spindle cells. The cells had a variegated appearance and showed pleomorphism, prominent nucleoli and brisk mitosis. There was no evidence of lymphovascular or perineural invasion and no component of ductal carcinoma in situ. All resection margins and deep margins were clear. All resected axillary lymph nodes were negative. The tumour was classified as Grade 3, staged pT3N0Mx.

She was rediscussed in the multidisciplinary team meeting. The meeting outcome was to treat her with adjuvant radiotherapy (RT) utilizing external beam RT (EBRT) with a Telecobalt-60 machine (42.6 Gray in 16 fractions) with photon boost to the surgical bed, marked by the initial clips placed (10 Gray in 5 fractions) using right and left tangential fields. In June 2021, she completed EBRT uneventfully. Since then, she has been on 3 monthly follow-up visits with USS of bilateral breast and axillae, serum CA15-3 level and clinical breast examination alongside CT scan of thorax done 6 monthly. None of the aforesaid modalities have shown evidence of residual or recurrent disease and she has had no fresh complaints.

Discussion

Metaplastic breast cancer is an infrequent cancer of the breast, the identification, elucidation and management of which is an evolving field, gaining momentum over the last two decades [8].

The median age of presentation is 48-59 years i.e. perimenopausal women. [9] Earlier database analyses have shown a higher mean age of diagnosis of 61 years. [10] Our patient did not fit this demographic, with a younger age of presentation and pre-menopausal status. A higher prevalence is noted in African-American and Hispanic women. [10] There is a need to extend the databases to include Asian and African populations to identify risk groups in low-middle-income countries.

Clinically, the majority present with a large, well-circumscribed mass, usually >5cm. [11] MpBC tends to have a large tumour size, rapid growth and less axillary lymph node involvement. [6,12] The present case had a similar large size at presentation keeping with the literature.

The diagnosis of MpBC is histopathological, thus is highly dependent on postoperative pathology. There is no typical imaging to discern it from the other variants of BC, and pathologically, as it is a mixture of two or more homologous or heterologous components, it can be very difficult to differentiate it from other rare benign or malignant histologies. [13]

Metaplastic carcinomas are on the spectrum of basal carcinomas, displaying a basal/myoepithelial and epithelial-to-mesenchymal molecular structure**.** [14] It is a rare heterogenous subtype characterised by squamous, spindle cell and mesenchymal phenotype with or without conventional adenocarcinoma component. [15]

Histopathological categorization is of cardinal importance as it guides the prognosis with the squamous variant being the worst. Diagnosis from cytology is challenging as both epithelial and mesenchymal elements are essential components. They are known to display positivity for cytokeratin, S-100 and vimentin or myoepithelial markers like CD10, p63, and smooth muscle actin. These tumours are mostly sporadic but can arise from previous lesions like fibroadenoma, spindle cell carcinoma, papilloma and complex sclerosing lesions. [16] Beatty et al. identified 24 MpBC cases which showed high nuclear grade, negative ER/PR and HER2 status, EGFR positivity and no significant difference in multidisciplinary treatment patterns, recurrence, or survival, in comparison to typical BC. [17] Prior studies have found that MpBC typically has molecular alterations in epithelial-to-mesenchymal transition; amplification of epidermal growth factor receptor (EGFR/HER1); PI3K/AKT, nitric oxide and Wnt/β-catenin signalling; altered immune response; and cell cycle dysregulation. [6]

First described in 1987, low-grade adenosquamous carcinoma of the breast is a rare variant of metaplastic carcinoma. This variant is characterised by having both squamous and glandular differentiation embedded in a bland background of spindle cells. [18, 19] We describe a similar histological description in our case,

and the patient being cancer-free 3 years on, provides further evidence of the favourable prognosis due to the low-grade nature of these tumours.

Most MpBC is triple-negative tumours, and thus the management principles follow those of conventional TNBC. These cancers are treated with anthracycline, taxane and platinum-based chemotherapy. The larger size of the tumours, lack of hormone therapy as a systemic treatment, and the increased risk of metastasis make a case for the increased use of systemic chemotherapy though the literature bases lack substantial evidence to support this practice. [5, 10] Our patient received NACT, following which the axillary nodes did shrink (negative axillary dissection specimen), but the tumour however grew in size. The cut section did however demonstrate a large area of necrosis, which was pre-empted by the interval sonomammogrphy showing internal echoes. Variation in response to NACT exists based on the histologic subtype, with some benefit observed in matrix-producing MpBC. [9] The role of NACT in MpBC is still unclear, but may continue to remain the standard of practice due to the higher risk of metastasis in the absence of it, and until newer novel therapies are developed.

There have been limited studies regarding the use of adjuvant radiotherapy, most of which have demonstrated better overall survival (OS), DFS and reduced recurrence rate. [20] Following the conventional principles of BC treatment, radiation to the tumour bed is commonly given with BCS, which has shown some favourable outcomes. Unfortunately, the published literature has small patient cohorts. [21]

Most patients with MpBc receive surgery as a viable treatment option, especially if presented early with locally advanced operable tumours. Both mastectomy and breast conservation surgery were performed, with the former being more commonly performed due to larger tumour size, and high tumour:normal breast tissue ratio. [10, 22]

Novel molecular targeted therapies such as poly ADP-ribose polymerase (PARP) inhibitors, angiogenesis inhibitors (bevacizumab), protein kinase inhibitors and mammalian target of Rapamycin (mTOR) inhibitors (temsirolimus or everolimus) have shown good potential for research in MpBC. The increased expression of EGFR provides an opportunity for targeted tumour therapy in these tumours. [13]

Predictors of a poorer outcome are the presence of skin invasion, younger age at presentation (<39 years), and appearance of squamous cell carcinoma in the lymph nodes. [11, 16]

MpBC represents a heterogeneity in breast malignancies, with a need for tailoring treatment for the different variants of breast cancer, rather than approaching it as a single entity. The scarcity of reported cases of this tumour makes it a therapeutic challenge for oncologists worldwide. The lack of clear guidelines for management warrants the need for more research on the entity, with a special focus on targeted therapy. It also emphasises the need to identify variants of BC and focus on a tailored approach, rather than a one-size-fits-all approach.

Ethical Statement

Informed consent of the patient was obtained for publishing details of her disease and treatment

Conflict of Interest

None.

Acknowledgments

The authors have nothing to report.

Data Availability Statement

This is a case report of a single patient, whose details were recorded and reported. Identification data have not been disclosed to respect the privacy of the patient.

Author Contributions

All authors had full access to the details of the case and take responsibility for the accuracy of all information provided. Conceptualisation & design - Soirindhri Banerjee. Methodology - Ishika Mahajan. Investigation - Soirindhri Banerjee and Shivam Chakraborty. Writing original draft - Soirindhri Banerjee and Shivam Chakraborty. Review & Editing - Ishika Mahajan, Aruni Ghose and Stergios Boussios

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