Neoadjuvant Chemotherapy and Immunotherapy in Metaplastic Breast Cancer: A Case Report

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Abstract

Metaplastic Breast Cancer (MpBC) is a rare and complex entity accounting for approximately 0.2% to 5% of all breast cancers. We present here a case of MpBC in a 57-years-old woman who had a history of atrial fibrillation. Her lesion was classified cT3N0M0. She was treated with neoadjuvant chemotherapy associated with immunotherapy by checkpoint inhibitors. A good clinical and radiological response was observed, and the patient underwent right lumpectomy plus sentinel lymph node biopsy with oncoplasty and contralateral symmetrization. Histology confirmed a good response with a reduction in the size of the lesion and negative sentinel lymph nodes. The patient received radiotherapy and is currently in remission.

Keywords: Metaplastic Breast Cancer (MpBC) • Oncoplasty • Immunotherapy by checkpoint inhibitors

Introduction

Metaplastic Breast Cancer (MpBC) is a rare and complex entity, accounting for approximately 0.2% to 5% of all breast cancer cases [1]. This atypical form of breast cancer is characterized by its aggressive nature and distinct histological presentation, which includes a diverse epithelial neoplastic cell differentiation towards squamous and/or mesenchymal elements, such as spindle, chondroid, osseous, and rhabdomyoid cells [1,2]. This heterogeneity is also manifested by some distinct special MpBC subtypes with a less aggressive behavior, such as low-grade adenosquamous carcinoma and fibromatosis-like metaplastic carcinoma. The surrogate molecular profile of MpBC typically presents as triple negative (lacking ER, PgR, and HER2), yet its prognosis is often worse than other forms of Triple-Negative Breast Cancers (TNBC) that are not MpBC. This subtype generally shows a limited response to systemic treatment, with a median survival of 8 months following metastasis onset, and an increased propensity for loco regional and/or distant recurrences compared to other invasive ductal carcinomas [3]. This variability underscores the complexity and therapeutic challenge that this disease represents. The current literature on MpBC remains limited, and there are no standardized treatment guidelines at present that are specifically designed for this breast cancer subcategory. This makes the management of these patients particularly challenging.

Current studies, including the work of Reddy et al. in Breast Cancer Research in 2020, highlights the obstacles and opportunities in understanding and treating MpBC, indicating an urgent need to deepen our knowledge of this pathology in order to develop more effective and personalized therapeutic strategies [1].

Case Presentation

Patient information

A 57-years-old postmenopausal and nulliparous female patient reported detecting a 5 cm firm mass in her right breast upon self-examination. She was not undergoing hormone replacement therapy. Her medical history was notable for atrial fibrillation, and she had no familial history of breast cancer.

Clinical findings

Clinical examination revealed a significant, hard mass in the upper part of the right breast, with no detectable axillary lymphadenopathy. Mammography highlighted an irregular 5 cm lesion at the upper pole of the breast, surrounded by microcalcifications, confirmed by Magnetic Resonance Imaging (MRI) showing an enhanced area of 45 mm x 32 mm x 32 mm (Figure 1A-1C).

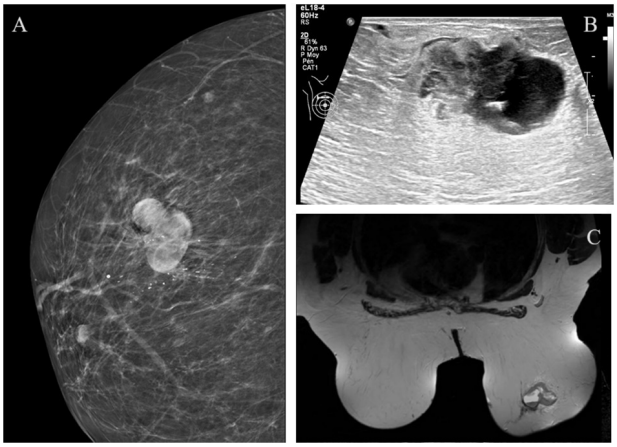

Figure 1. Irregular neoplastic mass in the upper part of the right breast seen on mammography A), ultrasound B) and MRI C) (45 mm x 32 mm x 32 mm).

Diagnostic evaluation

The core biopsy demonstrated the presence of an infiltrating carcinoma. The presence of spindle cells with focal osteoid formation indicated the presence of focal osteosarcomatous differentiation (Figure 2a and 2b). The neoplastic cells did not show any immunoreactivity for Estrogen Receptor (ER), Progesterone Receptor (PgR) or HER2. The neoplastic cells showed nuclear immunoreactivity for Ki67, with a proliferation index estimated at 60%. The tumor showed focal immunoreactivity for EMA and the broad-spectrum cytokeratin AE1/AE3. The PD-L1 (clone 22C3) CPS score was 40. The biopsy of the distant microcalcifications was found to be benign fibrocystic disease. No distant metastasis was identified, and germline genetic testing was negative.

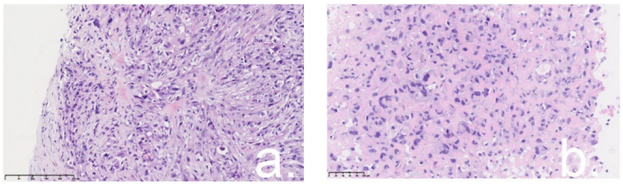

Figure 2. Hematoxylin/eosin stain of the biopsy-diagnosed metaplastic carcinoma prior to neoadjuvant chemotherapy. The tumor contains spindle cells with severe atypia a) and osteoid formation b).

Initial therapeutic strategy

After a multidisciplinary consultation, a neoadjuvant treatment combining chemotherapy and immunotherapy (NAC) according to the Keynote-522 protocol was initiated. The intention was to administer 12 cycles of Carboplatin, Paclitaxel, and Pembrolizumab (CPP), followed by 4 cycles of dose-dense Epirubicin, Cyclophosphamide, and Pembrolizumab (ECP).

Follow-up and outcomes

The patient developed grade 3 autoimmune hepatitis after the first 10 CPP cycles. It was successfully managed with corticosteroids, returning to grade 0, which allowed the continuation of treatment with 4 EC cycles, as pembrolizumab was permanently discontinued. A favorable clinical and radiological response was observed during the treatment (Figure 3). Following the response and after a multidisciplinary consultation, conservative surgery, including a right tumorectomy and a sentinel lymph node biopsy, complemented by oncoplasty and contralateral symmetrization due to gigantomastia, followed by radiotherapy, was performed.

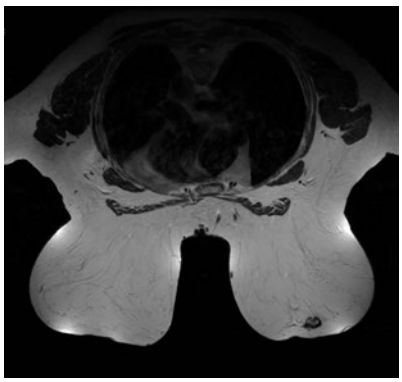

Figure 3. MRI showing the reduction in size of the right breast neoplastic lesion (16 mm x 13 mm x 16 mm) at the end of the neoadjuvant therapy.

After extensive sampling and rigorous histopathological evaluation, a fibrous tumor bed of 40 mm x 30 mm was identified, containing the residual carcinoma as multiple foci. The largest tumor focus measured 17 mm x 14 mm, without any associated in situ component, and with free resection margins. The cellularity of the fibrous tumor bed was estimated at 5% (Figure 4A-4E). All three axillary sentinel lymph nodes were negative and did not contain any isolated tumor cells. The Residual Cancer Burden score was 1.537, corresponding to an RCB-II class. The proliferative activity as measured by Ki67 was reduced to 2%. The overall surrogate molecular profile was not altered, with an Allred score of 0 for ER, an Allred score of 2 for PgR (nuclear immunoreactivity in <1% of neoplastic cells), and negative HER2 immunohistochemistry (score 0).

Ten months after the end of the treatment, the patient was in good health, without any sign of recurrence.

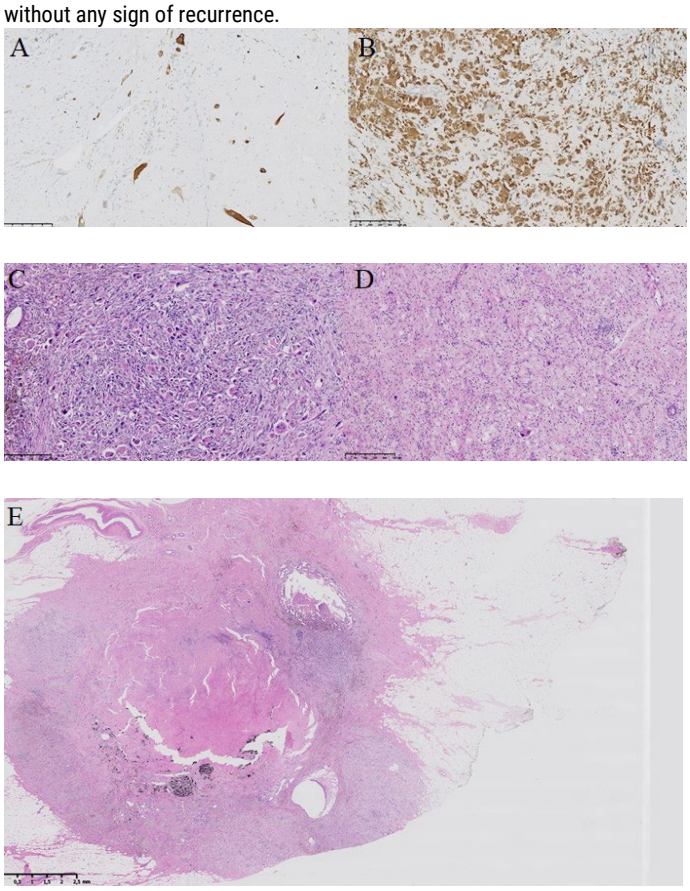

Figure 4. Residual metaplastic carcinoma after neoadjuvant chemotherapy. Immunohistochemistry for cytokeratin-AE1/AE3 highlights the neoplastic cells in areas with low cellularity (A). Immunohistochemistry for CD68 (B) illustrates the presence of numerous foamy macrophages (D). The fibrous tumor bed (E) also contained areas with high cellularity (C). The residual tumor cells had large quantities of eosinophilic cytoplasm and highly pleomorphic, hyperchromatic nuclei (C, D). Near the fibrous tumour bed, there was residual black carbon (E).

Discussion

Metaplastic Breast Cancer (MpBC) is a rare pathology often associated with resistance to traditional chemotherapy. Our case demonstrates significant tumor regression following neoadjuvant chemotherapy combined with pembrolizumab immunotherapy, underscoring the importance of considering innovative approaches for these notoriously difficult-to-treat cancers.

Despite limited studies of neoadjuvant chemotherapy for MpBC, some data and case reports indicate that when treatment is effective, outcomes can be comparable to other breast cancer subtypes. The Haque et al. analysis of the National Cancer Database covering 2004 to 2017 showed that of all MpBC patients who underwent NAC and definitive surgery (n=903), 9.8% (n=88) had a pathological Complete Response (pCR). The 5-year Overall Survival (OS) was significantly higher than for the non-pCR patients (93 vs 63%, p<0.001), and similar to non MpBC (93 *tq*, 93%) [4].

It is also worth noting that Yam C. et al., in their prospective clinical trial, showed a lower pCR rate in the MpBC group than in the non-MpBC group (23 *tq*, 40%, p: 0.07). The OS curves become similar between those two groups in case of pCR [5].

Joneja *cr _j.* reported the high prevalence of PD-L1 expression in MpBC tumor tissues (46%) compared to other tumor tissues (6% in HR^+ and

HER^{2+} and 9% in TNBC), supporting the use of immunotherapy [6]. Spectacular responses to immunotherapy have been documented even in advanced and chemo-resistant cases, suggesting an underestimated potential for beneficial responses in early stages of the disease [7,8].

Our patient exhibited a PD-L1 CPS of 40, indicating a high likelihood of a favorable response to immunotherapy, corroborated by our clinical observation. This reinforces the notion that MpBC might be particularly sensitive to a combined approach of neoadjuvant chemo-immunotherapy.

Lastly, the literature suggests a high level of genetic and molecular heterogeneity. This variability, especially frequent PI3KCA mutations and PI3K/AKT/mTORpathway alterations, poses challenges but also offers opportunities for targeted therapies [5,9,10]. Yam *cr _j*. highlighted a strong mesenchymal gene expression signature and poor survival for MpBC in a prospective study, suggesting the importance of continuing research for better molecular characterization and development of tailored therapeutic strategies [5].

These elements clearly illustrate the importance of optimizing neoadjuvant treatment in MpBC and the urgency of conducting more in-depth studies to evaluate the effectiveness of immunotherapy in combination with neoadjuvant chemotherapy.

Conclusion

Metaplastic Breast Cancer (MpBC) is known for its resistance to conventional chemotherapy, presenting significant treatment challenges. This case report highlights a patient's notable response to a neoadjuvant therapy regimen combining chemotherapy with immunotherapy, emphasizing the potential of PD-L1 as a therapeutic target in this chemoresistant cancer subtype. Despite autoimmune complications, the observed efficacy highlights the crucial role of PD-L1 in treatment strategies. Establishing comprehensive multicentric registries to collect data on MpBC is imperative, as it will enhance our understanding, enable the development of targeted treatments, and potentially transform clinical outcomes. Collaborative research focused on molecular profiling is essential to optimize care for MpBC patients.

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