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Case Report

# A Complete Pathologic Response of Triple Negative Invasive Ductal Carcinoma and Inflammatory Breast Cancer Following Neoadjuvant Chemotherapy

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**Abstract**

Neoadjuvant chemotherapy is a mainstay in therapy for Triple Negative Breast Cancer (TNBC) and is found to decrease the nodal metastasis of the disease prior to surgical excision. Triple negative breast cancer is typically aggressive with rapid growth and poor outcomes, having high recurrence rates as well as short intervals from recurrence to death. Chemotherapy is the only systemic treatment available for TNBC patients. These patients that are treated with neoadjuvant chemotherapy successfully and attain a complete pathological response demonstrate improved survival. Inflammatory Breast Cancer (IBC) is also typically very aggressive, and rare, accounting for only 1-6% of breast cancers diagnosed in the United States. Inflammatory breast cancer is a clinical diagnosis and is typically hormone receptor negative, and HER2 positive [1]. This case presentation is that of a combination of rare, aggressive breast cancers which obtained a complete pathological response to neoadjuvant chemotherapy.

## Introduction

Triple Negative Breast Cancers (TNBC) are invasive cancers that are negative for estrogen receptors (ER), progesterone receptors (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) markers. Invasive ductal carcinoma is the most common breast cancer, occurring in 50-70% of breast cancers [2]. Around 15% of all breast cancers are triple negative. Women who are estrogen and/or progesterone receptor positive are treated with tamoxifen and/or aromatase inhibitors as part of their course of treatment, whereas women who are HER2 receptor positive are treated with Herceptin (trastuzumab) [3]. This is not successful therapy for TNBC, and has not been found to be a prognostic indicator in IBC [4]. Therefore neoadjuvant chemotherapy is an effective therapy for triple negative breast cancer and is found to decrease the nodal metastasis of the disease prior to surgical excision. Triple negative breast cancer is typically aggressive, with rapid growth and poor outcomes, having high recurrence rates as well as short intervals from recurrence to death. Chemotherapy is the only systemic treatment available for TNBC patients [5] successfully and attain a complete pathological response demonstrate improved 5 year survival of 75%. And those who receive radiation therapy have a significantly improved overall survival when compared to those who did not receive adjuvant radiation therapy [6] (77.9% with RT vs. 59.8% without RT). Radiation therapy is indicated for the majority of patients who undergo breast conservation therapy and is also indicated for a sub-set of patients following mastectomy if high-risk features for loco regional recurrence exist, for example multiple positive lymph nodes, tumors >5 cm, presence of lymphovascular invasion or positive surgical margins [6].

Any woman could get TNBC, however there are known risk factors: BRCA positive patients, specifically BRCA 1 positive patients are at increased risk of being triple negative. Of note, not all BRCA positive breast cancers are triple negative. Premenopausal women also have an in- creased risk of TNBC and research is ongoing in this field to determine the association there [3]. Inflammatory breast cancer, unlike TNBC, is more frequently HER2 positive, along with ER/PR negative. It is also a rare and aggressive cancer, accounting for only 1-6% of the breast cancers diagnosed in the United States [1]. Historically, IBC is a lethal disease with less than a 5% survival rate beyond 5 years when treated with surgery or radiation therapy. Because of its rarity, IBC is often misdiagnosed as mastitis or generalized dermatitis [7] (Figures 1 and 2).

## Case Presentation

This patient is a postmenopausal, 56 year old female who presented to her primary care physician after falling off a ladder, complaining of a bruise on her breast and a “lump” under her

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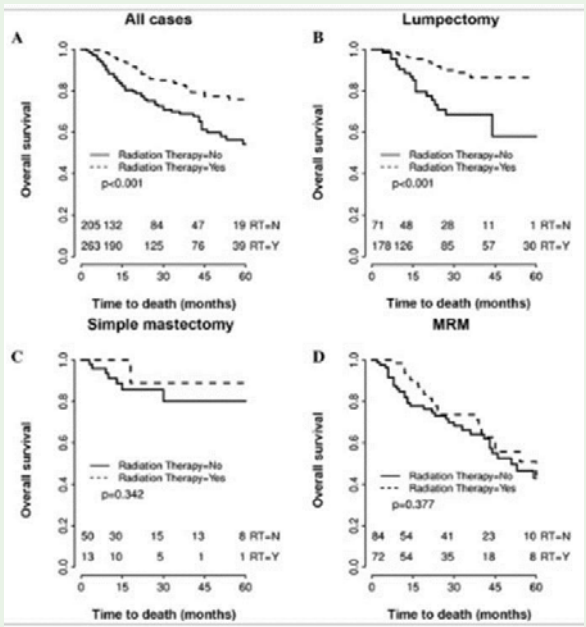


**Figure 1:** Survival curves for 468 patients with TNBC according to the receipt of adjuvant radiation therapy versus no radiation therapy (RT). (A): Entire collection of 468 patients. (B): Patients who received Lumpectomy (n=249). (C): Patients who underwent simple mastectomy (n=63). (D): Patients who received MRM (n=156) [17].

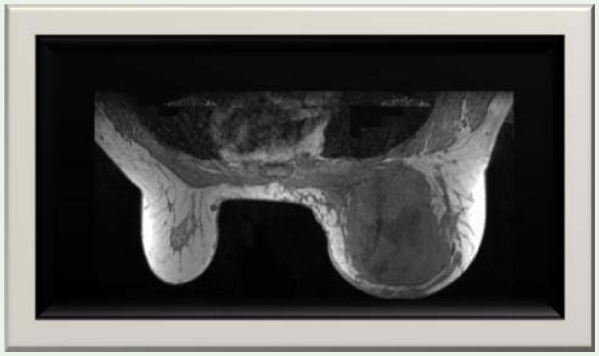

**Figure 2:** MRI prior to any neoadjuvant chemotherapy.

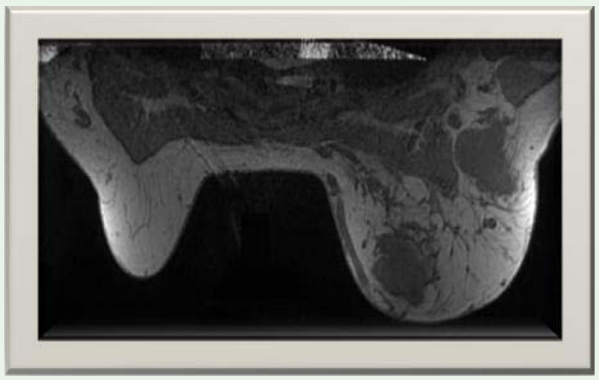

**Figure 3:** Pre-treatment MRI imaging of axilla revealing clinically positive lymph nodes.

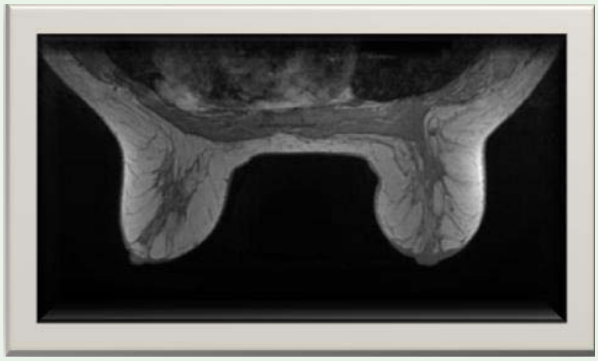

**Figure 4:** MRI identifying marked improvement neoadjuvant chemotherapy, prior to surgical following chemotherapy.

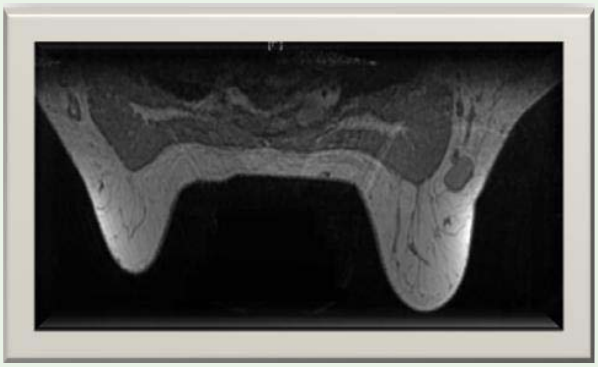

**Figure 5:** MRI of approximately the same level as Figure 3, revealing dramatic effects of neoadjuvant intervention.

right arm. She was treated with antibiotics without improvement in breast swelling, and was referred for mammography. Mammogram revealed a breast imaging- reporting data system, BIRADS, score of 0, indicating incomplete examination and the necessity for further imaging studies. Ultrasound then identified a BIRADS-4 lesion, a lesion that is highly suspicious for malignancy and biopsy is recommended. Ultrasound guided fine needle aspirate of the concerning lesions on the right breast and axilla revealed poorly differentiated, invasive ductal carcinoma which was ER-negative, PR-negative, and HER2neu-negative. Magnetic Resonance Imaging reveals the 8cm right breast mass with invasion into the chest wall (Figure 2), as well as a multiple abnormal lymph nodes (Figure 3). The patient's PET-scan was negative for distant metastasis.

This patient presented with T4 disease, in that her primary tumor did involve the level of the skin with a blue-like discoloration, which is an indicator of possible inflammatory breast cancer component, in addition to her tumor marker status. N3 disease, in that she had positive nodes at biopsy >2mm with nodes below the level of the clavicle, and M0 disease, as she had no signs of metastasis on pet-scan. Her clinical stage, based on the presenting data prior to surgery is Stage IIIC (T4N3M0). Neoadjuvant chemotherapy began one week after diagnosis, with Adriamycin, Cytoxan, and Taxol, as recommended from National Comprehensive Cancer Network guidelines [1]. After 6 cycles of neoadjuvant chemotherapy, she underwent surgical resection via modified radical mastectomy, as

is recommended when faced with inflammatory breast cancer. Pre-operatively, repeat MRI indicated visibly substantial response from her chemotherapy treatments (Figures 4 and 5).

Postoperatively, pathologic evaluation of the specimen identified complete pathologic resolution of disease in both the auxiliary lymph node specimen of the modified radical mastectomy as well as the entirely submitted breast specimen. Seventeen total nodes were identified, with one being totally necrotic, all with no signs of metastasis. The patient proceeded with post-surgical radiotherapy, as is indicated by her surgical staging. Post-mastectomy radiation therapy (PMRT) is indicated for loco regional treatment of clinical stage I, IIA, or IIB disease or T3, N1, M0 if auxiliary nodes are positive (1-3, strongly consider PMRT; ≥4 positive nodes: PMRT to chest wall as well as infraclavicular and supraclavicular nodes). Even if the auxiliary nodes are negative, the recommendation for the aforementioned stages is to consider PMRT if the tumor is >5cm.

In follow-up, this patient recently underwent mammography of her left breast which was BI- RADS-3, a high likelihood of being benign, with the chances of malignancy of ~0.3-2% [8].

Short-term follow-up was recommended, and she proceeded to sonographic examination. Ultra- sound of bilateral breasts reveals BIRADS 1, negative for malignant disease. It was recommended she follow up in one year for repeat imaging studies. It is anticipated based that she will continue to do well. Five years after diagnosis, TNBC patients are no more likely to experience a recurrence than women with other types of breast cancer. Recurrence is also less likely in women with TNBC in the longer term, over a 10 year period [3]. Inflammatory breast cancer, however, has a much shorter recurrence free survival of approximately 2.3 years according to one retrospective study at MD Anderson Cancer Center, which also revealed 4.2 year median overall survival in their patients with IBC [9].

## Discussion

A Kansas City Medical Center study indicated that neoadjuvant chemotherapy reduces the extent of auxiliary surgery necessary; even in clinically node negative TNBC, due to the significant response of nodal disease [10]. This patient required modified-radical mastectomy regardless, as she had clinical findings supporting IBC. Even though clinically positive nodal disease, she still exhibited a complete pathological response to her neoadjuvant chemotherapy. The Food and Drug Administration funded a study which reports patients with TNBC who attain complete pathological response defined at ypT0, ypN0 or ypT0/is, ypN0 have improved survival. The prognostic value is greatest in those with aggressive tumor subtypes [11], as seen in this patient with clinically node positive disease. There are continued studies and development of improved neoadjuvant chemotherapy regimens ongoing [12]. Current studies are underway investigating the new medication Veliparib, as well as the addition of Bevacizumab to current Regimens [13,14]. Veliparib is a potent, orally bioavailable polymerase inhibitor that enhances the efficacy of platinum drugs, which are a commonly used chemotherapy regimen for breast cancers [15]. Bevacizumab is targeted therapy which works by inhibiting angiogenesis through binding and inhibiting vascular endothelial growth factor (VEGF) [16]. With improved regimens of chemotherapy, there could also be increased options for patients in surgical resection, allowing for the possibility of Breast Conservation Therapy (BCT) with radiation in women who prior to neoadjuvant chemotherapy did not have that option, which could lead to decreased morbidity associated with auxiliary lymph node dissections. However, a retrospective study of 14,000 patients out of Italy revealed that complete pathological response is not an adequate endpoint for disease free survival and overall survival in patients with breast cancer [17].

## Conclusion

Given that TNBC and IBC are so aggressive, it is important that continued studies be per- formed for further development in chemotherapy medication regimens, as it is a multidisciplinary approach. TNBC has increased rates of complete pathological responses, as does HER2- positive subtypes with neoadjuvant chemotherapy. Surgery, however, is not the primary treatment for IBC, as it has been associated with poor outcomes, and the use of BCT has been associated with poor cosmesis and a small sampling of data indicate it rates of local recurrence may be higher with BCT when compared to mastectomy [1]. Those patients who do not have a good response to neoadjuvant chemotherapy are recommended to go further chemotherapy or even radiation prior to surgery in the treatment of IBC. A recent study from Cedars-Sinai is now showing that BCT is possible with TNBC, as it is not associated with increased local recurrence of disease [18-20]; however this is not yet possible for IBC. With IBC, longer disease-free survival is seen with combination preoperative chemotherapy and mastectomy, than with preoperative chemotherapy alone, as well as decreased local recurrence [1].

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