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Heterogeneity of Metaplastic Carcinoma of Breast - A Diagnostic Challenge

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Abstract

Background: *Metaplastic carcinoma of breast (MCB) is a rare and aggressive type of invasive breast cancer. As it encompasses a variety of distinct histopathologic designations, diagnostic challenges abound. Here, we have documented the incidence of MCB in our tertiary care hospital for a period of 2 year.*

Materials and Methods: *This prospective study was carried out in the department of histopathology for a period of 2 years (Sep 2015 to Aug 2017). All the previously diagnosed breast carcinoma cases by FNAC and trucut were included in this study. All these patients were operated in the department of General surgery/ Oncosurgery of our institute. Followed by, the biopsy samples which were analyzed with routine histopathology and immunohistochemistry. With extensive squamous/malignant spindle cell differentiation, increased matrix production and unusually papillaroid patterns, we have diagnosed metaplastic carcinoma.*

Results: *There were 921 cases of invasive ductal carcinoma of breast (IDC) studied for a period of 2 years. Among them 8 cases were diagnosed as different types of metaplastic carcinoma. Out of which 5 cases showed extensive squamous differentiation, 1 case showed extensive squamous differentiation with papillaroid patterns, 1 case of MCB with spindle cell component & 1 case of matrix producing carcinoma.*

Conclusion: *MCB merits presentation because of its rarity and difficulty to diagnose, especially if the tumor is composed of areas showing papillaroid pattern or showing direct transition of carcinomatous component to spindle cell,cartilagenous or osseous matrix. Histomorphology and immunohistochemistry is the mainstay for diagnosis of MCB. It is of significant concern because of its prognosis and treatment which is poor in comparison to classical IDC of breast.*

Keywords: *Invasive breast cancer, papillaroid, squamous differentions, Histomorphology and immunohistochemistry.*

Introduction

Metaplastic carcinomas account for less than 1% of all invasive mammary carcinomas. The average age at presentation is 55. Metaplastic carcinoma of the breast (MCB) was first described in 1973 by Huvos et al1 and was defined as a mammary carcinoma with mixed epithelial and sarcomatoid components. The histologic classification of metaplastic carcinoma is primarily based on the morphologic findings of tumor cell types: purely epithelial (squamous, adenosquamous and spindle cell carcinomas) or mixed epithelial and mesenchymal (carcinoma with chondroid/osseous metaplasia and carcinosarcoma) components [(1)]. It has been suggested that the tumor cells originate from myoepithelial cells but many authors suggest that the origin was from basal like cells. Recently, there has been an increase in diagnoses, most likely due to the increased cognizance of MCB by pathologists [(2,3)]. Today, MCB represents 0.25% to 1% of all breast cancers diagnosed annually [(4,5)]. The prognosis and treatment of MCB is overall unknown, and compared with patients with invasive ductal carcinoma (IDC), patients with MCB have larger, higher-grade tumors with less hormone receptor positivity and less involvement of the regional lymph nodes [(6,7)]. Additionally, compared with patients with IDC, patients with MCB have worse outcomes in 5-year survival rates, ranging from 49% to 68% [(5,6)]. In this article, we will discuss clinicopathologic presentation, pathologic features, differential diagnosis, treatment options, and prognosis of this rare type of breast cancer.

Materials & Methods

This prospective study was carried out for a period of 2 years (September 2015 to August 2017) in the Department of Pathology, a tertiary care teaching hospital, Odisha. Patients with breast lumps presented to the surgical and oncosugical department of our institutes and were advised for FNAC and trucut biopsy. 921 cases were given the diagnosis of IDC breast who underwent surgery like lumpectomy, Radical mastectomy (RM) and modified Radical mastectomy (MRM). Which was followed by submission of these surgical biopsy samples to the histopathology department. These were analyzed with routine histopathological stain (Haemato-xylin and Eosin) and immunohistochemistry. The patients' age, tumor size, histologic grade, subgroups of MCB, IHC of ER, PR, HER2 expression, Ki67 (Fig3A), axillary status were noted from definitive pathology reports. Adjuvant and induction treatment strategies were collected from hospital files. The tissue of Fibroadenoma breast was considered as positive control for immunohistrochemistry of ER & PR and for Her2 & Ki67 positive control was Invasive Duct Carcinoma of breast & reactive hyperplasia of lymphnode tissue respectively. For the negative control the primary antibody was replaced by a tampoon solution. Additional IHC of vimentin (Fig3B), S-100 protein, p63 & CK5/6 was done in specified cases of Matrix producing carcinoma & MCB with spindle cells differentiation.

Results

All patients were female with a median age of 53 (34–67) years. The common presenting symptom was palpable mass in the breast, firm in consistency. Median tumor size was 7 cm (3–15 cm). Two patients had lumpectomy and 6 patients had mastectomy (both RM & MRM). Three patients received chemotherapy with Neoadjuvants. Only two patient showed lymphnode metastasis, rest six patients did not have any lymphnode metastasis.[Table -1] The most common type of MCB encountered was squamous cell carcinoma (5 cases, Fig1 A & B) followed by one case with predominant papillary & squamous differentiation (Fig2A), one case showing spindle cell component & the rarest one showing matrix producing carcinoma (MPC) (Fig – 2B). All the eight patients were found to be Triple negative with a Ki67 ranging from 35% to 65% [Table2,Fig3A].

Table 1 Clinicopathological distribution of MCBs

CARCINOMA TYPE	AGE	RADIOLOGICAL APPEARANCE	TYPE OF SURGERY	GROSS APPEARANCE	SIZE	LYMPHNODE STATUS	GRADE OF TUMOR	FOLLOW UP & TREATMENT
MCB with squamous differentiation (5 cases)	34, 45, 49, 52 & 58 years	Heterogeneous solid mass	1 lumpectomy, 1 RM & 3 MRM	Well circumscribed, firm in consistency	3cm, 6cm, 8cm, 12cm & 15cm in greatest dimension	One case showed involvement of 2 axillary nodes	All were grade III tumors	Follow up - 1 year, 8 months, 1.5 years, 7 months & 6 months Treatment - 4 cases had surgery & 1 case had surgery with neoadjuvant
MCB with papillary features (1 case)	57 years	Heterogenous solid mass	RM	Well circumscribed, firm in consistency with few papillary projections	13cm in greatest dimension	No lymphnode involvement	Grade III	Untraceable Surgery + neoadjuvant
MCB with spindle cell component (1 case)	61 years	Well circumscribed lesion with smooth margins, radiolucent halo & calcifications in small areas	RM	Well circumscribed, grayish white having whorled like pattern	5cm in greatest dimension	No lymphnode involvement	Grade III	8 months Surgery + neoadjuvant
MPC (1 case)	67 years	Well circumscribed lesion with ring enhancement in the periphery	lumpectomy	Well circumscribed, firm, grayish white	3.5cm in greatest dimension	No lymphnode involvement	Grade III	9 months Surgery

Table 2 Distribution of IHC pattern in different types of MCBs

CARCINOMA TYPES	ER	PR	HER2/ NEU	VIMENTIN	S-100	CK5/6	p63	Ki67
MCB with squamous features (5 cases)	negative	negative	negative	negative	negative	Positive (3 cases) Negative (2 cases)	negative	35%, 38%, 42%, 49% & 57%
MCB with papillary features (1 case)	negative	negative	negative	negative	negative	negative	negative	61%
MCB with spindle cell component (1 cases)	negative	negative	negative	positive	negative	positive	negative	65%
MPC (1 case)	negative	negative	negative	negative	negative	negative	Positive	35%

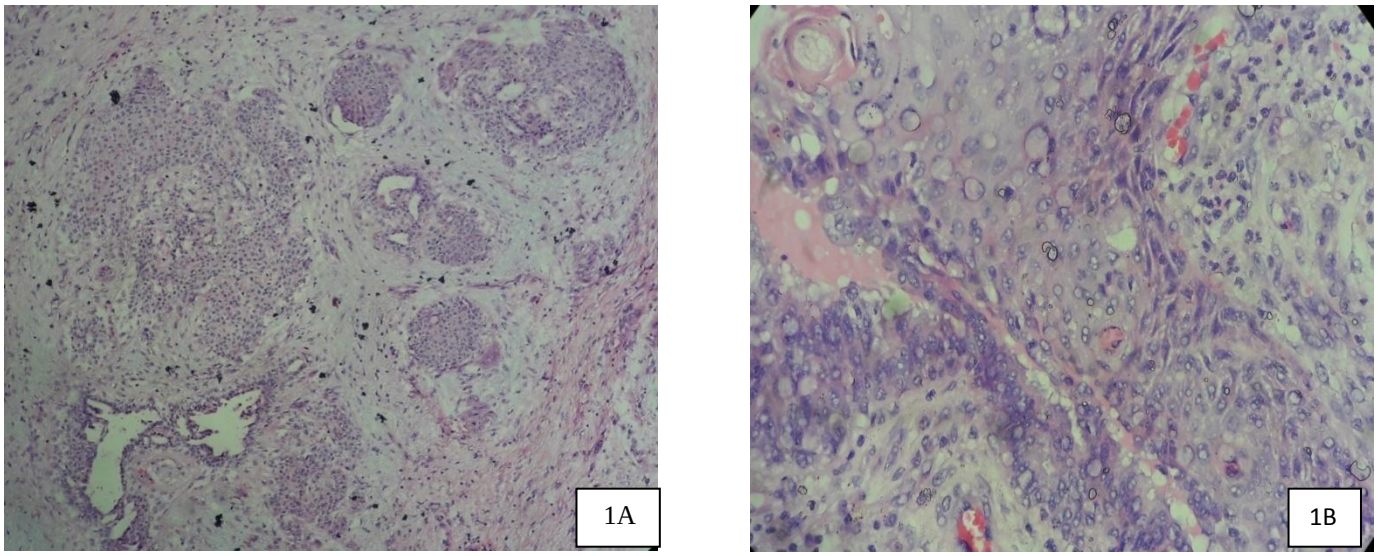
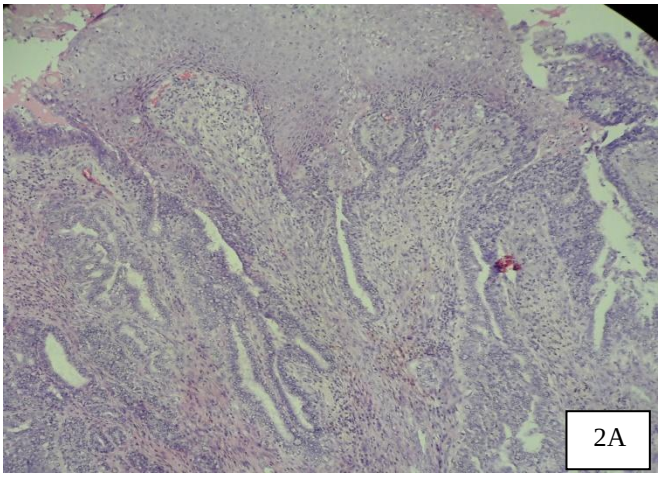


Fig-1A & B-Photomicrograph showing MCB with squamous differentiation. (H&E,40x,400x)



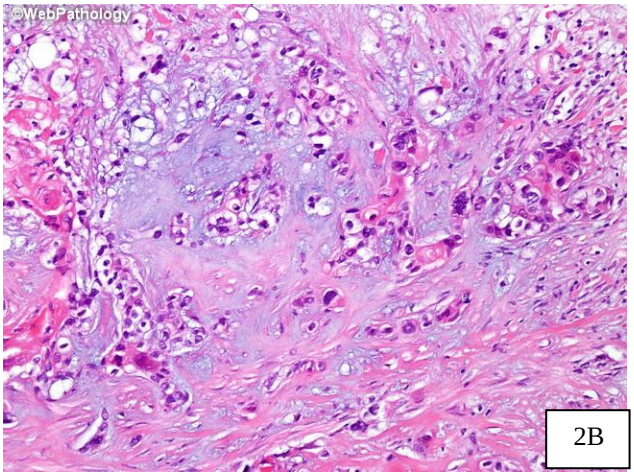
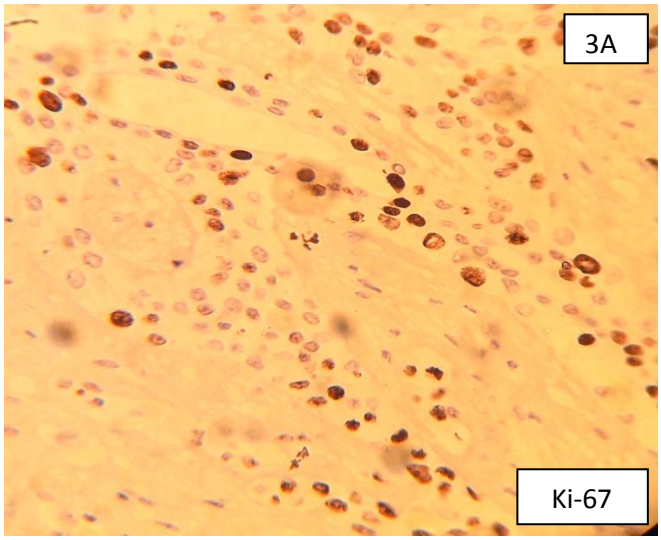


Fig-2 A- Photomicrograph showing MCB with differentiation and papillaroid pattern (H&E,100x)

Fig – 2B – Photomicrograph of MPC showing squamous neoplastic ductal cells in chondroid matrix(H&E, 400x,)

.



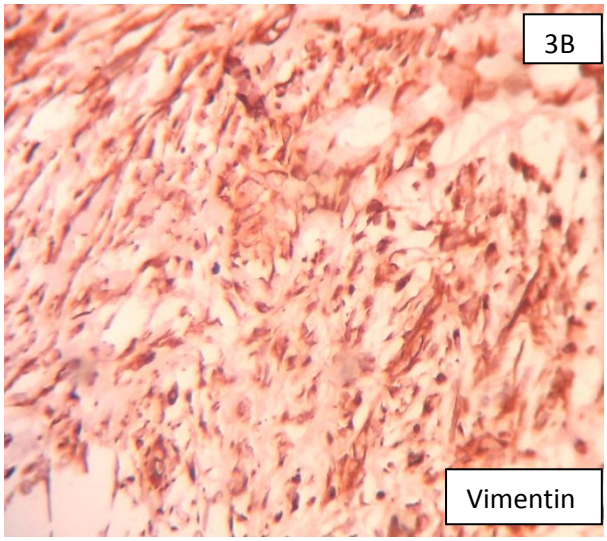


Fig-3A & B-Photomicrograph showing Ki-67(42%) & Vimentin (spindle cell variant of MCB) positivity

Discussion

Epithelial-mesenchymal transition has been reported to be an etiological factor in metaplastic carcinoma, thus are positive for both epithelial cell & mesenchymal cell markers (Lien#c et.al. oncogene 2007, 26;7859-7871). Thus Wargoz classified MCB into five types according to histopathological features which are - 1) Spindle cell 2) Squamous cell 3) Matrix producing 4) Carcinosarcoma 5) MCB with osteoclastic giant cells. According to College Of American Pathologists (CAP protocal of Breast carcinoma 2016), the MCB is classified as follows - *epithelial type of MCB* is further classified into (1) squamous cell carcinoma, (2) adenocarcinoma with spindle cell differentiation, (3) adenosquamous carcinoma, whereas *mixed type of MBC* is classified into (1) carcinoma with chondroid metaplasia, (2) carcinoma with osseous metaplasia, and (3) carcinosarcoma. The mesenchymal element usually shows no clear line of differentiation; more rarely angiosarcomatous, leiomyosarcomatous, osteosarcomatous, chondrosarcomatous or rhabdomyosarcomatous patterns may be seen. All the tumors were ER, PR & Her2neu negative. In addition the spindle cell type of MCB stained positive for both cytokeratin & vimentin (Fig 3B). The MPC stained positive for p63 which is a myoepithelial marker & negative for CK5/6 which is a basal cell marker,

whereas many authors have mentioned it to be CK5/6 positivity. The Ki67 activity was invariably high but was moderate in case of MPC. Wargotz and Norris described a "matrix forming" pattern with a better prognosis than expected in metaplastic carcinoma. Mitoses are variable in number but are usually plentiful. Cytokeratin expression in metaplastic carcinomas may be focal and patchy, which underscores the need for staining several sections and carefully assessing cytokeratin expression in all fields. Metaplastic breast carcinoma usually affects females over 50 years old [8] as seen in our study, the mean age is 53yrs. Typically the tumor size of MBC at presentation is frequently larger than 3 cm.[9] Large tumor size is suggested to be a result of rapid growth rate due to poorly differentiated or undifferentiated tumors compared to invasive ductal carcinoma which has a relatively long preclinical phase that allows early detection by mammography.[10] Only 29.5% of MBC were found to be <2 cm in size compared with 65.2% of invasive ductal carcinoma in a study by Pezzi et al.[10] Metastasis to axillary lymphnodes is not so common in MBC. Despite low rates of axillary involvement MBC has high potential for distant metastases via hematogenous route (mostly lung and bone).[10] The differential diagnosis of metaplastic carcinomas with predominantly spindle cell component depends on the degree of spindle cell atypia observed in the tumor. Spindle cell carcinoma was reported to be the most common type in western countries and China[11] whereas squamous cell carcinoma was the most common type in Hong Kong, Singapore and Taiwan. Metaplastic carcinomas with evident spindle cell atypia must be distinguished from malignant phyllodes tumor and primary or metastatic sarcoma. The distinction between metaplastic carcinoma and malignant phyllodes tumors[12,13] of the breast is critical because the treatment and prognosis differ significantly. Cytokeratin & EMA positivity is seen in sarcomatous area of MCB while it is negative in case of malignat phylloides along with leaf-like architecture seen in malignant phylloides. The MPC in addition has to be differentiated from well differentiated chondrosarcoma by the absence of vimentin & S-100 positivity in MPC.

Conclusion

The optimal treatments for MCB are relatively unknown, but current surgical therapy practices are comparable with those of IDC. Surgical treatment and axillary staging parallel those of IDC with the use of breast conservation therapy, and this is appropriate for a select group of patients. Traditional chemotherapy and hormonal therapies for IDC are the current standard for MCB. However being triple negative & basal-like phenotype of MCB, many studies have shown this therapy to be ineffective. The prognosis of MPC of breast is said to be better than that of other MCBs with 5 years survival of 68% (Wargotz et.al.). Hence this rare tumor with peculiar pathogenesis, histomorphology as well as prognostic implication needs accurate diagnosis with different treatment protocol & targetted therapy.

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