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Original Article

Histopathological Spectrum of Metaplastic Carcinoma of the Breast: A Rare Case Series and a Review of Literature

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Abstract

Introduction Metaplastic breast carcinoma (MBC) is one of the rare varieties of breast cancers (BCs) accounting for 0.2 to 2% of diagnosed cases. The tumor is known for its aggressive behavior with a large size at the time of diagnosis and rapid propagation.

Objectives The study aimed to evaluate all cases of MBC diagnosed over 4 years at a tertiary care institute and classify them according to the WHO classification of breast tumor (5th edition).

Materials and Methods All cases of MBC diagnosed in the last 4 years were reviewed retrospectively. Slides were prepared for both histopathological and immunohistochemical analyses. Relevant data were recorded.

Results All seven patients included in the study were females with aged between 39 and 61 years. The mean size of the tumor mass was 7.14 ± 1.41 cm. None of the cases showed nodal involvement. The most common histological subtype was squamous cell carcinoma (3, 42.8%), two cases were MBC with heterologous differentiation (28.5%), and one case each of adenosquamous carcinoma and spindle cell carcinoma (14.2%) was diagnosed. All the cases were p63 positive and ER, PR, HER2/neu, CD34, and CD10 negative. Additional immunohistochemical markers were used to rule out the relevant differentials, whenever required.

Conclusion This study aims to provide an account of the cases of MBC encountered in the last 4 years in the institute. This would be helpful in future diagnosis and treatment of this rare and prognostically poor subtype of BC.

Keywords
- metaplastic breast carcinoma
- histopathology
- immunohistochemistry.

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Introduction

Breast cancer (BC) is one of the most common types of malignancy among the female population all over the world as well as in our country. However, metaplastic breast carcinoma (MBC) is one of the rare varieties encountered in day-to-day practice.[1] The rarity of this tumor has kept this entity unknown to us for a long time until it was first described and discovered in 1973.[2] The metaplastic carcinoma accounts for 0.2 to 1% of all BCs.[3,4] It was in the year 2000 that the World Health Organization (WHO) recognized MBC as a distinguished entity.[5]

In the most recent edition of WHO classification of breast tumors, MBC has been defined to be a "heterogeneous group of invasive breast tumors characterized by differentiation of neoplastic epithelium towards squamous cells and/or mesenchymal looking elements including but not restricted to spindle, chondroid and osseous cells."[6] The pathogenesis and molecular mechanisms are still unclear in this case and somehow considered to be different from other forms of BCs.[7] Epithelial mesenchymal transition genes might have some key role in pathogenesis.[8] The tumor is known for its aggressive behaviors having large size at the time of diagnosis and rapid propagation to a worse outcome.[9] Despite being aggressive, the tumors are often node negative and most of the cases act as basal tumors being triple negative on immunohistochemistry (IHC).[10]

In the present study, retrospective analysis of all cases diagnosed in a tertiary care center as MBC in a span of 4 years has been done, with emphasis on their histological morphologies and immunohistochemical expression to classify them as per the recent WHO classification. This classification was done to help better understand this rare entity, which would guide the diagnosis and appropriate classification of such tumors and ultimately assist in rendering better patient care.[6]

Materials and Methods

A retrospective observational study was undertaken. Nonprobability sampling technique was employed and the sample size was 7.

Records of specimens received in the department of pathology for the last 4 years were studied and specimens of the breasts were shortlisted. The total number of breast specimens was found to be 457. From those specimens, cases that were rendered the diagnosis of MBC were identified and included in the study. Seven cases were found to be diagnosed as MBC. Relevant medical records of those seven patients were retrieved from the archives. All other cases were excluded from the present study.

The following relevant data were noted for each patient: age and sex of the patients, symptoms, signs, radiological data, surgery performed and gross findings of the specimen received such as site, size, and appearance of the tumor. The paraffin blocks of the specimens that were preserved in the department of pathology were retrieved and then slides were prepared for histological and immunohistochemical staining.

Hematoxylin and eosin stained slides were used for histological evaluation as per the diagnostic criteria per WHO classification of breast tumors (5th edition).[6] All cases were stained with the following immunohistochemical markers: estrogen receptor (ER), progesterone receptor (PR), HER2/neu, Ki-67, p63, CD10, and CD34. Paraffin blocks were sectioned at 5-µm thickness and then deparaffinized and incubated with a panel of antibodies (ER—PathnSitu, clone EP1; PR—PathnSitu, clone EP2; Her2/neu—PathnSitu, clone PRM116; Ki-67—PathnSitu, clone MIB1; p63—PathnSitu, clone 4A4; CD10—PathnSitu, clone EP206; CD34—PathnSitu, clone EP88). Cases that showed positive expression of p63 and negative expression of CD34 were confirmed to be MBC.[6] Two cases that showed heterologous mesenchymal components were further stained with the following antibodies: vimentin (PathnSitu, clone EP21), S100 (PathnSitu, clone EP32), and Pan CK (PathnSitu, clone EKHP). IHC staining positivity was considered in cases of unequivocal expression of markers in $\geq$1% of tumor cells.[9]

All the findings were meticulously tabulated and analyzed.

Inclusion and exclusion criteria: Cases of MBC were retrieved from the archives. The patients were contacted and they were included in the study only after they provided written informed consent. Cases other than those of MBC were excluded from the study.

Primary and secondary outcomes: The details of MBC cases were explored and elucidated.

Statistical analysis: The statistical analysis is not relevant to the present study.

Ethics: The study was conducted following approval by the Institutional Ethics Committee (Ref. no.: MC/KOL/IEC/NONSPON/1291/03/22, dated March 16, 2022). The patients were included in the study only after obtaining their written informed consent. The study protocol has been approved by the institute's committee on human research. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

All the patients included in the present study were females and their ages varied between 39 and 61 years. The mean age of the patients was 50.28 ± 7.62 years. The specimens of the breast had been received following modified radical mastectomy. Each of the patients presented with painless breast mass at the time of diagnosis. Five cases had a mass in the left breast and two cases presented with a right breast mass. Most of the women (6, 85.7%) were in the postmenopausal age group (►**Table 1**)

Preoperative core biopsy findings were available in six of seven patients (85.7%) in the present study. All six cases were reported as MBC. Four of these cases (66.7%) were subtyped as squamous cell carcinoma (SCC), whereas subtyping were not been done for the other two (33.3%). One of the cases reported as SCC on core biopsy was later rendered the

Table 1 Clinicopathological characteristics of cases of metaplastic breast carcinoma

Case	Age (y)	Laterality	Gross size (cm)	Histological subtype	Immunohistochemical analysis[a]	Pathological stage
1	46	Left	6.4	MBC-SCC	p63, CK5/6 positive	pT3N0
2	61	Left	3	MBC-SCC	p63, CK5/6 positive	pT2N0
3	58	Left	7.2	MBC with heterologous differentiation	p63, pan CK, Vimentin, S100 positive	pT3N0
4	39	Right	4.5	MBC-adenosquamous carcinoma	p63, CK5/6 positive	pT2N0
5	43	Left	5.4	MBC with heterologous differentiation	p63, pan CK, vimentin, S100 positive	pT3N0
6	56	Right	20	MBC-spindle cell carcinoma	Vimentin, SMA, p63 positive; CD10, CD34 negative.	pT3N0
7	49	Left	3.5	MBC-SCC	p63, CK5/6 positive	pT2N0

Abbreviations: MBC, metaplastic breast carcinoma; SCC, squamous cell carcinoma.
[a]All cases were negative for ER, PR, Her2/neu.

diagnosis of adenosquamous carcinoma after mastectomy. None of the seven cases received neoadjuvant chemotherapy and were treated with upfront surgery (modified radical mastectomy).

Gross examination findings of the specimens revealed that the tumor sizes varied from as small as 3 cm to as large as 20 cm in maximum diameter. The mean size of the tumor mass was 7.14 ± 5.42 cm.

On microscopic examination, the tumors were diagnosed as MBC and subtyped and graded as per the WHO classification of breast tumors (5th edition).[6]

Axillary lymph node examination of all cases showed no nodal involvement. The most common subtype was SCC, which was found in three cases (42.8%) and two cases (28.5%) were diagnosed as metaplastic carcinoma with heterologous differentiation showing chondroid areas. One case each was diagnosed as adenosquamous carcinoma (14.2%) and spindle cell carcinoma (14.2%; ►**Figs. 1** and **2**). Ductal carcinoma in situ (DCIS) was noted in two of the seven cases (28.6%).

Three cases diagnosed as SCC showed atypical squamous cell proliferation within the stromal component of the breast tissue with the formation of cyst-like spaces lined by

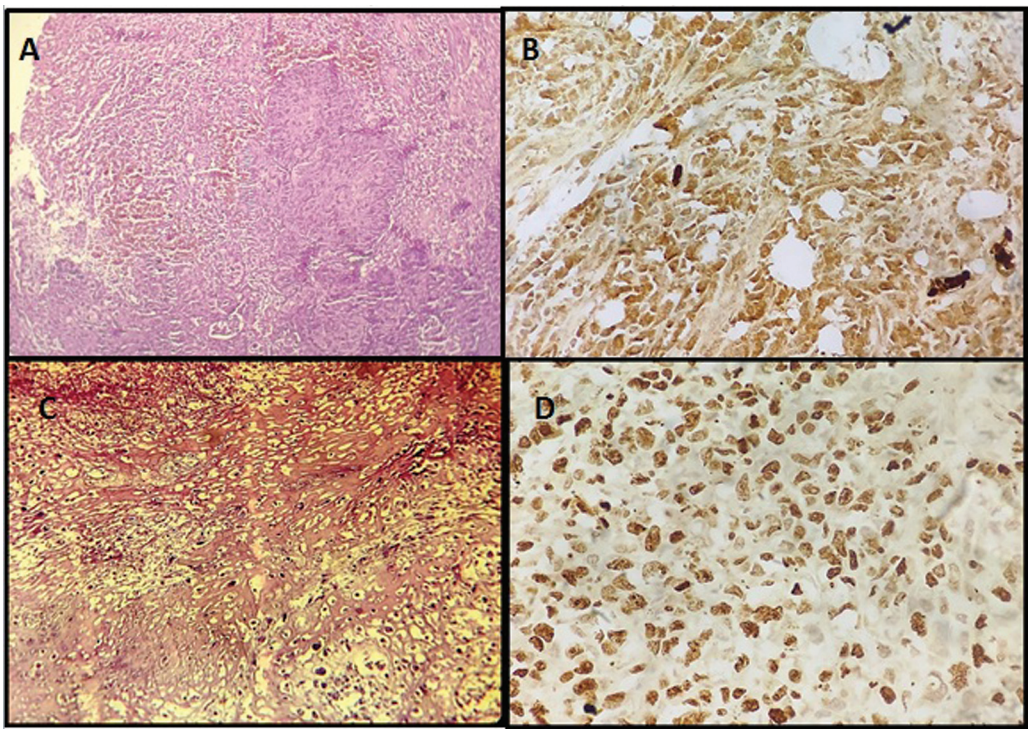

Fig. 1 (**A**) Microscopic appearance of metaplastic breast carcinoma (MBC) of squamous cell carcinoma (SCC) subtype (hematoxylin and eosin [H&E], ×100). (**B**) Positive expression of p63 immunostain in SCC subtype of MBC (×400). (**C**) Microscopic appearance of MBC with heterologous (cartilaginous) differentiation (H&E, ×400). (**D**) Ki-67 expression of 40% by the tumor cells of MBC.

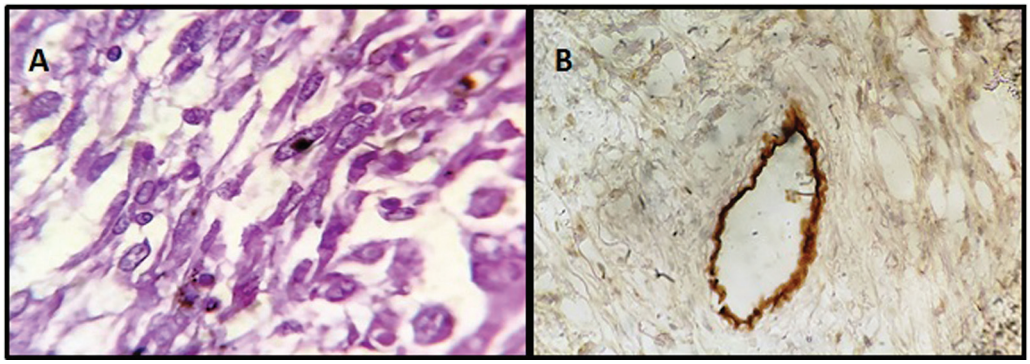

Fig. 2 (**A**) Microscopic appearance of the spindle cell carcinoma subtype of metaplastic breast carcinoma (MBC; hematoxylin and eosin [H&E], ×400). (**B**) CD34 negative cells in spindle cell carcinoma (internal control: blood vessel showing positivity for CD34; ×400).

squamous cells with hyperchromatic, pleomorphic nuclei. No evidence of primary SCC elsewhere was found, which ruled out the possibility of metastatic SCC of the breast. SCC type of metaplastic carcinoma showed the presence of p63 and CK5/6 IHC stains.

Two cases showed heterologous differentiation of its components. One of them revealed proliferation of mature cartilaginous tissue, which represented mesenchymal differentiation admixed with epithelial glandular components. The cartilaginous component of the tumor showed positive IHC staining with vimentin and S100. In another case, osseous along with rhabdoid differentiations were found. The osseous component showed positive IHC staining with S100 and the rhabdoid component was positively stained with vimentin and desmin.

Adenosquamous carcinoma was diagnosed in one case showing histological features of infiltrative small round glandular structures with focal areas of squamous differentiation with a desmoplastic stroma. Adenosquamous carcinoma type of MBC showed positive p63 and CK5/6 staining in epithelial cells of glandular structures and areas of focal squamous differentiation.

One case, however, showed proliferation of atypical pleomorphic spindle cells with hyperchromatic nuclei and prominent nucleoli arranged in fascicles and sheets with invasion of stromal tissue. The case was differentiated from primary stromal sarcoma and other spindle cell neoplasms (e.g., malignant phyllodes tumor) of the breast by using the relevant immunohistochemical markers and diagnosed as spindle cell carcinoma. Spindle cell carcinoma showed positivity with vimentin, SMA, and p63 stains, and the cells were negative for CD10 and CD34 stains.

Pathological staging of all seven cases was done. Four of the cases (57%) showed pathological stage 3 (pT3). These included two cases of MBC with heterologous differentiation, one case each of SCC and spindle cell carcinoma. Two cases (28.6%) of SCC and one case (14.4%) of adenosquamous carcinoma were of pathological stage 2 (pT2). All cases showed an N0 status.

Immunohistochemical analysis showed that all seven cases were absent for detection of ER, PR, and Her2/neu. CD34 and CD10 were also negative. All the cases showed positivity for p63. High Ki-67 expression (average score: $46 \pm 0.25\%$) was noted in all cases except one case of SCC type of MBC where the Ki-67 expression was $\leq 1\%$.

Discussion

In the present study, cases of MBC were evaluated with respect to the various clinicopathological parameters. Due to the lack of characteristic imaging patterns and histological similarities between various malignant breast lesions, MBC is difficult to diagnose. Postoperative histopathological and immunohistochemical analyses are the main modalities of diagnosis at present.

MBC is one of the rarest forms of BC. There is a dearth of reports of MBC cases from the eastern regions of the country. In the current study, the incidence rate was 1.53%, which was similar to studies done by Nelson et al and Znati et al.[4,11] It was also similar to the incidence rate mentioned by the WHO classification of breast tumor.[6] The age group of the patients of the present study varied between 39 and 61 years, which was corroborative with other studies.[12–14] A study by Pezzi et al showed MBC occurs mostly in postmenopausal women with a rapid increase in tumor size, advanced stage at the time of diagnosis, and hormonal receptor negative status.[15] These findings were comparable with those of the current study. The most common site of tumor mass according to this study was the left breast, which was similar to study done by Salimoğlu et al.[16]

The gross tumor sizes varied from as small as 3 cm to as large as 20 cm in maximum diameter. The mean size of the tumor mass was 7.14 ($\pm$ 1.41) cm in this study. These findings are similar to other studies.[11,17] A study by Gultekin et al showed the relationship between tumor size, survival rate, and recurrence.[14]

SCC (42.8%) was the most common histological type of MBC diagnosed in the present study, followed by two cases of metaplastic carcinoma with heterologous differentiation (28.5%) and one case each of adenosquamous carcinoma (14.2%) and spindle cell carcinoma (14.2%). A study by Salimoğlu et al showed similar findings, with SCC being the most common histological type of MBC.[16]

In comparison to invasive breast carcinoma, NOS (not otherwise specified) of similar size and grade, lymph node metastases are quite rare in MBC.[18] In the current case series,

axillary lymph node dissection was done in every case and all of them showed negative lymph node involvement. These findings corroborated with other studies.[14,17]

No single immunohistochemical marker is constantly positive in all cases of MBC. Hence, use of a panel of IHC markers is essential. According to Rakha et al, at least one marker of epithelial differentiation is expressed by most MBCs.[19] The majority of MBCs are p63 positive and all seven cases of the present series showed p63 positivity. This result was similar to other studies.[20,21] CD34 was consistently negative in all seven cases excluding phyllode tumors as a differential diagnosis. However, CD10 is known to be positive in 50 to 70% of MBC cases, although all the tumors turned out to be CD10 negative in the current series.[6]

IHC showed all of the tumors were ER, PR, Her2/neu, CD34, and CD10 negative. These findings were similar to the study done by Yamaguchi et al.[9]

The limitations of the present study were the paucity of cases and limited resources, which restricted the panel of IHC markers used. It was beyond the scope of this study to include sophisticated investigations like tumor genomics/comprehensive genomic profiling.

Conclusion

MBC is a rare entity of BC associated with a worse prognosis than other types of BC, although low-grade adenosquamous carcinoma shows a better prognosis than other types of MBC. The diagnostic difficulty of MBCs is due to its morphological and molecular heterogeneity and lack of a marker, which is consistently expressed in all cases. The present study aims to provide a comprehensive idea about the common histological subtypes and immunoprofile of MBC cases in routine practices.

Patient Consent

Written informed consent was obtained from the patients included in the study.

Funding

None.

Conflict of interest

None declared.

References

1 McKinnon E, Xiao P. Metaplastic carcinoma of the breast. Arch Pathol Lab Med 2015;139(06):819–822
2 Graziano L, Graziano P, Bitencourt AG, Soto DB, Hiro A, Nunes CC. Metaplastic squamous cell carcinoma of the breast: a case report and literature review. Rev Assoc Med Bras 2016;62(07): 618–621
3 Schroeder MC, Rastogi P, Geyer CE Jr, Miller LD, Thomas A. Early and locally advanced metaplastic breast cancer: presentation and survival by receptor status in Surveillance, Epidemiology, and End Results (SEER) 2010-2014. Oncologist 2018;23(04):481–488
4 Nelson RA, Guye ML, Luu T, Lai LL. Survival outcomes of metaplastic breast cancer patients: results from a US population-based analysis. Ann Surg Oncol 2015;22(01):24–31
5 Jha A, Agrawal V, Tanveer N, Khullar R. Metaplastic breast carcinoma presenting as benign breast lump. J Cancer Res Ther 2017;13(03):593–596
6 Reis-Fiiho JS, Gobbi H, McCart Reed H, et al. Metaplastic carcinoma. In: Lokuhetty D, White VA, Watanabe R, Cree IA, eds. WHO Classification of Breast Tumours: WHO Classification of Tumours. Lyon, France: IARC; 2019:134–138
7 Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, et al. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics. Cancer Res 2009;69(10):4116–4124
8 Lien HC, Hsiao YH, Lin YS, et al. Molecular signatures of metaplastic carcinoma of the breast by large-scale transcriptional profiling: identification of genes potentially related to epithelial-mesenchymal transition. Oncogene 2007;26(57):7859–7871
9 Yamaguchi R, Tanaka M, Kondo K, et al. Immunohistochemical study of metaplastic carcinoma and central acellular carcinoma of the breast: central acellular carcinoma is related to metaplastic carcinoma. Med Mol Morphol 2012;45(01):14–21
10 Lim KH, Oh DY, Chie EK, et al. Metaplastic breast carcinoma: clinicopathologic features and prognostic value of triple negativity. Jpn J Clin Oncol 2010;40(02):112–118
11 Znati K, Chahbouni S, Hammas N, et al. Twelve cases of metaplastic carcinoma of the breast: experience of the university hospital of Fez Morocco. Arch Gynecol Obstet 2011;283(04):845–849
12 Luini A, Aguilar M, Gatti G, et al. Metaplastic carcinoma of the breast, an unusual disease with worse prognosis: the experience of the European Institute of Oncology and review of the literature. Breast Cancer Res Treat 2007;101(03):349–353
13 Al Sayed AD, El Weshi AN, Tulbah AM, Rahal MM, Ezzat AA. Metaplastic carcinoma of the breast clinical presentation, treatment results and prognostic factors. Acta Oncol 2006;45(02):188–195
14 Gultekin M, Eren G, Babacan T, et al. Metaplastic breast carcinoma: a heterogeneous disease. Asian Pac J Cancer Prev 2014;15 (06):2851–2856
15 Pezzi CM, Patel-Parekh L, Cole K, Franko J, Klimberg VS, Bland K. Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base. Ann Surg Oncol 2007;14(01):166–173
16 Salimoğlu S, Sert İ, Emiroğlu M, et al. Metaplastic breast carcinoma: analysis of clinical and pathologic characteristics—a case series. Meme Saglik Derg 2016;12(02):63–66
17 Schwartz TL, Mogal H, Papageorgiou C, Veerapong J, Hsueh EC. Metaplastic breast cancer: histologic characteristics, prognostic factors and systemic treatment strategies. Exp Hematol Oncol 2013;2(01):31–40
18 Paul Wright G, Davis AT, Koehler TJ, Melnik MK, Chung MH. Hormone receptor status does not affect prognosis in metaplastic breast cancer: a population-based analysis with comparison to infiltrating ductal and lobular carcinomas. Ann Surg Oncol 2014; 21(11):3497–3503
19 Rakha EA, Coimbra ND, Hodi Z, Juneinah E, Ellis IO, Lee AH. Immunoprofile of metaplastic carcinomas of the breast. Histopathology 2017;70(06):975–985
20 Wang J, Wang X, Wang WY, Liu JQ, Xing ZY, Wang X. Feasibility analysis of sentinel lymph node biopsy in patients with breast cancer after local lumpectomy. Zhonghua Zhong Liu Za Zhi 2016; 38(07):548–551
21 Zhang WL, Ma WJ, Chen S, Wu XZ, Zhang HR, Zhang JH. Molecular mechanisms of resistance to phosphatidyl inositol 3-kinase inhibitors in triple-negative breast cancer cells. Zhonghua Zhong Liu Za Zhi 2016;38(08):578–588

