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Case Report

Case Report on Complete Response to Treatment of Metastatic Metaplastic Breast Cancer with Sacituzumab Govitecan

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Abstract

Metaplastic breast cancer (MBC) is rare, has a worse prognosis than invasive ductal breast carcinoma, and most cases are triple-negative phenotype. Due to its low incidence, clinical studies of the disease are rare, and relatively poor outcomes are observed in clinical practice despite treatment. The present case report focuses on a patient with triple-negative MBC, clinical stage IIIB at diagnosis, and with local disease progression during standard neoadjuvant treatment. The patient was referred for surgical treatment but developed a distant recurrence of the disease shortly after. She was then treated with sacituzumab govitecan, an antibody-drug conjugate (ADC), and responded very well to treatment. Because this aggressive disease has a low response rate to chemotherapy, a better understanding of its molecular biology and therapeutic possibilities using new agents such as ADCs is crucial to advancing treatment.

Keywords: Metaplastic Breast Cancer; Antibody-Drug Conjugate; Sacituzumab Govitecan; Case Report

Introduction

Breast cancer is a global health problem and became the most common neoplasm in 2020 with approximately 2.3 million new cases and 685.000 deaths worldwide [1]. Metaplastic carcinoma is rare and accounts for 0.2% to 5% of breast cancers [2]. It is histologically defined by the presence of one or more cell populations that have undergone metaplastic differentiation and have been converted from glandular cells to a non-glandular morphology [3], commonly with epithelial and mesenchymal components [4].

Approximately 90% of metaplastic breast cancers (MBCs) present with triple-negative phenotype, which is characterized by the lack of expression of hormone receptors (HRs) and human epidermal growth factor receptor type 2 (HER2). Compared with non-metaplastic triple-negative tumors, MBCs are associated with worse prognoses, are twice as likely to recur, and have lower disease-free survival rates and worse overall survival outcomes [3].

The most common clinical presentation of this disease is a large, rapidly growing mass in the breast in women usually after the age of 50. Nodal involvement is less common than in other breast cancers, and in most cases, MBC presents a high histological grade and high expression of Ki67 [2]. Around 90% of patients present with localized disease at diagnosis, and 50% of these metastasize [5].

The characteristics related to worse 5-year overall survival are tumor size greater than 5 cm, lymph node involvement, and high Ki67 [5].

Due to the low incidence of MBCs, their inclusion in randomized clinical trials is very sparse and there is no standard treatment regimen. Therefore, treatments used end up being similar to those for invasive ductal carcinomas, however, metaplastic tumors are less responsive to chemotherapy [2]. Chen et al. evaluated the response rates of 46 cases of metaplastic tumors in patients who received neoadjuvant chemotherapy or chemotherapy as the first-line treatment for metastatic disease, with results of 18% and 8%, respectively [6]. None of the patients responded to anthracycline, cyclophosphamide, or vinorelbine, and a small cohort of patients showed a partial response to taxane.

In the metastatic setting, the median overall survival (OS) of metaplastic carcinoma is poor. As reported by Takala et al. the median OS is around 3.4 months [7].

Because this is an aggressive disease with a low response rate to chemotherapy and no known biomarkers to drive treatment so far, a better understanding of its molecular biology and new therapeutic options is crucial.

Clinical oncology has entered the era of personalized and precision medicine with the approval of new drugs that have changed the course of treatment and resulted in significant improvements in patient outcomes. These include target therapy, immunotherapy, and antibody-drug conjugates (ADCs). Among the ADCs currently approved for breast cancer is sacituzumab govitecan, which was approved for use in triple-negative and hormone receptor-positive/HER2-negative metastatic disease based on the ASCENT [8] and TROPiCS-02 [9] studies, respectively.

The present case is about a patient with metastatic metaplastic breast carcinoma who achieved a complete metabolic response while being treated with sacituzumab govitecan.

Case Report

A 60-year-old female patient, post-menopausal, noticed a rapidly growing nodule in her left breast. She underwent a biopsy of this lesion and received the diagnosis of metaplastic carcinoma grade 2 in June 2022. Immunohistochemistry indicated a triple negative tumor with a Ki67 of 90%, and systemic staging tests revealed no evidence of metastasis. In the patient´s first oncological consultation, physical examination revealed an inflammatory mass occupying the entire left breast, with clinical staging cT4dcN0M0.

Neoadjuvant protocol was initiated in accordance with the Keynote 522 study [10]. In the first phase, four cycles of doxorubicin and cyclophosphamide were administered concomitantly with the immunotherapy pembrolizumab every 21 days. At the end of this phase, there was no objective clinical response, and ulceration of the breast lesion was present (Figure 1). The second phase then began with proposed 12 weekly cycles of carboplatin/paclitaxel associated with pembrolizumab every 21 days. However, in the second cycle, clinical evaluation revealed that the patient's disease had progressed (Figure 2).

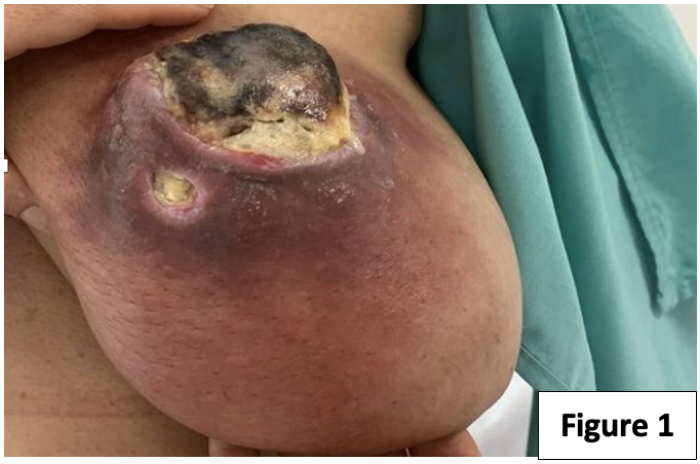

Figure 1: Breast lesion after 4 cycles of doxorrubicin, cyclophosphamide and pembrolizumab.

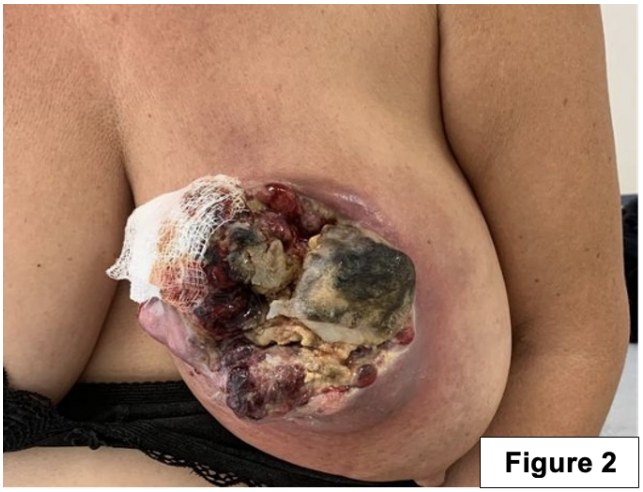

Figure 2: Breast lesion after 2 cycles of carboplatin/paclitaxel associated with pembrolizumab.

Given the worsening of the disease locally, neoadjuvant treatment was suspended, and the patient underwent mastectomy of the left breast and axillary lymphadenectomy on 09/30/2022 (Figure 3). The histopathological report on the surgical specimen found it compatible with metaplastic carcinoma, grade 3, with a marked mitotic index, tumor extension of 140 mm, moderate tumor necrosis, mild lymphocytic infiltrate (1%), and the presence of vascular invasion. Perineural invasion was not identified. Extensive, contiguous skin infiltration was also noted, but with free surgical margins. The neoplastic cellularity of the tumor bed was 80%. RCB was class II. No neoplasia was found in the 23 lymph nodes examined.

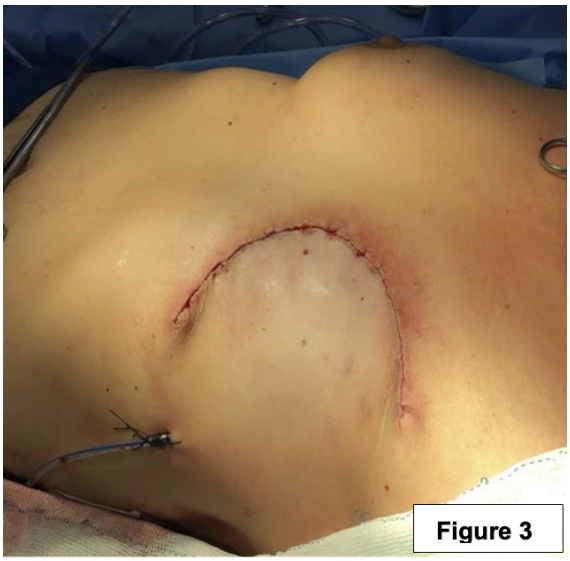

Figure 3: Mastectomy of the left breast and axillary lymphadenectomy.

Based on the Keynote-522 trial, adjuvant pembrolizumab was maintained [10]. New imaging tests were performed for oncological restaging, and evidence of pulmonary nodules was revealed by computed tomography. A PET-CT was done on 02/01/2023 and showed enlargement in the mediastinal lymph node, such as in the upper and lower paratracheal on the right, in the paraaortic, in the left pulmonary hilum, and the left axilla, in addition to pulmonary nodules (the largest one measuring 2.3 x 2cm, SUV 9.21), suspected of secondary dissemination (Figure 4). Disease progression was noted five months after the mastectomy, thus underscoring the aggressiveness of this neoplasm.

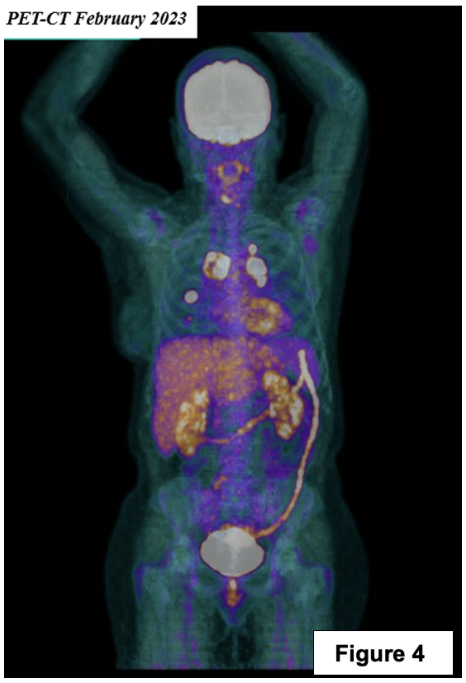

Figure 4: PET-CT showing nodal and pulmonary secondary dissemination of the disease.

In the face of documented progression after more than two lines of treatment, including refractory response to anthracycline, paclitaxel, platinum, and pembrolizumab, it was prescribed sacituzumab govitecan, administered at 10 mg/kg on day 1 and day 8 every 21 days, based on ASCENT study [8], starting on 03/27/2023.

The first response assessment was carried out on 05/25/2023, after 3 cycles of treatment, and PET-CT demonstrated a significant partial metabolic response, with involution of the left axila lymph node, in the mediastinal para-aortic and the left pulmonary hilum. Involution of glycolytic hypermetabolism and reduction in the size of pulmonary nodules in the middle lobe was also observed. However, paratracheal lymph node enlargement on the right (2R and 4R) persisted with stable dimensions (Figure 5). Treatment continued and a new PET-CT was performed on 07/21/2023 showing an additional response in paratracheal lymph nodes, compatible with a complete metabolic response (Figure 6). On 10/23/2023, the patient underwent PET-CT again for oncological restaging, with maintenance of the complete metabolic response (Figure 7).

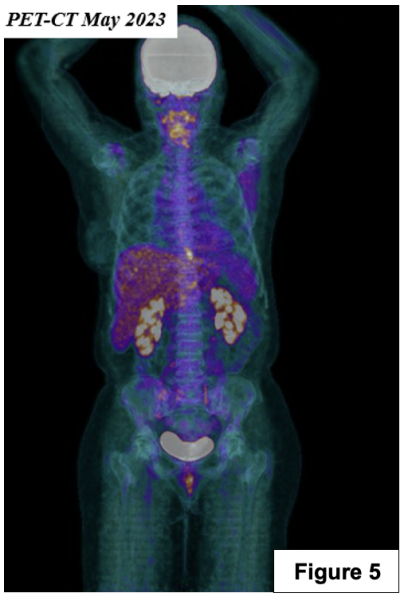

Figure 5: PET-CT demonstrated a significant partial metabolic response, with involution of the left axila lymph node, in the mediastinal para-aortic and the left pulmonary hilum.

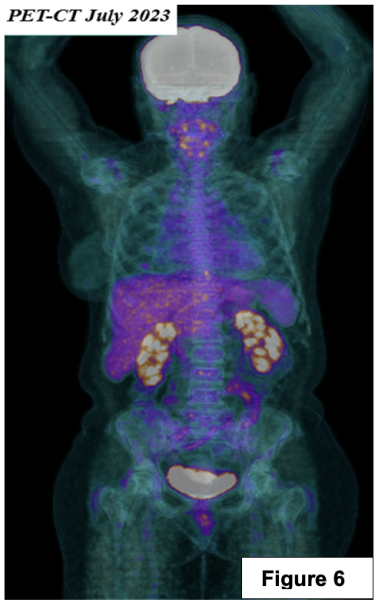

Figure 6: PET-CT with complete metabolic response.

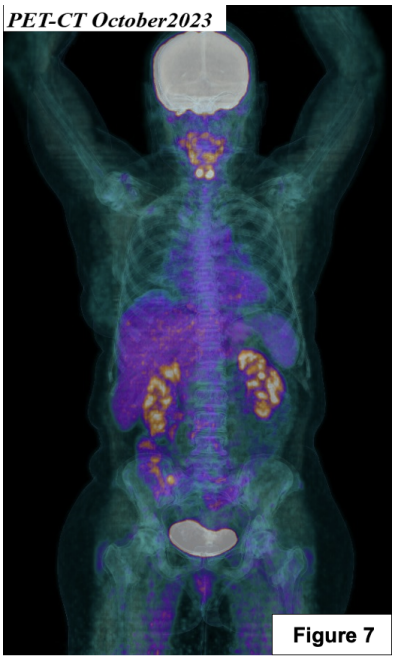

Figure 7: PET-CT with maintenance of complete metabolic response.

The patient has demonstrated good tolerance to the treatment and did not require delays or dose reductions due to adverse events. A blood count is performed before each treatment application, with no evidence of ADC-related myelotoxicity to date. The most relevant adverse event observed was grade 2 alopecia, which is described in 46% of patients in the pivotal study [8].

Discussion

This is a report of a triple-negative MBC, clinical stage IIIB at diagnosis, who experienced local disease progression during neoadjuvant treatment with combined chemotherapy and immunotherapy. Due to progression, neoadjuvant treatment was suspended, and the patient underwent oncological surgery. However, shortly after the surgical procedure and while receiving adjuvant pembrolizumab, recurrence of pulmonary and nodal disease was evidenced, and treatment with sacituzumab govitecan was then begun. Because this is a recently approved drug, to the best of our knowledge, there is only one case of metaplastic carcinoma described in the literature that has responded to it so

far [11]. Sacituzumab govitecan is an ADC composed of an anti-trop 2 monoclonal antibody coupled with SN-38, a metabolite of irinotecan, and a topoisomerase I inhibitor. The anti-trop2 antibody binds to trop-2 expressed on the surface of tumor cells and delivers a cytotoxic agent to the cell, leading to cellular apoptosis. The drug also acts through the bystander effect, which causes the death of cells close to the one directly linked to the ADC [8].

Although the ideal treatment for this disease in the early setting is still a subject of study, all available data agreed with the low response of MBC to neoadjuvant chemotherapy and with a pathological complete response (pCR) rate varying between 0% and 25% [12]. Due to the aggressiveness of the tumor and poor response to neoadjuvant treatment, oncological surgery should be considered as the first therapeutic option in localized diseases at risk for progression during treatment. In a subanalysis of the ARTEMIS study, 39 patients with triple-negative metaplastic tumors who received anthracycline-based neoadjuvant chemotherapy were included, demonstrating evidence of 23% in pCR and correlating this with OS [13]. However, it is important to analyze this pCR data along with other publications, according to which response rate with chemotherapy may be as low as 0% [6].

The molecular analysis of this disease is heterogeneous. In a series of genomic analyses with 192 patients, higher incidences of mutations in TP53 and PIK3CA were detected, at 65% and 35%, respectively [5]. Recent studies have demonstrated higher expression of PDL1 among metaplastic tumors (46%) when compared to HER2-positive (6%) and triple-negative tumors (9%) [14]. There are only a few case reports describing the response to anti-PD1 in the metastatic scenario. In a phase II clinical trial, the combination of ipilimumab and nivolumab resulted in an 18% response rate, 2-month progression-free survival, and 12-month OS in the metaplastic breast cancer cohort [15]. Such results, combined with the challenges faced in response to conventional chemotherapy, are encouraging for studies focused on this histology to better understand its molecular profile and the possibility of new therapeutic targets.

Conclusion

Metaplastic breast cancer is a chemoresistant disease with a poor prognosis. The case reported here demonstrates the response to therapy with the ADC sacituzumab govitecan in a patient who was refractory to treatment using anthracycline, taxane, platinum, and pembrolizumab. With the use of sacituzumab govitecan, it was possible to achieve a complete metabolic response, resulting in clinical improvement and maintained quality of life. The role of ADCs is thus clearly promising in treating aggressive diseases with poor rates of response to conventional therapies.

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Consent: Written consent was obtained from the patient to publish this case report.

Ethical Approval: Ethical review and approval was required for this case report in accordance with the local legislation and institutional requirements. Oncoclínicas Group Ethical Review Board approved it in November 2023 (reference number 6.543.275).

Authors contributions: All authors contributed to data collection, to writing the manuscript, and final approval of the case report.

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