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CASE REPORT

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A unique presentation of metaplastic breast carcinoma, NOS: A case report

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Key Clinical Message

A rare form of invasive breast carcinoma, NOS, also known as matrix-producing carcinoma made up of epithelial and mesenchymal components. Usually, they are triple negative and clinically aggressive and respond poorly to neoadjuvant systemic therapy.

Abstract

Metaplastic breast carcinomas (MBCs) are ductal carcinomas that undergo metaplasia to form nonglandular growth patterns. They are extremely rare, constituting less than 1% of all invasive breast carcinomas. Matrix-producing carcinoma is an exceedingly rare form of MBC distinguished by a ductal carcinomatous component with direct transition to areas of cartilaginous or osseous differentiation without the presence of an intervening spindle cell element. MBCs are clinically aggressive, but matrix-producing subtypes have a relatively better prognosis. The tumors are usually triple negative. Therefore, surgery and chemotherapy are the main therapeutic approaches. Our report describes this unique form of MBC with prominent osseous differentiation in a 33-year-old female patient. Its distinct histological features and peculiar clinical behavior necessitate a thorough understanding of this one-of-a-kind disease entity.

KEYWORDS

breast, carcinoma, epithelial and mesenchymal differentiation, matrix-producing, metaplastic

1 | INTRODUCTION

Metaplastic breast carcinoma (MBC) is a clinically aggressive and extremely rare form, accounting for 0.2%–1% of all invasive mammary carcinomas.[1] It represents a heterogeneous group of neoplasms generally characterized by an intimate admixture of an invasive breast carcinoma with atypical squamous, spindle cell, or mesenchymal/matrix-producing differentiation. Metaplastic spindle cell and squamous cell carcinomas may present in a pure form without any recognizable ductular component. MBC with osseous differentiation is the rarest subtype,[2,3] usually triple negative. Thus, the tumors tend to have a poor prognosis.[1] Herein, we present a rare case of a 33-year-old

African female patient with MBC with osseous metaplasia managed in our institution and provide a brief review of the literature.

2 | CASE REPORT

A 33-year-old female attended a breast cancer screening outreach program with a 6-month history of a left breast mass. The mass started as a small swelling that progressively increased in size over time. She denied a history of difficulty breathing, back pain, nipple discharge, night sweats, and weight loss. She reported having a regular menstrual cycle of 28 days with a flow of 5 days. She denied a history of oral contraceptive use. She had two children whom she breastfed exclusively, with no history of smoking or alcohol intake and no family history of breast disorders on both the maternal and paternal sides.

On initial examination, she had a fair nutritional status, had mild pallor, was not dyspneic, and was not jaundiced. On local examination, her left breast was larger than the right with an obvious large fungating mass located in the upper inner and outer quadrants, measuring 12 × 15 cm, with foul-smelling discharge, peau d'orange of the surrounding skin, and visible dilated veins but no nipple retraction and nipple discharge. There were palpable axillary lymph nodes involving the anterior, central, and apical groups, which are mobile, firm, nonmatted, and the largest measured 2 × 2 cm. There was no contralateral breast mass or supraclavicular lymphadenopathy. The left axillary lymph nodes were palpable. Her respiratory, cardiovascular, and abdominal examinations were normal.

Her laboratory workup results, including complete blood count, complete metabolic panel, lipid results, and thyroid-stimulating hormone, were essentially normal except for mild anemia with a hemoglobin of 10.8 g/dL. Her biopsy results revealed an infiltrative tumor made up of solid islands of malignant epithelial cell clusters scattered in the stroma, characterized by atypical spindle cells with areas of osseous metaplasia. Tumor necrosis, together with atypical mitoses and hemorrhage, were associated (Figures 1 and 2). The diagnosis of MBC with osseous metaplasia was entertained. A differential diagnosis of extraskeletal primary osteosarcoma of the breast was considered. Hormonal receptor status determination results highlighted triple negatives (ER = 0%, PR = 0%, and HER-2 = 0%). A CT scan and a bone scan were recommended for staging. However, due to the financial constraints of the patient, they were not done. Instead, an abdomino-pelvis ultrasound and chest X-ray were performed. The ultrasound and X-rays results were negative for metastases. Her clinical staging was $cT_{4b}N_{1a}M_0$.

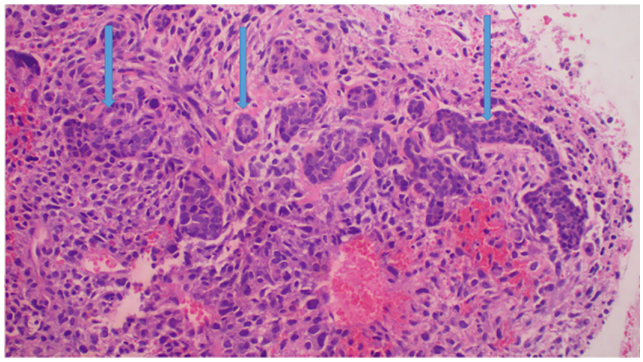

FIGURE 1 Photomicroscopic images of metaplastic carcinoma highlighting two distinct (biphasic) components: clusters or sheets of epithelial cells forming nests or cords of atypical cells with moderately enlarged nuclei (blue arrows).

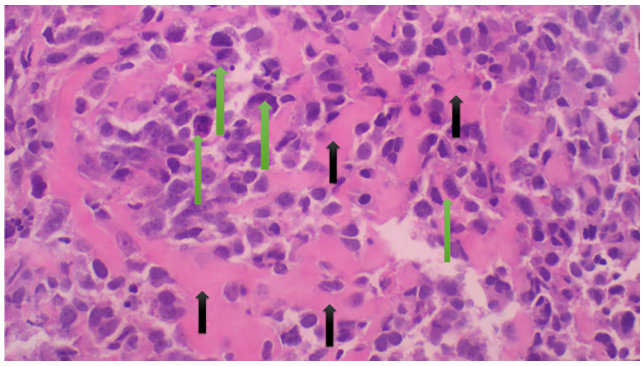

FIGURE 2 Diffuse proliferation of the mesenchymal cell component, whose individual cells are atypical and oval-to-spindled shaped (green arrows), with osteoid matric deposition, resembling osteosarcoma (black arrows); H & E staining 10 × original magnification.

A modified radicle mastectomy with axillary lymph node sampling was performed. The final mastectomy pathology report concluded the diagnosis of high-grade invasive MBC with prominent osseous differentiation, triple hormonal receptor-negative, pT4bN1M0, with negative surgical margins. She received radiotherapy and six cycles of adjuvant chemotherapy (5-flourouracil, doxorubicin, paclitaxel, and cyclophosphamide). To date, 1 year has passed since she finished oncological care; she is disease-free and is kept under follow-up.

3 | DISCUSSION

Osseous metaplasia in MBC is a rare phenomenon that may be benign or malignant.[4,5] Ultrastructural analysis supports the evidence that the tumor cells are of both epithelial and myoepithelial derivations. Being biphasic tumors, the origin of metaplastic breast tumors has been

widely debated, and thus, the cellular origin of these tumors remains speculation. Bone morphogenic proteins are thought to induce chondrogenic or osteogenic expression in stem cells while suppressing differentiation into muscle or fat.[6] These growth factors act as external triggers to induce specific transcription factors that lead to a cascade of phenotype-specific genes leading to a differentiated cell. Some studies described modified fibroblasts that changed through metaplasia as possible mechanisms of development. Chronic inflammation, ischemia, or trauma have also been implicated in initiating the cascade of events that lead to metaplasia.[7] Other theories suggest that these tumors arise from the combination of a common multipotent progenitor cell, giving rise to both sarcomatous and carcinomatous cells. However, instances where no causes could be established are not uncommon.[8–10]

Contrary to the index case, MBC usually affects females with median ages of 40–65 years,[11] presenting as large tumors as seen in our case, fixed to underlying tissues, making it difficult to treat. The neoplasm has high rates of recurrence, at 35%–62%.[12,13] P53 mutations are highly visible with frequencies ranging from 53% to 64%. Tumor protein p63, which is a member of the p53 family, is also expressed in these neoplasms and is used as a myoepithelial marker; however, it has no prognostic value. Biopsies taken for immunohistochemistry studies usually present with ER, PR, and Her-2 negatives; hence, there is no value for hormonal therapy.[14] The diagnosis of MBC is based on histological findings.[15] Breast imaging may be challenging since only the benign features of the disease are observed. On mammography, osseous lesions are seen as dense calcifications. Pleomorphic and linear microcalcifications are not frequently documented. Instead, a round or oval mass with a circumscribed margin is described.[1,9] Similarly, ultrasonographic findings may not be useful since an oval, round, or lobular solid hypoechoic mass with circumscribed or indistinct margins is observed, making the lesion easily misinterpreted as benign.

As evidenced in our patient, MBC typically presents with high-grade tumors at an advanced stage, possibly due to rapid growth rate. The tumor presents like an invasive breast carcinoma of no special type and tends to have a large tumor size, less nodal involvement, and a higher American Joint Committee on Cancer (AJCC) stage.[15,16] Therefore, they are locally aggressive with poor outcomes. Important factors in determining outcome are tumor size and mesenchymal component, with a worse survival rate seen in patients with tumors >5 cm. A high proportion of matrix is seen in these tumors, and spindle cells have a more favorable outcome. MBCs are managed as other breast cancers, such as infiltrating ductal carcinoma, express a triple-negative status. Several reports suggest that anti-PD-1/L1 is potentially active in this disease.[17] Patients may be treated with breast-conserving surgery. However, due to the large tumor size at presentation, as it was mirrored in our patient, conserving surgery may be less applicable. Neoadjuvant chemotherapy has shown limited value; thus, mastectomy with axillary lymph node clearance followed by adjuvant chemotherapy is the mainstay of the management of this rare neoplasm.[18,19] Radiotherapy showed limited value in the adjuvant setting; however, there are very few studies with limited data on survival and recurrence rates postradiotherapy, and hence the need for more randomized trials on the management of this rare neoplasm.

4 | CONCLUSION

Metaplastic carcinoma with osseous metaplasia is a rare form of invasive breast carcinoma, NOS. Usually, they are triple negative, clinically aggressive, and respond poorly to neoadjuvant systemic therapy. The tumor should be considered whenever a calcified breast lesion is encountered, and demonstration of osteoid matrix mineralization by morphology will help in diagnosis. Due to the heterogenicity of this neoplasm, awareness of this rare neoplasm should raise an appraisal for the early diagnosis and ultimately improve the treatment outcomes of patients with this disease.

AUTHOR CONTRIBUTIONS

Alex Mremi: Conceptualization; data curation; funding acquisition; investigation; writing – original draft. **Jay Lodhia:** Data curation; investigation; writing – review and editing. **Mujaheed Suleman:** Data curation; investigation; writing – review and editing. **Theresia Edward Mwakyembe:** Data curation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors have declared that no competing interests exist.

DATA AVAILABILITY STATEMENT

There are no data generated from this study.

ETHICS STATEMENT

The patient provided written informed consent to allow for her deidentified medical information to be used in this publication. A waiver for ethical approval was obtained from the authors' institution review board committee.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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REFERENCES

1. Böler DE, Kara H, Sağlıcan Y, Tokat F, Uras C. Metaplastic carcinoma of the breast: a case series and review of the literature. *J Oncol Sci*. 2016;2(2–3):38-42.
2. Salih AM, Kakamad FH, Saeed YA, Muhialdeen AS. Metaplastic breast carcinoma with osseous differentiation: a rare case report. *Int J Surg Case Rep*. 2017;34:100-102.
3. Lang R, Fan Y, Fu X, Fu L. Metaplastic breast carcinoma with extensive osseous differentiation: a report of two cases and review of the literature. *Tumori*. 2011;97(4):e1-e5.
4. Thushara K, Rupashree S, Babu RK. Benign osseous metaplasia of breast – a rare case report. *Ann Int Med Den Res*. 2020;6(1):PT01-PT02.
5. Ahmed FH, Abdelrahman S, Ibrahim A. Primary osseous metaplasia of right breast. *Open J Pathol*. 2020;10(3):108-112.
6. Reddy TP, Rosato RR, Li X, Moulder S, Piwnica-Worms H, Chang JC. A comprehensive overview of metaplastic breast cancer: clinical features and molecular aberrations. *Breast Cancer Res*. 2020;22(1):1.
7. Yahaya J, Mremi A. Metaplastic carcinoma of breast: a report of two cases. *Oxf Med Case Reports*. 2020;2020(9):omaa070.
8. Yu JI, Choi DH, Huh SJ, et al. Unique characteristics and failure patterns of metaplastic breast cancer in contrast to invasive ductal carcinoma: a retrospective multicenter case–control study (KROG 13-07). *Clin Breast Cancer*. 2015;15(2):e105-e115.
9. Kashyap R, Vellathussery Chakkalakkoombil S, Ch Toi P, Satheesan D. Metaplastic breast carcinoma with osseous differentiation presenting as calcified breast mass-radio-pathological correlation. *Breast J*. 2020;26(9):1825-1827. doi:10.1111/tbj.13866
10. Pollock JM, Green A, Donnell C, Dyess DL, Tucker JA. Metaplastic breast carcinoma with osseous differentiation: a case report. *South Med J*. 2006;99(2):168-170. doi:10.1097/01.smj.0000198641.86704.ed
11. Chuthapisith S, Warnnissorn M, Amornpinyokiat N, Pradniwat K, Angsusinha T. Metaplastic carcinoma of the breast with transformation from adenosquamous carcinoma to osteosarcomatoid and spindle cell morphology. *Oncol Lett*. 2013;6(3):728-732. doi:10.3892/ol.2013.1464
12. Shruti S, Siraj F. Matrix-producing metaplastic breast carcinoma – a rare tumor with heterologous elements. *Ger Med Sci*. 2017;15:Doc17. doi:10.3205/000258
13. Bhosale SJ, Kshirsagar AY, Sulhyan SR, Sulhyan SR, Jagtap SV. Matrix-producing metaplastic breast carcinoma – a rare malignancy. *Am J Case Rep*. 2013;14:213-215. doi:10.12659/ajcr.883958
14. Tsukuda K, Tsuji H, Kunitomo T, et al. Breast cancer with cartilaginous and/or osseous metaplasia diagnosed by lymph nodal metastasis: a case report. *Acta Med Okayama*. 2009;63(6):367-371. doi:10.18926/AMO/31828
15. Mremi A, Mwakyembe T, Wampembe E, Serventi F, Lodhia J. Primary breast squamous cell carcinoma: a case report at a tertiary hospital in northern Tanzania. *Clin Case Rep*. 2023;11(6):e7586. doi:10.1002/ccr3.7586
16. 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. doi:10.1245/s10434-014-3782-7
17. Kim I, Rajamanickam V, Bernard B, et al. A case series of metastatic metaplastic breast carcinoma treated with anti-PD-1 therapy. *Front Oncol*. 2021;11:635237.
18. El Zein D, Hughes M, Kumar S, et al. Metaplastic carcinoma of the breast is more aggressive than triple-negative breast cancer: a study from a single institution and review of literature. *Clin Breast Cancer*. 2017;17(5):382-391. doi:10.1016/j.clbc.2017.04.009
19. Thapa B, Arobelidze S, Clark BA, et al. Metaplastic breast cancer: characteristics and survival outcomes. *Cureus*. 2022;14(8):e28551.

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