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Dramatic Response to Carboplatin, Paclitaxel, and Radiation in a Patient With Malignant Myoepithelioma of the Breast

Malignant myoepithelioma of the breast (MMB) is extremely rare and often presents as a diagnostic challenge. Myoepithelial cells are normally located between the stroma and luminal epithelium [1] and extend from the collecting (retroareolar) duct to the extreme tip of the acini of mammary glands [2]. These cells have characteristics of both epithelial and smooth muscle cells. Myoepithelial tumors arise mainly in the salivary glands, but can occur in the skin, soft tissue, retroperitoneum, lung, vulva, and breast. Myoepithelial cells are involved in the pathogenesis of several types of breast lesions, which include multifocal myoepitheliomatosis, adenoid cystic carcinoma, adenomyoepithelioma, and malignant myoepithelioma [3, 4]. Malignant myoepithelioma is the only cancer composed of pure myoepithelial cells, which are mostly spindle-shaped, but may occasionally be epithelioid. Most case reports of MMB in literature emphasize the diagnosis and pathology, but few discuss treatment and outcomes. In general, MMB is treated by wide surgical excision, lymph node dissection, and adjuvant radiotherapy to reduce recurrence risk [5]. The role of chemotherapy and choice of agents are not clearly defined. There is no role for hormonal modulation or human epidermal growth receptor 2 (HER2) receptor blockade, given that MMBs are triple-negative tumors. Here, we report a rare case of aggressive MMB in a 52-year-old woman who experienced a dramatic response to carboplatin, paclitaxel, and radiation.

Case Report

A 52-year-old Asian female had a growing left fungating breast mass for approximately 1.5 years while being treated with holistic medicine. She developed progressive anorexia, weight loss of 30 pounds, fatigue, weakness, and leg swelling a few months before presentation. At presentation, she had chest pain and dyspnea and was diagnosed with bilateral pulmonary embolism. General exam revealed cachexia, 3+ pitting edema of lower extremities, and poor performance status of Eastern Cooperative Oncology Group (ECOG) 2. Breast exam revealed a large left breast that was ulcerated and bleeding. Lymph node exam was significant for axillary adenopathy. Chest computed tomography (CT) showed a left breast mass of 23.3 × 17.3 × 11.1 cm that was extending through the chest wall to the extrapleural space (Fig. 1). There was adjacent left axillary, supraclavicular, and metastatic mediastinal lymphadenopathy. There was no evidence of central nervous system, bone, or intra-abdominal metastasis. Her lower extremity venous duplex revealed extensive nonocclusive thrombus extending from the left common femoral vein through the popliteal vein. Her laboratory values were significant for albumin (21 g/L), sodium bicarbonate (18 mmol/L), anion gap (19 mmol/L), lactic acid (more than 10 mmol/L), and hemoglobin (87 g/L). Pathology revealed a malignant tumor composed of round to polygonal cells. The cells had moderate amounts of cytoplasm with areas of clear cell change and conspicuous nucleoli. Moderate nuclear pleomorphism was seen, and mitoses were abundant (Fig. 2A), with up to eight mitotic figures per one high-power field. There was a minimal amount of tumor-infiltrating lymphocytes. Immunohistochemistry stains showed positivity for smooth muscle actin, HHF-35, pancytokeratin, S-100, and e-cadherin (Fig. 2B–2D). There was focal weak staining of CD10, and 90% of the tumor cells were positive for Ki-67. The cells were negative for estrogen receptor (ER), progesterone receptor (PR), HER2, cytokeratin 5/6, p63, and chromogranin. The stains supported the diagnosis of myoepithelial carcinoma. Next-generation sequencing revealed neurofibromatosis type 1 (NF1) duplication exons 31–35, MAGI2^{G835S}, and TP53^{S241F}. EGFR, CCND3, vascular endothelial growth factor A (VEGFA), and MYC amplifications were equivocal. As expected, there was no ERBB2 alteration.

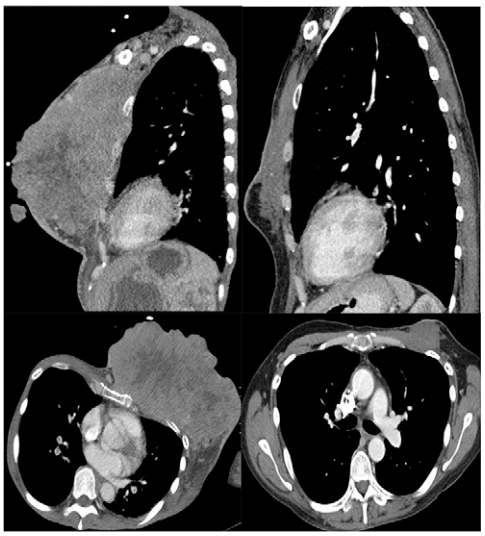

Figure 1. Computed tomography (CT) scan of the chest illustrates impressive response to chemotherapy. Left: Baseline CT scan with a large left breast mass with central necrosis and ulceration. Right: After 4 months of chemotherapy, the mass became significantly smaller.

The patient was treated with a single course of carboplatin area under the curve (AUC) 4 and paclitaxel 140 mg/m^2 (20% dose reduction because of cachexia and poor performance status). She received 20 Grays of radiation to the left breast in five fractions for palliation 1 week after chemotherapy. Radiation technique included paired obliques, given that the patient had frozen shoulder and standard tangents could not be used. The lateral oblique was designed to treat anterior to the left arm, and the anterior oblique was designed to avoid treating through the heart. Subsequently, she was discharged to a skilled nursing facility and eventually home. We changed her treatment to weekly carboplatin AUC 2 and paclitaxel 80 mg/m^2, an institutional standard in triple-negative breast cancer, and adjusted to her absolute neutrophil count [6]. After

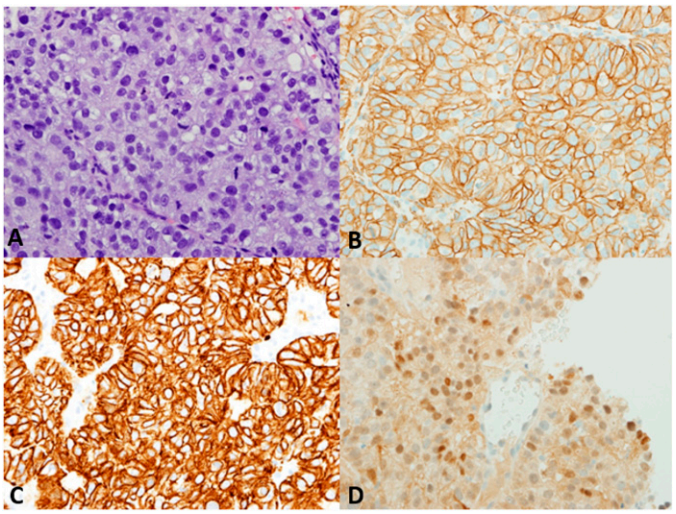

Figure 2. Histologic findings of the myoepithelial carcinoma of the breast by hematoxylin and eosin and various immunohistochemical stains. **(A):** Epithelioid myoepithelial cells with abundant mitoses and occasional conspicuous nucleoli. The cells also display clear cell change (hematoxylin and eosin). **(B):** Positivity for smooth muscle actin. **(C):** Positivity for cytokeratin pan antibody monoclonal. **(D):** Positivity for S-100. Magnification, ×400.

the first 2 cycles, she improved clinically with normal appetite, weight gain of 20 pounds, good performance status of ECOG 0, and significant decrease in her symptomatic breast mass. Her repeat laboratory values at this time revealed albumin 35 g/L, sodium bicarbonate 27 mmol/L, anion gap 7 mmol/L, and hemoglobin 107 g/L. She also had resolution of her peripheral edema and venous thromboembolism after 3 months on enoxaparin. A repeat chest CT after the third cycle showed dramatic reduction in her left breast mass to 12.9 × 4.1 × 2.7 cm and resolution of mediastinal lymphadenopathy (Fig. 1). She continues to have ongoing response to carboplatin and paclitaxel. Breast examination revealed no evidence of residual mass in her left breast, except residual thickening. We plan to continue this regimen until disease progression or intolerance.

Discussion

The clinical spectrum of MMB is heterogeneous, varying from local infiltration and recurrence to lymph node invasion and distant metastasis [7]. A case series reported that the median 2- and 5-year overall survivals were 88% and 55%, respectively. This article also suggested that a tumor of more than 2 cm confers poor prognosis [8]. Data from salivary gland tumors showed that the presence of necrosis and vascular invasion correlated with inferior disease-free survival [9]. Our patient presented with many adverse clinical features, including a large tumor, poor performance status, malnutrition, lactic acidosis, and pulmonary embolism. The tumor contained poorly differentiated epithelioid cells with abundant mitoses and a Ki-67 of 90%, predicting its aggressive behavior (Fig. 1).

There are at least two distinct histological variances of myoepithelial cancer of the breast reported in the literature [10]. Although most tumors show a mixture of several cell types, one type often predominates. Malignant myoepithelioma is most commonly composed almost entirely of interlacing spindled cells. However, tumor cells can also appear epithelioid with a polygonal shape, eosinophilic cytoplasm, and ovoid nuclei. Occasionally these epithelioid cells have clear cytoplasm and are called clear cells [11–13]. In our case, the tumor is entirely epithelioid, with cells displaying clear cytoplasm. The prognostic difference between spindle and epithelioid MMB is unknown. Because of histologic variance, immunohistochemistry is required to make the correct diagnosis. The rate of positive stains for myoepithelial carcinoma by immunohistochemistry for keratin, S-100, and mucin are 93%, 87%, and 63%, respectively. Fewer tumors stain positive for muscle-cell markers such as calponin (86%), smooth muscle actin (36%), and desmin (14%) [14]. Ductal carcinoma with myoepithelial differentiation appears to predominantly overexpress epidermal growth factor receptor (EGFR) compared with invasive ductal carcinoma (70% versus 22%) [15]. EGFR overexpression in these breast tumors confers to inferior prognosis. Next-generation sequencing should be conducted for myoepithelial carcinoma to identify EGFR and other actionable mutations as potential therapeutic targets. In our case, EGFR amplification was equivocal.

Our patient received upfront carboplatin, paclitaxel, and radiation for her stage IV MMB and experienced a dramatic clinical and radiographic response. We chose the carboplatin and paclitaxel regimen based on its broad-spectrum activity. Chemotherapy and radiotherapy appeared to produce complementary antitumor effects in this case. To our knowledge, there are only two case reports that specifically discuss the role of chemotherapy in treating MMB. One article reported a 61-year-old female with spindle cell-predominant MMB who had stable disease on carboplatin and paclitaxel for approximately 18 weeks [5]. Another article reported a 74-year-old female with stage IIIb MMB (composed of mixed spindle-shaped and epitheloid cells) who had disease progression after three cycles of neoadjuvant docetaxel, doxorubicin, and cyclophosphamide. Postoperatively, she received weekly carboplatin, paclitaxel, and bevacizumab. Tumor response was not assessed because she died 2 weeks later from an infectious complication. The efficacy of carboplatin and paclitaxel was observed in a 37-year-old woman with recurrent metastatic vulvar myoepithelial carcinoma, who maintained complete remission for 3 years [16]. Interestingly, the vulvar myoepithelial tumor contained pure epithelioid phenotype cells, similar to our case.

We will need more clinical data to assess whether epithelioid-predominant MMB preferentially responds to carboplatin and paclitaxel. A case series suggested that a sarcoma-like chemotherapy regimen—which consists of four cycles of ifosfamide, etoposide, and cisplatin, followed by three cycles of ifosfamide, etoposide, and vincristine—may have activity against myoepithelial carcinoma of the soft tissue in the pediatric population [17]. Of the four evaluable cases, two cases had partial response, one case had minor response, and one case had stable disease [17]. Although it is unclear whether we can extrapolate these results to adult patients with MMB, it is a viable option for those who progress on carboplatin and paclitaxel. Next-generation sequencing of the myoepithelial carcinoma biopsy did not identify any actionable genomic alterations, other than the potential NF1 duplication exons 31–35. NF1 mutations have been reported in 2% of breast cancers but appeared more commonly in triple-negative breast tumors [18–20]. Although NF1 inactivation predicts sensitivity to MEK [21, 22] and mammalian target of rapamycin inhibitors [23, 24], based on preclinical and limited clinical data, it is not known whether these therapeutic approaches would be relevant to NF1 duplication exons 31–35. Important genomic alterations, such as EGFR, CCND3, and VEGFA amplifications, were equivocal.

In conclusion, MMB is a rare tumor with significant morphological heterogeneity, which poses significant diagnostic challenges. Comprehensive histological and immunohistochemical evaluations are essential for an accurate diagnosis. The clinical behavior of MMB is usually aggressive, and the lack of ER/PR/HER2 expression restricts therapeutic options. Given the lack of standard treatment guidance, the efficacy of carboplatin, paclitaxel, and radiotherapy demonstrated in our patient with metastatic MMB is promising.

Author Contributions

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Manuscript writing: Phu N. Tran, Lefan Zhuang, Chaitali Nangia, Rita S. Mehta
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Disclosures

The authors indicated no financial relationships.

References

1. Gudjonsson T, Adriance MC, Sternlicht MD et al. Myoepithelial cells: Their origin and function in breast morphogenesis and neoplasia. J Mammary Gland Biol Neoplasia 2005;10:261–272.

2. Tavassoli FA, Eusebi V. Tumors of the Mammary Gland, AFIP Atlas of Tumor Pathology. Washington, DC: American Registry of Pathology, 2009.

3. Tavassoli FA. Myoepithelial lesions of the breast: Myoepitheliosis, adenomyoepithelioma, and myoepithelial carcinoma. Am J Surg Pathol 1991; 15:554–568.

4. Lakhani EI Sr, Schnitt SJ, Tan PH et al., eds. WHO Classification of Tumours of the Breast. Lyon, France: IARC Press, 2012:120–123.

5. Endo Y, Sugiura H, Yamashita H et al. Myoepithelial carcinoma of the breast treated with surgery and chemotherapy. Case Rep Oncol Med 2013; 2013:164761.

6. Mehta RS. Dose-dense and/or metronomic schedules of specific chemotherapies consolidate the chemosensitivity of triple-negative breast cancer: A step toward reversing triple-negative paradox. J Clin Oncol 2008;26: 3286–3288; author reply 3288.

7. Irvanlou G, Mahjoub F. Malignant myoepithelioma of the breast. Acta Med Iran 1997;35:90–94.

8. Behranwala KA, Nasiri N, A'Hern R et al. Clinical presentation and long-term outcome of pure myoepithelial carcinoma of the breast. Eur J Surg Oncol 2004;30:357–361.

9. Kong M, Drill EN, Morris L et al. Prognostic factors in myoepithelial carcinoma of salivary glands: A clinicopathologic study of 48 cases. Am J Surg Pathol 2015;39:931–938.

10. Abd el-All HS. Breast spindle cell tumours: About eight cases. Diagn Pathol 2006;1:13.

11. Cartagena N Jr, Cabello-Inchausti B, Willis I et al. Clear cell myoepithelial neoplasm of the breast. Hum Pathol 1988;19:1239–1243.

12. Miura Y, Kurose A, Kondo M et al. Clear cell myoepithelial carcinoma of the breast: A case report. Tohoku J Exp Med 2003;200:103–109.

13. R S, Padu K, Singh Th B et al. Myoepithelial carcinoma of the breast. J Clin Diagn Res 2013;7:1191–1193.

14. Hornick JL, Fletcher CD. Myoepithelial tumors of soft tissue: A clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. Am J Surg Pathol 2003;27:1183–1196.

15. Shien T, Tashiro T, Omatsu M et al. Frequent overexpression of epidermal growth factor receptor (EGFR) in mammary high grade ductal carcinomas with myoepithelial differentiation. J Clin Pathol 2005;58:1299–1304.

16. Noronha V, Cooper DL, Higgins SA et al. Metastatic myoepithelial carcinoma of the vulva treated with carboplatin and paclitaxel. Lancet Oncol 2006;7:270–271.

17. Bisogno G, Tagarelli A, Schiavetti A et al. Myoepithelial carcinoma treatment in children: A report from the TREP project. Pediatr Blood Cancer 2014;61:643–646.

18. Güran S, Safali M. A case of neurofibromatosis and breast cancer: Loss of heterozygosity of NF1 in breast cancer. Cancer Genet Cytogenet 2005;156:86–88.

19. Salemis NS, Nakos G, Sambaziotis D et al. Breast cancer associated with type 1 neurofibromatosis. Breast Cancer 2010;17:306–309.

20. Craig DW, O'Shaughnessy JA, Kiefer JA et al. Genome and transcriptome sequencing in prospective metastatic triple-negative breast cancer uncovers therapeutic vulnerabilities. Mol Cancer Ther 2013;12:104–116.

21. Ameratunga M, McArthur G, Gan H et al. Prolonged disease control with MEK inhibitor in neurofibromatosis type I-associated glioblastoma. J Clin Pharm Ther 2016;41:357–359.

22. Chang T, Krisman K, Theobald EH et al. Sustained MEK inhibition abrogates myeloproliferative disease in Nf1 mutant mice. J Clin Invest 2013; 123:335–339.

23. Lim SM, Park HS, Kim S et al. Next-generation sequencing reveals somatic mutations that confer exceptional response to everolimus. Oncotarget 2016;7: 10547–10556.

24. Janku F, Kaseb AO, Tsimberidou AM et al. Identification of novel therapeutic targets in the PI3K/AKT/mTOR pathway in hepatocellular carcinoma using targeted next generation sequencing. Oncotarget 2014;5: 3012–3022.

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