Revisiting Metaplastic Carcinoma of Breast: An Emphasis on the Clinico-pathological and Immunohistochemical Variables Analyzed at a Tertiary Cancer Centre in South India

Geetha V Patil Okaly¹, Akshatha C¹, Sandhya N³, Akina Prakash¹, M N Suma¹, Ashwini Nargund³, Shankar Anand¹, C Ramachandra², Libin Babu Cherian*²

Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore, India
Department of Surgical Oncology, Kidwai Memorial Institute of Oncology, Bangalore, India

KEYWORDS

CK: cytokeratin, EGFR: epidermal growth factor receptor, IBC: Invasive breast carcinoma, IHC: immunohistochemistry, NST: No special type, MC: Metaplastic carcinoma.

ABSTRACT

Background & Objective: Metaplastic carcinoma is a diverse variant of invasive breast carcinomas (IBC) characterized by dedifferentiation of malignant cells towards squamous and/or mesenchymal elements. It accounts for 0.3-1.2% of all IBC. These tumors are typically triple-negative by hormonal profiling with a high proliferation index and a dismal prognosis. Lymph node metastasis is an unusual feature in metaplastic carcinoma.

Methods: The present study analyses 30 cases (26 cases of modified radical mastectomy and 4 cases of lumpectomy) of metaplastic carcinoma over 2018-2020 (3 years). Four oncopathologists reviewed routine histopathologic and immunohistochemical-stained slides. The clinical details were collected from the Medical Records Department of the Cancer Institute.

Results: A total of 20 (66.67%) cases were patients >50 years of age, 21(70%) out of which were diagnosed as invasive carcinoma, grade 3 according to the Nottingham histological score. Five (16.7%) cases presented with lymph node metastasis. While immunohistochemically 28 (93.3%) cases were triple-negative CK5/6, p63, EGFR, and Ki-67 (more than 40%) positivity was noted in 25 (83.3%), 26 (86.7%), 20 (66.7%), and 25 (83.3%) cases, respectively.

Conclusion: Metaplastic carcinoma is characteristically triple-negative breast malignancies (TNBC) exhibiting a high Ki-67 index and a lower rate of lymph node metastasis. CK5/6, p63, and EGFR are pertinent immunohistochemical markers that may aid in diagnosis. However, these markers are non-specific for the disease and morphologic features are always the key to diagnosis of the process.

Introduction

Metaplastic carcinoma (MC) is a diverse cluster of invasive breast cancers characterized by transforming the neoplastic epithelium towards epithelial and/or stromal-looking elements. MC can affect any anatomical area of the breast. They present at an advanced stage, and their etiology is multifactorial (1). It is triple-negative by hormonal profile, and pathogenesis is associated with late-stage tumor dedifferentiation than arising from basal-type stem cells. TP53 and PIK3CA are the most frequently mutated genes with decreased expression of E-cadherin and increased expression of molecules of epithelial-stromal transition such as SNAIL, TWIST, and SLUG. The tumors present as a well-circumscribed mass or display indistinct irregular borders. Cystic degeneration is not uncommon, especially in MC associated with squamous cell carcinoma (2,3). The variant histological types of MC include the low-grade type of MC, namely adenosquamous carcinoma, fibromatosis like metaplastic carcinoma and the high-grade types, spindle cell carcinoma, squamous cell carcinoma, metaplastic carcinoma with heterologous mesenchymal differentiation and mixed metaplastic carcinoma. The majority of cases express CK5/6, p63, and EGFR. EGFR is commonly amplified in these tumors, and somatic mutation appears to be vanishingly rare. Myoepithelial markers like SMA, CD10, and mapsin are positive in 50-70% of cases. CD34, desmin, and SMMHC are frequently negative. There may be an aberrant expression of beta-catenin. Whole exon and targeting sequencing analysis of MC have demonstrated complex genomic landscape mutations including TP53, RBI, mutations in chromatin remodeling genes ie,
arid1a, kmt2c1, as well as mutations in pi3k-akt pathway genes including pik3ca, pik3cb, pik3cg, pik3r1, akt1, akt2, and akt3 and ras-raf-mapk pathway (NF1, KRAS, and NRAS) and WNT pathway (FAT1, CCND3, and CCN6) (4,5) Other histological variants of invasive breast carcinoma include invasive breast carcinoma, NST, tubular carcinoma, cribriform carcinoma, mucinous carcinoma, mucinous cystadenocarcinoma, carcinoma with apocrine features, and micropapillary carcinoma. The various variants of invasive breast carcinoma, NST includes medullary variant, lymphoepithelial variant, glycogen-rich variant, clear cell variant, sebaceous variant, invasive carcinoma with Choriocarcinoma like features, and invasive carcinoma with pleomorphic giant cells.

Material and Methods

Tissue Blocks and histopathologic slides of thirty MC cases were retrieved from the pathology department archives, and corresponding immunohistochemistry slides were procured for three years, from 2018 to 2020. The slides were reviewed by two experienced oncopathologists. Relevant clinical information was also obtained from the patients and corroborated with the histopathological findings.

Results

Of the modified radical mastectomy, 26 cases and 4 cases of lumpectomy were studied. All cases of MCs were ER, PR, and Her2/neu negative. A total of 20/30 (66.6%) cases were patients more than 50 years of age, with 12 (40%) cases presenting with skin ulceration, satellite nodules, or inflammatory carcinoma. Also, 21 (70%) cases were Nottingham histologic grade 3. Different histopathological variants of MC were streamlined, including 10 (33.3%) cases of adenosquamous carcinoma, 4 (13%) cases of fibromatosis like MC, 5 (16%) cases of spindle cell carcinoma, 7 (23%) of squamous cell carcinoma and 4 (13%) of MC with heterologous elements. In addition, 5 (16.6%) cases presented with lymph nodal metastasis, with one case involving more than six lymph nodes were observed. Of the total cases, 28 (93.3%) were of triple-negative immunophenotype, and 2 (6%) were ER and PR IHC- with Her2/Neu positive, while 25 (83.3%) cases, 26 (86.7%) cases, 20 (66.67%) cases were positive for CK5/6, p63, and EGFR, respectively. Twenty-five (83.3%) cases showed a high proliferation index >40%.

Fig. 1. A: photomicrograph showing epithelial elements composed of squamous elements. B: photomicrograph showing mesenchymal elements composed of the chondroid stroma.

Fig. 2. A: p63 diffuse nuclear staining in the squamoid elements. B: CK5/6 diffuse cytoplasmic staining in the squamoid elements. C: EGFR diffuse membrane staining in the squamoid elements.
Fig. 3. Age distribution in the cases of MC.

Table 1. Age range of the cases of MC

| Age group         | Number of cases |
|-------------------|-----------------|
| 20-30 years       | 2 (6%)          |
| 31-40 years       | 2 (6%)          |
| 41-50 years       | 6 (20%)         |
| 51-60 years       | 9 (30%)         |
| 61-70 years       | 11 (36%)        |

Fig. 4. Distribution of histological types of metaplastic carcinoma

Table 2. Distribution of the histological types of MC

- Adenosquamous carcinoma
- Fibromatosis like metaplastic carcinoma
- Spindle cell carcinoma
- Squamous cell carcinoma
- MC with heterologous differentiation
Histological variants of MC | Number of cases
---|---
Adeno-squamous carcinoma | 10 (33.3%)
Fibromatosis like metaplastic carcinoma | 4 (13%)
Spindle cell carcinoma | 5 (16%)
Squamous cell carcinoma | 7 (23.3%)
MC with heterologous differentiation | 4 (13.3%)

Table 3. Stage distribution of the cases of MC

| Stage | Number of cases |
|---|---|
| Stage I | 4 (13%) |
| Stage II | 5 (16.7%) |
| Stage III | 9 (30%) |
| Stage IV | 12 (40%) |

Table 4. Distribution of immunohistochemical markers of CK5/6, p63 and EGFR in the cases of MC

| | CK5/6 | P63 | EGFR |
|---|---|---|---|
| Negative | 05 (16.7%) | 04 (13.3%) | 10 (33.3%) |
| Positive | 25 (83.3%) | 26 (86.7%) | 20 (66.7%) |

Fig. 5. IHC distribution of the cases of metaplastic carcinoma

Discussion

MC is an infrequent tumor (4% of the malignancies) (6, 7), and constitute only 1.5% of IBC (3). The frequency of MC in our center is 2% among all IBCs. The actual number of cases is not known because it can unusually present as a solitary mass that radiology might miss (8, 9). MC most commonly affects females in the fifth to the sixth decade with a median age of 55 (10,11,12). It usually presents as a palpable firm breast lump, well-circumscribed or occasionally infiltrative borders inflicting any breast quadrant with no quadrant predisposition, unlike the IBC, NST, which has a predisposition to occur in the upper and outer quadrant of the breast. Rarely lesions can involve the skin and chest wall, causing ulceration, peau d'orange appearance, and inflammatory carcinoma in the early course of the disease (13,14). Neither mammograms nor ultrasound of the breast demonstrate specific diagnostic images but show neoplasms most often fairly delineated, without associated microcalcifications. Still, off and on, irregular lesions may be seen (1,10). Breast neoplasms originate from the TDLU, which results in invasive
breast carcinoma, finally causing metaplasia of the neoplastic tissue. This differentiation was correlated with the use of IHC (7, 15, 16, 17).

According to the latest edition of the WHO classification, the metaplastic carcinomas are classified into the low grade and the high-grade types, namely low-grade adenosquamous carcinoma, fibromatoses like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, MC with heterologous elements and unclassified MC. This differentiation is purely based on histopathological grounds, and IHC has no significance. Prognostically spindle cell carcinoma, squamous cell carcinoma, and metaplastic carcinoma with heterologous elements have worrisome prognoses compared to adenosquamous carcinoma and fibromatosis like metaplastic carcinoma. Spindle cell carcinoma and fibromatosis like MC must be differentiated with phyllodes tumor and can become a difficult diagnostic conundrum. Using IHCs such as CK5/6, EGFR and p63 can aid in differentiating from phyllodes tumor (13, 14, 16, 17).

Hormonal profile display ER, PR, her2neu negative in 90% of cases (estrogen receptor-, progesterone receptor-, and human epidermal growth factor receptor 2 (HER2)-negative cases) correlates with our study depicting 93% of cases (3, 11, 13).

Lymph node involvement is rarely seen. The incidence of metastases ranges from 5 to 24% (12, 13, 17). In invasive breast carcinoma, NST, the incidence is much higher (up to 50%).

Although we could not follow up on these cases, we determined that disease-free survival and overall survival corroborate with the tumor size, in which tumors more than 5 cm have a worse prognosis than smaller tumors. Other factors include histological type, Nottingham histological score, axillary lymph node metastasis, and distant metastasis. Although axillary lymph node involvement is rare, there is an inclination towards pulmonary metastases; so TNM pathological staging system is of little use as a prognostic factor. Most distant metastases occur through the hematogenous route, most frequently affecting the pleura, lungs, liver, and abdominal viscera (2, 8, 12, 21).

Fadwa et al. detailed that 85.7% of MC cases expressed luminal breast type of cytokeratins (CK8, CK18 and/or CK19). Out of the five cases (70-75%), three cases were carcinomas, and two cases were SCCs that displayed IHC expression to EGFR. Increased expression of ERBB1 was reported in 80-85% of cases of MBC, with up to 25-38% of cases confirmed by reflux fluorescent in situ hybridization. ERBB1 showed association with squamous or spindle differentiation. Although MBC has been proclaimed to have high levels of ERBB1 upregulation and amplification, they were found to lack ERBB1 activating mutations; therefore, it is obscure whether EGFR tyrosine kinase inhibitors are effective for the management of MBC (31).

Gary M Tse et al. emphasized that in MC with epithelial component only, p63 was only expressed in the epithelial squamous cell type but not in the glandular component. Eight of the 10 neoplasms were immunopositive for p63. For the malignancies with spindled type, either singly or in combination with an epithelial component, p63 exhibited expression in 14 of 24 cases. Pure stromal and epithelial types were all immunonegative for p63 IHC staining by immunohistochemistry, thus making p63 IHC staining highly sensitive and specific for confirming metaplastic carcinoma (32).

Five-year overall survival may range from 40 to 68% (8, 13, 17), and over 50% of the regional and distant metastatic recurrences appear before that time. The management line is modified radical mastectomy, with axillary lymph node dissection and sentinel lymph node biopsy (SLNB) or radical supra mastectomy, depending on the extent of the tumor dissemination (22, 23, 24, 25). MC is usually less amenable to chemotherapy and radiation therapy (27, 28, 29, 30). A variant of MC called matrix-producing metaplastic carcinoma appears to be prognostically better compared to the other variants (18, 19, 26).

Conclusion
Metaplastic carcinoma is classically TNBC with a high MIB labeling index and lower lymph node metastasis rate than other invasive breast carcinoma variants. CK5/6, p63, and EGFR are pertinent immunohistochemical markers for MC that may aid in the diagnosis. While these IHC markers are important in distinguishing MC from phyllodes tumors, these markers are non-specific for the disease and morphologic features are always the key for diagnosis.

Acknowledgments
The completion of this undertaking could not have been possible without the participation and assistance of so many people whose names may not be enumerated. Their contributions are sincerely appreciated and gratefully acknowledged. However the group would like to express their deep appreciation and indebtedness particularly to following:
Dr. C.S. Premlata, Dr. Raghavendra H. V, Dr. Balu C.
To all the relatives, friends and others who in one way or another shared their support either morally, financially and physically and above all the great almighty, the author of knowledge and wisdom, for the countless love.

Conflict of Interest
The authors declared no conflict of interest.

Funding
None.
References

1. Günhan-Bilgen I, Memiş A, Üstün EE, Zekioglu O, Özdemir N. Metaplastic carcinoma of the breast: clinical, mammographic, and sonographic findings with histopathologic correlation. AJR Am J. 2002;178(6):1421-5. [DOI:10.2214/ajr.178.6.1781421] [PMID]

2. Park JM, Han BK, Moon WK, Choe YH, Ahn SH, Gong G. Metaplastic carcinoma of the breast: mammographic and sonographic findings. J Clin Ultrasound. 2000;28(4):179-86. [DOI:10.1002/(SICI)1097-0096(200005)28:4.CO;2-Y]

3. Massuet A, Fernández S, Rimola J, Andreu FJ, Tortajada L, Sentís M. Carcinoma metaplastico de mama: resonancia magnética y correlación radiopatológica. Radiología 2006;48:155-163. [DOI:10.1016/S0033-8338(06)73146-0]

4. Amillano Párraga K, Elorriaga Barandiaran K, Alberro Aduriz JA, Martín López A, Rezola Solaun R, Plazaola Alcibar A. Carcinoma metaplastico de mama: Revisión a propósito de un caso. Oncología (Barc.) 2004;27(9):42-6. [DOI:10.4321/S0378-48352004009000006]

5. Kuo SH, Chen CL, Huang CS, Cheng AL. Metaplastic carcinoma of the breast: analysis of eight Asian patients with special emphasis on two unusual cases presenting with inflammatory-type breast cancer. Anticancer Res. 2000;20(3B):2219-22.

6. Bellino R, Arisio R, D’Addato F, Attini R, Durando A, Danese S, Bertone E, Grio R, Massobrio M. Metaplastic breast carcinoma: pathology and clinical outcome. Anticancer Res. 2003;23(18):669-3.

7. Moreno J, Urquijo E, González-Lopera S, Díez J, Burgos J, Luján S, Rodríguez-Escudero FJ. Carcinoma metaplastico de mama: estudio clínico-histolóógico de siete casos. Clín Invest Ginecol Obstet. 2003;30(7):222-31. [DOI:10.1016/S0210-573X(03)77264-5]

8. Smith DM, Rongaus VA, Wehmann TW, Agarwal PJ, Classen GJ. Metaplastic breast carcinoma. J Am Osteopath Assoc 1996;96:419-21. [DOI:10.7556/jaoa.1996.96.7.419]

9. Patterson SK, Tworek JA, Roubidoux MA, Helvie MA, Oberman HA. Metaplastic carcinoma of the breast: mammographic appearance with pathologic correlation. AJR Am J. 1997;169(3):709-12. [DOI:10.2214/ajr.169.3.9275883] [PMID]

10. Rayson D, Adjei AA, Suman VJ, Wold LE, Ingle JN. Metaplastic breast cancer: prognosis and response to systemic therapy. Ann Oncol. 1999;10(4):413-9. [DOI:10.1023/A:1008329910362] [PMID]

11. Kurian KM, Al-Nafussi A. Sarcomatoid/metaplastic carcinoma of the breast: a clinicopathological study of 12 cases. Histopathology. 2002;40(1):58-64. [PMID]

12. Wargotz ES, Does PH, Norris HJ. Metaplastic carcinomas of the breast. II. Spindle cell carcinoma. Hum Pathol. 1989;20(8):732-40. [DOI:10.1016/0046-8177(89)90065-8]

13. Johnson TL, Kini SR. Metaplastic breast carcinoma: a cytohistologic and clinical study of 10 cases. Cytopathology. 1996;14(3):226-32. [DOI:10.1002/(SICI)1097-0339(199604)14:3.CO;2-F]

14. Khan HN, Wyld L, Dunne B, Lee AH, Pinder SE, Evans AJ, Robertson JF. Spindle cell carcinoma of the breast: a case series of a rare histological subtype. Eur J Surg Oncol. 2003;29(7):600-3. [DOI:10.1016/S0748-7983(03)00107-0]

15. Fisher ER, Palekar AS, Gregorio RM, Paulson JD. Mucopidermoid and squamous cell carcinomas of breast with reference to squamous metaplasia and giant cell tumors. Am. J. Surg. Pathol. 1983;7(1):15-27. [DOI:10.1016/S0748-7983(03)00107-0]

16. Kaufman MW, Martí JR, Gallager HS, Hoehn JL. Carcinoma of the breast with pseudosarcomatous metaplasia. Cancer. 1984;53(9):1908-17. [DOI:10.1002/1097-0000478-198301000-00002] [PMID]

17. Denley H, Pinder SE, Tan PH, Sim CS, Brown R, Barker T, Gearty J, Elston CW, Ellis IO. Metaplastic carcinoma of the breast arising within complex sclerosing lesion: a report of five cases. Histopathology. 2000;36(3):203-9.

18. Catroppo JF, Lara JF. Metastatic metaplastic carcinoma of the breast (MCB): an uncharacteristic pattern of presentation with clinicopathologic correlation. Cytopathology. 2001;12(5):285-91. [DOI:10.1002/dc.2056] [PMID]

19. Goldhirsh A, Glick JH, Gelber RD, et al.: Meeting Highlights: International Consensus Panel on the Treatment of Primary Breast Cancer.
274 Metaplastic Carcinoma

J Clin Oncol. 2001;19(18):3817-27. [DOI:10.1200/JCO.2001.19.18.3817] [PMID]

20. Gary M Tse, Puay-Hoon Tan, Benjaporn Chaiwun, Thomas C Putti, Philip C W Lui, Alex K H Tsang, Fiona C L Wong, Anthony W I Lo. p63 is useful in the diagnosis of mammary metaplastic carcinomas. Natl Libr Med. 2006;38 (1):16-22 [DOI:10.1080/00313020500444625] [PMID]

21. Lai HW, Tseng LM, Chang TW, Kuo YL, Hsieh CM, Chen ST, Kuo SJ, Su CC, Chen DR. The prognostic significance of metaplastic carcinoma of the breast (MCB)--a case controlled comparison study with infiltrating ductal carcinoma. The Breast. 2013;22(5):968-73. [DOI:10.1016/j.breast.2013.05.010] [PMID]

22. Al Sayed AD, El Weshi AN, Tulbah AM, Rahal MM, Ezzat AA. Metaplastic carcinoma of the breast clinical presentation, treatment results and prognostic factors. Ann Oncol 2006;45(2):188-95. [DOI:10.1080/02841860500513235] [PMID]

23. Kiran A, Veena M, Hasan H, Ghazala M. An usual case of metaplastic breast carcinoma (sarcomatoid variant) Indian J Surg. 2003;65:377-78.

24. Pitts WC, Rojas VA, Gaffey MJ, Rouse RV, Esteban J, Frierson HF, Kempson RL, Weiss LM. Carcinomas with metaplasia and sarcomas of the breast. Am J Clin Pathol. 1991;95(5):623-32. [DOI:10.1093/ajcp/95.5.623] [PMID]

25. Takuwa H, Ueno T, Ishiguro H, Mikami Y, Kanao S, Takada M, Sugie T, Toi M. A case of metaplastic breast cancer that showed a good response to platinum-based preoperative chemotherapy. Breast Cancer. 2014;21(4):504-7. [DOI:10.1007/s12282-011-0269-2] [PMID]

26. Hennessy BT, Giordano S, Brogliio K, Duan Z, Trent J, Buchholz TA, Babiera G, Hortobagyi GN, Valero V. Biphasic metaplastic sarcomatoid carcinoma of the breast. Ann Oncol. 2006;17(4):605-13. [DOI:10.1093/annonc/mdl006] [PMID]

27. Tseng WH, Martinez SR. Metaplastic breast cancer: to radiate or not to radiate? Ann Surg Oncol. 2011;18(1):94-103. [DOI:10.1245/s10434-010-1198-6] [PMID] [PMCID]

28. Gültekin M, Eren G, Babacan TA, Yazıcı G, Hurmuz P, Yıldız F, Altundag K, Guler N, Ozisik Y, Gürkaynak M. Metaplastic breast carcinoma: A heterogeneous disease. Asian Pac J Cancer Prev. 2014;15(6):2851-56 [DOI:10.7314/APJCP.2014.15.6.2851] [PMID]

29. Bae SY, Lee SK, Koo MY, Hur SM, Choi MY, Cho DH, Kim S, Choe JH, Lee JE, Kim JH, Kim JS. The prognoses of metaplastic breast cancer patients compared to those of triple-negative breast cancer patients. Breast Cancer Res Treat. 2011;126(2):471-8. [DOI:10.1007/s10549-011-1359-8] [PMID]

30. Song Y, Liu X, Zhang G, Song H, Ren Y, He X, Wang Y, Zhang J, Zhang Y, Sun S, Liang X. Unique clinicopathological features of metaplastic breast carcinoma compared with invasive ductal carcinoma and poor prognostic indicators. World J Surg Oncol. 2013;11(1):1-9. [DOI:10.1186/1477-7819-11-129] [PMID] [PMCID]

31. Altuf FJ, Mokhtar GA, Emam E, Bokhary RY, Mahfouz NB, Al Amoudi S, Al-Gaithy ZK. Metaplastic carcinoma of the breast: an immunohistochemical study. Diagnostic Pathol. 2014;9(1):1-0. [DOI:10.1186/1746-1596-9-139] [PMID] [PMCID]

32. Gary MT, Puay-Hoon T, Chaiwun B, Putti TC, Lui PC, Tsang AK, Wong PC, Lo AW. p63 is useful in the diagnosis of mammary metaplastic carcinomas. Pathology. 2006;38(1):16-20. [DOI:10.1080/00313020500444625] [PMID]

How to Cite This Article

Patil Okaly, G V, Akshatha, C, Sandhya, N, Prakash, P, Suma M N, Nargund A, et al. Revisiting Metaplastic Carcinoma of Breast: An Emphasis into the Clinico-pathological and Immunohistochemical Variables Analyzed at a Tertiary Cancer Centre in South India. Iran J Pathol. 2022; 17(3): 268-274. doi: 10.30699/IJP.2022.541798.2757

Vol.17 No.3 Summer, 2022 IRANIAN JOURNAL OF PATHOLOGY