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Case Report

Complete Response of Triple-Negative Metaplastic Carcinoma of the Breast Using Pembrolizumab

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Abstract
Metaplastic breast cancer (MpBC) is a rare form of breast malignancy with a poor prognosis and limited treatment guidance. Here, we report on a case of triple-negative MpBC that was successfully treated following the Keynote-522 clinical algorithm using pembrolizumab, paclitaxel, carboplatin, adriamycin, and cyclophosphamide in a neo-adjuvant fashion. The radiographic and histologic findings of the tumor are reviewed here along with the treatment regimen and response. No major toxicities associated with pembrolizumab were observed in this case. This case report serves as an example of complete pathological response of triple-negative MpBC with pembrolizumab plus chemotherapy and demonstrates the need for further research on chemoimmunotherapy for MpBC.

Introduction

Metaplastic breast cancer (MpBC) is a rare (<1%) and typically aggressive, high-grade subtype of breast malignancy characterized by histologic heterogeneity with a combination of squamous, adenocarcinoid, sarcomatoid, or other cell types [1, 2]. MpBC has been shown to exhibit a higher frequency of PD-L1 expression (43%) compared to other cancers. MpBC is

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generally associated with poor overall survival and progression-free survival (PFS) relative to the more common ductal carcinoma due to more advanced stage at presentation, high incidence of triple negative receptor status, high recurrence rate, and a lack of a well-studied standard of care [2]. MpBC also has higher chemoresistance and likelihood of metastasis compared with other TNBC histologic subtypes [3]. Due to its rarity, the literature on MpBC is limited to single-case reports and retrospective single-institution series. However, the 2023 National Comprehensive Cancer Network (NCCN) provided the lumped guidance for MpBC with other breast cancer subtypes, including ductal carcinoma [4]. Notably, rare cases of low-grade metaplastic carcinoma have been reported, and those may not respond as well to chemoimmunotherapy [5]. Cases of high-grade metastatic MpBC have been reported with partial or complete response to pembrolizumab with or without chemotherapy [6, 7].

While the standard of care for high-grade MpBC has not yet been established by a prospective randomized clinical trial, immunotherapy is being investigated in ongoing and future clinical trials for its activity in this rare subtype of breast cancer [3]. Immunotherapy, such as pembrolizumab, has recently emerged as a promising treatment approach for several types of cancer, including melanoma, head and neck, colorectal, and breast [8]. Herein, we present a case of a 71-year-old female with high-grade MpBC who successfully achieved a complete pathologic response using pembrolizumab, paclitaxel, carboplatin, adriamycin, and cyclophosphamide in the manner previously reported by the Phase III Keynote-522 clinical trial [9]. This case report adheres to the CARE case report guidelines. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534146).

Case Presentation

A 71-year-old African American female with ECOG of 1 and past medical history of type 2 diabetes mellitus, hypertension, and hyperlipidemia presented to her primary care provider 2 weeks after identifying a mass in her right breast. Physical examination was only notable for a palpable 6-cm right breast mass. Her last mammogram from 4 years prior was categorized as BI-RADS 1.

A new mammogram was ordered and showed a large, 5.8-cm BI-RADS 5 mass with indistinct margins in the posterior third of the right breast's upper outer quadrant. The mass was described as high density and irregular with associated dystrophic calcifications, as seen in Figure 1. In addition, suspicious lymph nodes were located adjacent to the mass in the axilla, also seen in Figure 1. An ultrasound was ordered and showed a corresponding irregular anti-parallel mass with angular margins, hypoechoic features, and internal vascularity. By ultrasound, 3 lymph nodes had cortical thickness greater than 2.3 mm and were deemed suspicious, but the patient had a COVID vaccine within 4 weeks of the imaging procedures.

The patient underwent ultrasound-guided core biopsy which showed a poorly differentiated (high-grade) carcinoma with necrosis and areas of malignant spindle cells embedded within a chondromyxoid stroma, suggesting metaplastic carcinoma (shown in Fig. 2). ER, PR, and HER2 immunohistochemistry returned negative. Immunohistochemical testing for PD-L1 showed a Tumor Proportion Score (TPS) of 70% (shown in Fig. 3). Biopsy from one axillary lymph node returned negative for carcinoma. The lymph nodes were deemed to be reactive nodes related to proximate administration of vaccines in the same arm. The patient was staged at cT3N0M0.

The patient was presented to the tumor board and neoadjuvant chemotherapy per Keynote-522 was recommended. Treatment was initiated 10 weeks after her initial presentation to medical oncology. The patient received four cycles of neoadjuvant

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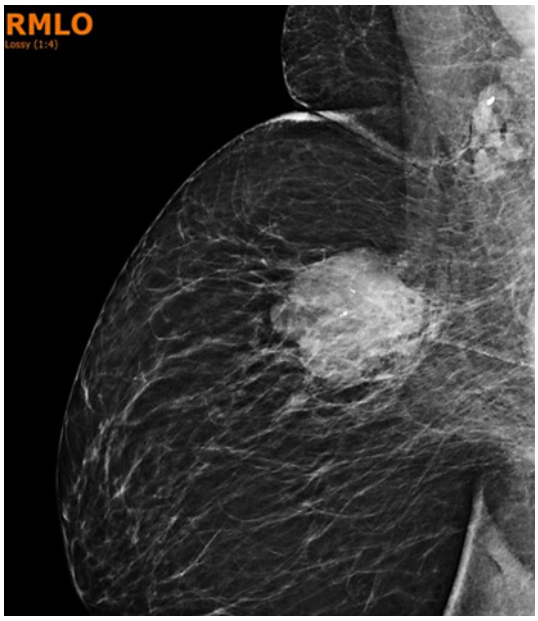

Fig. 1. Irregular breast mass with suspicious axillary lymph nodes. Mammogram right mediolateral oblique projection.

pembrolizumab 200 mg, paclitaxel 80 mg/m^2, and carboplatin AUC 1.5 every 21 days. The patient developed grade 2 peripheral neuropathy, and the dosage of paclitaxel was reduced to 65 mg/m^2. The fourth cycle was discontinued after 1 week due to side effects of neuropathy and fatigue. The patient then received four cycles of pembrolizumab 200 mg, doxorubicin 60 mg/m^2, and cyclophosphamide 600 mg/m^2 every 21 days to complete neoadjuvant therapy.

When compared with imaging at diagnosis (shown in Fig. 4a), repeat mammographic imaging after completion of neoadjuvant chemotherapy demonstrated excellent radiographic response with mild residual post-treatment architectural distortion and concentric shrinkage of the primary breast mass (shown in Fig. 4b). The patient then underwent right partial mastectomy with sentinel lymph node biopsy. The final surgical pathology specimen revealed a 1.4-cm area of fibrous scarring with no residual cancer cells and negative lymph nodes. Thus, the patient achieved a complete pathologic response.

For maintenance therapy, the patient received nine cycles of adjuvant pembrolizumab 200 mg every 21 days and adjuvant whole breast and regional nodal radiation to a dose of 40 Gy in 15 fractions with a 10 Gy in a 4 fraction boost to the lumpectomy cavity. The patient's treatment was complicated by sicca symptoms, but otherwise, she had no dose-limiting immune-related adverse events. She is currently living without cancer-related complications with an overall survival of 553 days and a PFS of 466 days.

Discussion

High-grade MpBC is an aggressive breast cancer with poor prognosis [1, 2]. Prior authors have concluded that MpBC is often not chemotherapy-responsive, especially with older chemotherapy regimens [10, 11]. However, rare cases of high-grade MpBC have shown a durable and rapid response to pembrolizumab with and without chemotherapy in both local and metastatic diseases [6, 7, 12]. Gorshein et al. [6] used pembrolizumab monotherapy, and Adams et al. [7] used pembrolizumab with nab-paclitaxel; both reports treated PD-L1-positive metastatic MpBC with a complete response [6, 7, 12]. Treatment was generally well tolerated,

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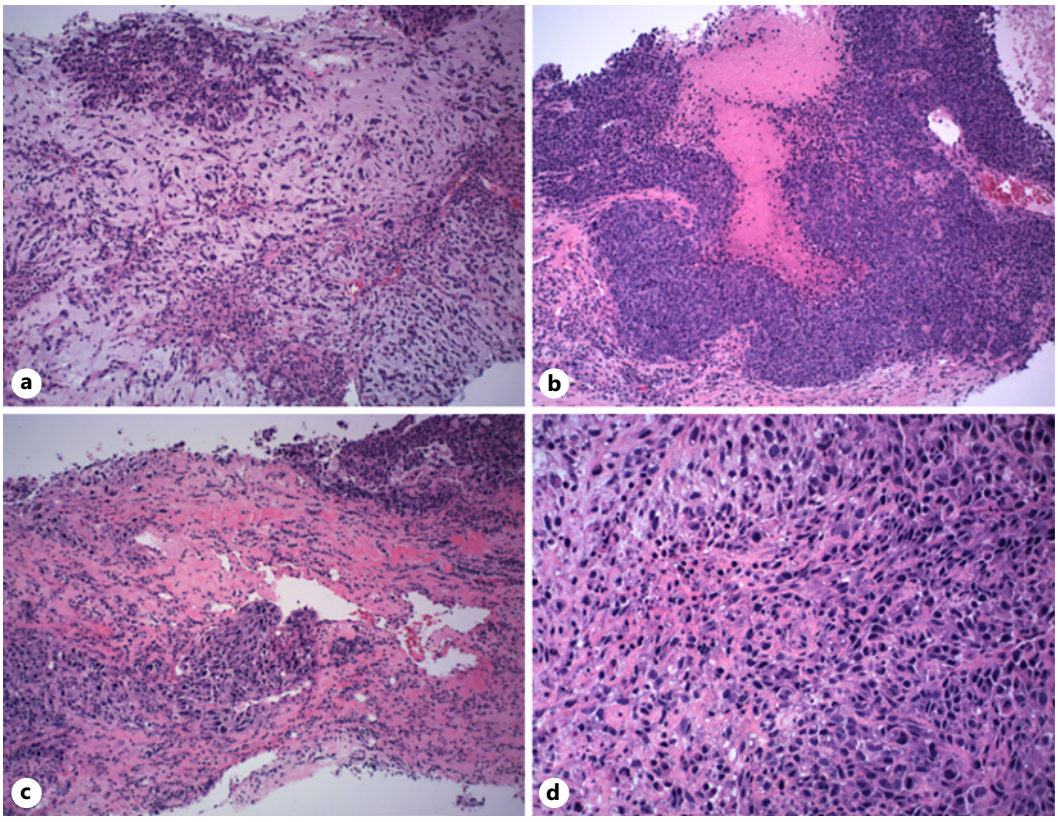

Fig. 2. a Photomicrograph showing malignant spindle cells embedded within a chondromyxoid strom (H&E, original magnification ×100). **b** Poorly differentiated carcinoma with necrosis (H&E, original magnification ×100). **c** Lymphovascular invasion (H&E, original magnification ×100). **d** Poorly differentiated carcinoma with marked cytologic atypia (H&E, original magnification ×100).

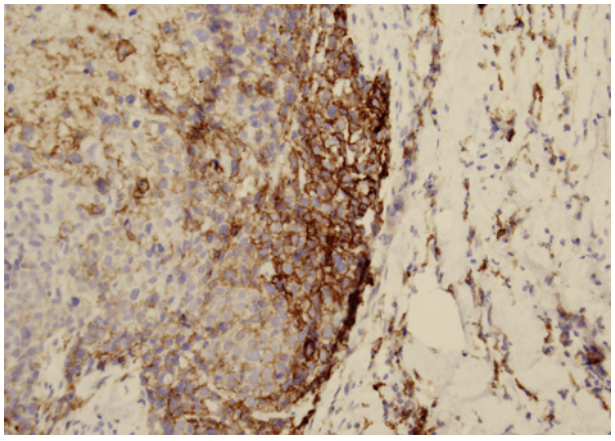

Fig. 3. Immunohistochemical testing for PD-L1 shows a Tumor Proportion Score (TPS) of 70% (×200 original image), performed using PD-L1 IHC 22C3 pharmDx on Dako Omnis.

with Gorshein et al. [6] reporting grade 2 colitis that resolved with prednisone. Examples of chemoimmunotherapy treating local MpBC are also scarce, with the only identified case of Gul et al. [12] reporting on high-grade PD-L1-positive MpBC treated with neoadjuvant pembrolizumab per Keynote-522. That patient presented at 42 years old with cT2N0M0

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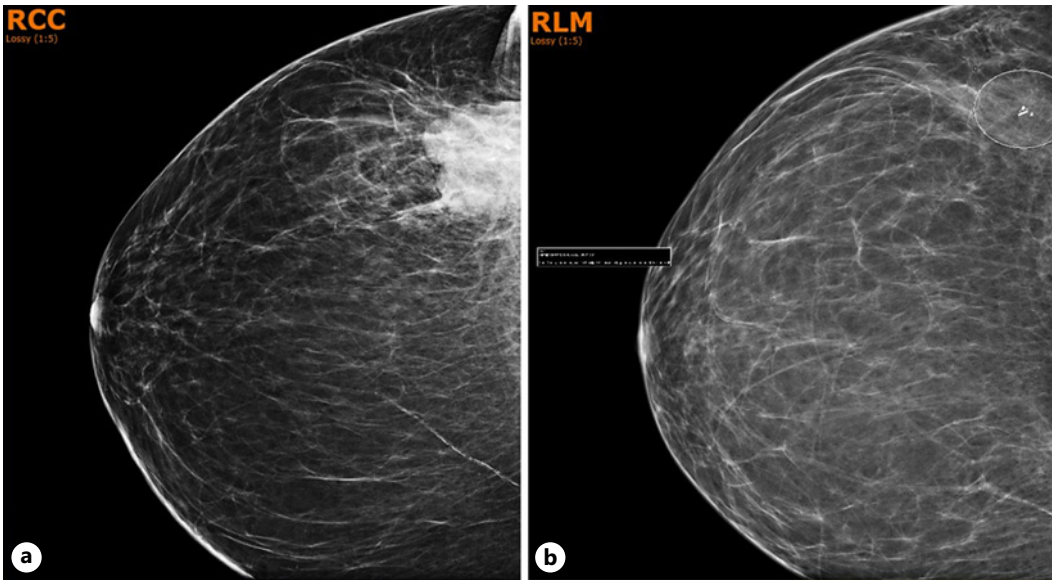

Fig. 4. Radiographic response to neoadjuvant chemotherapy. **a** Mammogram image at time of diagnosis showing an irregularly shaped mass. **b** Mammogram after conclusion of neo-adjuvant chemotherapy (clip and seed in place immediately prior to lumpectomy). Concentric shrinkage of the mass is apparent by a mammogram.

disease and achieved pathologic complete response without significant toxicity (sicca symptoms and subclinical hypothyroidism) [12]. In comparison with Gul et al. [12], the presented patient was older at onset with worse functional capacitya but also had a complete response to neoadjuvant pembrolizumab.

Pembrolizumab is an anti-PD-L1 agent, and MpBC has been found to have high rates of PD-L1 positivity [13]. However, Keynote-522 reports similar treatment success in cancers with and without PD-L1 expression, although it does not report on the statistical significance of that difference [9]. In contrast, the IMpassion130 trial found greater PFS with atezolizumab, another PD-L1 inhibitor, in patients with PD-L1-positive TNBC [14]. Therefore, the relevance of PD-L1 status in guiding treatment is unclear; in fact, PD-L1 staining for the reported patient was only completed for research purposes, following the completion of her maintenance therapy.

Immunotherapy, including pembrolizumab, is associated with a wide range of toxicities during or after treatment [8]. Many of these toxicities are hypothesized to be immune-mediated, such as hypothyroidism, hepatitis, pancreatitis, and pneumonitis [8]. Grade 3–4 adverse events only occur in 5% of patients but may be life-threatening, such as in the case of fulminant type 1 diabetes [8]. Therefore, the risk of immune-related toxicity is a major consideration when proceeding with immunotherapy. The reported patient experienced fatigue, grade 2 peripheral neuropathy, onycholysis, and hair loss during chemotherapy. No adverse events due to pembrolizumab were identified, apart from sicca symptoms. Her functional status declined slightly from ECOG of 1–2 once she began treatment, but it is not possible to isolate the cause in the context of her age and comorbidities. Given the lack of high-grade toxicity in the reported patient and the study by Gul et al. [12], pembrolizumab may be an enticing option to treat localized disease.

Triple-negative MpBC is an aggressive disease with few reports of complete response and no agreed-upon standard treatment. In the available cases of metastatic and local MpBC treated successfully with pembrolizumab, there are key differences in usage of

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chemotherapy, duration of immunotherapy, and neoadjuvant versus adjuvant treatment [6, 7, 12]. Furthermore, there is no consensus on the predictive nature of PD-L1 status in the response to checkpoint inhibitors [9, 14]. Therefore, further prospective research is indicated to control for these variables and establish pembrolizumab for high-grade MpBC.

Strength of this report is the clarity of histologic diagnosis of MpBC in this case and the robustness of response to therapy. A limitation is the absence of next-generation sequencing on tumor core samples to better understand driver mutations.

Conclusion

A case is reported of a high-grade, triple-negative PD-L1-positive MpBC patient who displayed pathological complete response to neoadjuvant pembrolizumab with standard paclitaxel, carboplatin, doxorubicin, and cyclophosphamide with no major adverse events. This case shows tolerance of immunotherapy in an elderly patient with baseline functional limitation, who otherwise may not have been considered a good candidate due to risk of toxicity. Given her outcome and prior cases of favorable clinical response to checkpoint inhibitors in MpBC, we conclude that treatment of high-grade triple-negative MpBC with a neoadjuvant regimen containing pembrolizumab is warranted in localized disease. Further research is indicated to establish therapeutic guidance for triple-negative MpBC in high grades and low stages of disease [6, 7, 12].

Statement of Ethics

This study was declared exempt by the University of Virginia Institutional Review Board. Written informed consent for publication of case: written informed consent was obtained from the patient for publication of the details of her medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.L. and O.E. created the initial drafts of the manuscript. P.D., A.S., J.S., and K.A. treated the patient, obtained imaging or pathology, and edited the manuscript. All authors were involved in the review of the manuscript and subsequent revisions. All authors approve the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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