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Case Report

Abscopal Effect Following Cryoablation in a Patient with Metastatic Breast Cancer

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Abstract

While breast cancer is a common disease with many available treatment options, many patients still have limited responses, especially those with metastatic breast cancer. Surgery of the primary tumor or metastatic sites is often not part of the treatment regimen for patients with metastatic breast cancer. Cryoablation is a relatively non-invasive procedure that is being investigated for patients with breast cancer. Patients with metastatic breast cancer who are not surgical candidates may derive benefit from cryoablation through the abscopal effect. In this case report, we present a patient with stage IV breast cancer who was treated with cryoablation of the primary breast tumor and showed evidence of an abscopal effect in regional and distant metastases.

Keywords: metastatic breast cancer; cryoablation; abscopal effect

1. Introduction

Breast cancer is one of the most common cancers among women in the United States, and it is identified at increased rates due to earlier detection methods [1]. Contemporary treatment modalities are numerous and include surgery, radiation, and systemic therapy, and are often used in a multidisciplinary approach. As a recent example, PARP inhibitors such as olaparib and talazoparib, have been approved for the subset of BRCA carriers with metastatic HER2-negative breast cancer [2]. Approximately 5–10% of breast cancer patients are diagnosed with metastatic breast cancer, and unfortunately have grimmer prognoses compared to those diagnosed with earlier stages of breast cancer [3]. The survival rate of metastatic breast cancer patients is 20% over a 5-year period, and these patients also have less treatment options compared to patients with early disease [4]. Surgical removal of the primary tumor in metastatic breast cancer patients often does not improve patient outcomes and so is not routinely part of the treatment regimen unless it is performed for palliation of symptoms. In contrast, systemic therapies have traditionally been used for metastatic disease [5].

Currently, studies are being performed to investigate percutaneous treatment options that directly target the primary tumor mass. Radiofrequency, cryo-, laser-, and microwave ablation techniques represent minimally invasive procedures to treat primary breast tumors for patients who are not traditional surgical candidates (lumpectomy or mastectomy). For patients with symptomatic tumors, ablative techniques may offer palliative benefits, such as reduction in patient discomfort. In a systematic review of 45 studies, it was found that 96% of imaging-guided ablation techniques on patients were technically successful, with radiofrequency and cryoablation completely ablating the lesion at the highest rate [6]. Cryoablation historically has been used for patients with benign masses (e.g., fibroadenomas) as well as invasive tumors of small size and in early stages. The ICE3 trial investigated the effectiveness and safety of cryoablation for low-risk, hormone positive, early-stage breast cancers as an alternative treatment modality to an operative approach [7]. There is an increasing body of work that support the use of cryoablation as an effective treatment option (Table 1). In addition, there is increasing potential for cryoablation in patients with metastatic breast cancer. Freezing cancer cells damages organelles while dehydrating and freezing the tumor, leading to localized necrosis [8]. This may subsequently result in the generation of an abscopal effect, whereby newly released tumor antigens are recognized by the immune system and confer responses to distant, untreated sites of metastatic disease. In this case report, we present a case of a patient diagnosed with stage IV breast cancer subsequently treated with cryoablation, who showed evidence of the abscopal effect.

2. Case Presentation

Our patient was an otherwise healthy, 52-year-old female with the diagnosis of stage IV triple positive invasive ductal carcinoma of the breast. She had biopsy-confirmed metastases to the axillary nodes and liver. The location of the primary tumor involved the lower outer quadrant of the left breast, and it was palpable as well as symptomatic with persistent pain and discomfort at the tumor site. She was deemed to not be a surgical candidate due to distant metastases and subsequently underwent

Table 1. Clinical trials, meta-analyses/reviews, and case reports supporting the use of cryoablation for breast cancer.

Study	Outcomes	Safety
Clinical Trial: ACOSOG Z1072 (2016)	Stage I tumors Complete ablation rate 75.9%	Grade 3/4 adverse events 0%
Clinical Trial: Memorial Sloan Kettering (2016)	Stage I tumors Feasibility 100%	Grade 3/4 adverse events 5.3%
Clinical Trial: Italy (2017)	Stage IV tumors Complete ablation rate 85.7% No abscopal effect reported	Grade 3/4 adverse events 0%
Clinical Trial: ICE3 interim analysis (2021)	Stage 1 tumors Local recurrence (3 years) 2.1%	Grade 3/4 adverse events 0%
Case Report: Memorial Sloan Kettering (2019)	Stage IV tumor Positive abscopal effect reported	No toxicity
Case Report: Naples FL (2019)	Stage IV tumor Positive abscopal effect reported	No toxicity
Systematic Review (2015)	Stage I/II tumors Complete ablation rate 73%	Grade 3/4 adverse events 0%
Meta-analysis (2017)	Stage I/II tumors Complete ablation rat 75%	Grade 3/4 adverse events 6.0%

multiple treatments of chemotherapy, as well as many biological and targeted hormonal therapies. Next generation sequencing was performed, but no targetable mutations were identified. Her treatment history is summarized in Fig. 1. From 2016 to 2018, she received Paclitaxel, Trastuzumab, and Pertuzumab, as well as hormonal therapy. Due to progressive disease in the liver in 2018, she was switched to Trastuzumab emtansine (TDM1), however this was stopped secondary to elevated liver function tests and she was changed to Fulvestrant and Lupron. Due to other side effects, in 2019, she was switched to Capecitabine in combination with endocrine therapy. Our patient was then switched to TDM1 in 2020 due to progressive disease. She was referred to our Surgical Oncology clinic in February of 2020 for consideration of cryoablation of her primary breast tumor. She was informed that cryoablation was not currently part of standard of care, but potentially could offer benefit in terms of the abscopal effect and was considered low risk, with the most common adverse effects being pain, localized edema, minor skin freeze burn, rash, and pruritis [7].

In May of 2020, she underwent breast cryoablation. The site of tumor was marked preoperatively, and its size was confirmed by ultrasound. It measured 2 cm × 1.5 cm × 1.5 cm at the 4–5 o'clock position of the left breast. We inserted a cryoablation probe (Sanarus Technologies) through the breast parenchyma into the tumor through a small (3–5 millimeter) incision. Ultrasound confirmed proper placement of the probe tip into the tumor in real time. Once appropriately positioned, cryoablation consisted of an 8-minute freeze cycle, a 10-minute thawing cycle, a second 8-minute freezing cycle, and a 1.5-minute warming cycle. Liquid nitrogen was circulated within the probe to achieve

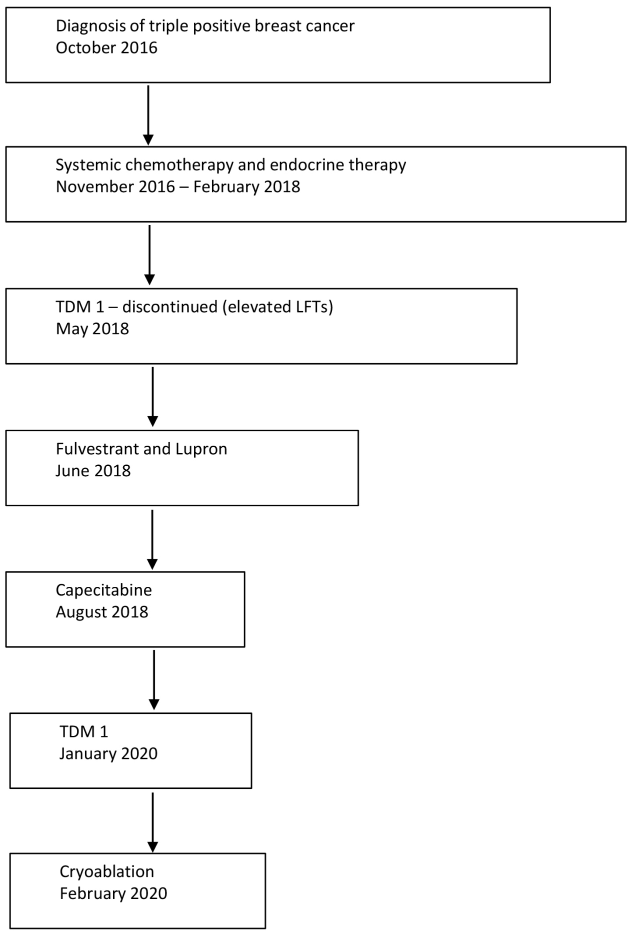

Fig. 1. Summary of patient's treatment for metastatic triple positive breast cancer.

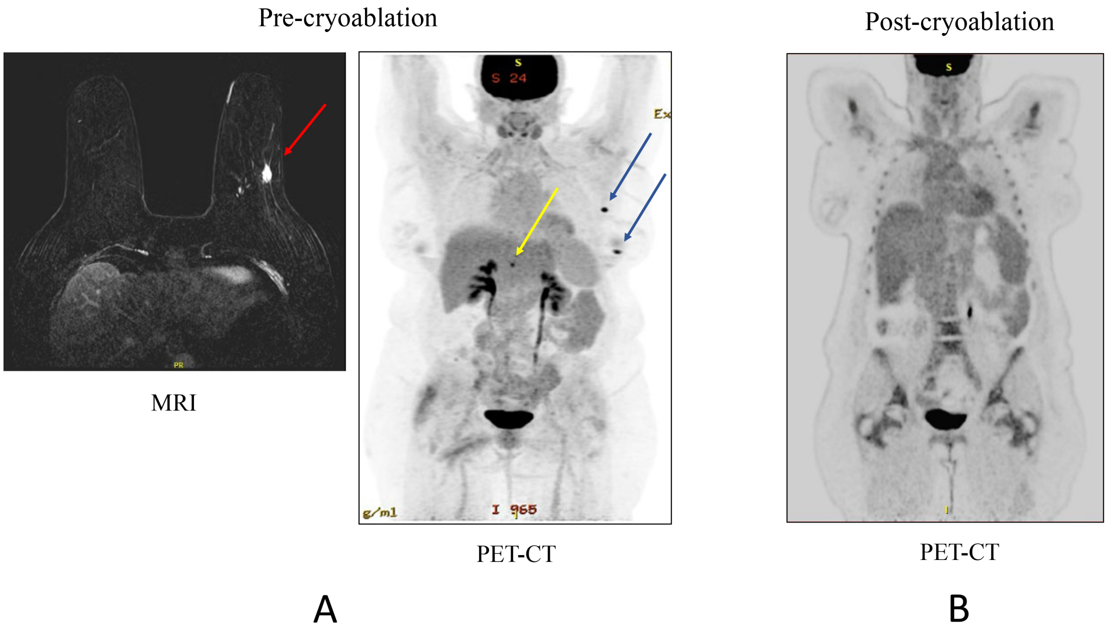

Fig. 2. Abscopal effect: MRI pre-cryoablation, PET-CT pre- (A) and post-cryoablation (B). Left panel: Precryoablation. The patient had an intact primary of the left breast (red arrow shown on MRI) as well as metastatic disease to her left axillary lymph nodes (blue arrows on PET-CT) and liver (yellow arrow on PET-CT). Right panel: Post-cryoablation. Approximately 6 months after the left breast cryoablation, there was no PET-avid signal within the breast at the site of the primary tumor, the regional lymph nodes or distant liver site of metastases. This was consistent with the abscopal effect.

freezing temperatures. The liquid nitrogen did not come into direct contact with the patient's tissues. However, the probe created a spherical ball of ice which froze and destroyed the surrounding tumor. The size of the ice ball was controlled with the duration of the freezing, and this was directly observed as the ice formed in real time under ultrasound to confirm that the tumor was ablated. Additionally, to protect the overlying skin, we had injected sterile saline into the dermis to buffer the freezing. Post-cryoablation ultrasound was obtained to confirm that the correct area was treated.

The patient was seen for follow-up in clinic three weeks later. On examination, her incision was well healed, and her breast did not show any signs of poor cosmetic effect or infection. She underwent surveillance PET-CT in July of 2020 and in November of 2020. On imaging in July, there was decreased metabolic activity within the left breast lesion, however there was demonstration of interval increase metabolic activity in some of the left axillary lymph nodes, anterior left chest wall, and right liver lobe. Interestingly, on imaging in November, there was complete resolution of hypermetabolic foci in the left breast, as well as in the sites of liver metastases and the left axillary hypermetabolic lymphadenopathy (Fig. 2). This was consistent with a complete radiographic response.

Since November of 2020, our patient was treated with Tucatinib, Trastuzumab, and Capecitabine. She underwent surveillance PET-CT in June of 2021 demonstrating isolated left axillary lymphadenopathy. This was biopsied and unfortunately proven to be recurrent metastatic breast cancer (ER/PR positive, HER2 positive), and axillary radiation therapy was initiated. In October of 2021, she underwent surveillance PET-CT and abdominal MRI which demonstrated evidence of progressive disease in multiple areas including lymphadenopathies, liver metastases, and peritoneal carcinomatosis. She was started on Fam-Trastuzumab Deruxtecan and has continued this therapy currently with stable disease.

3. Discussion

Despite advances in the treatment for patients with metastatic breast cancer, more effective options are needed. Surgery of the primary tumor or metastatic sites is often not part of the treatment regimen for patients with metastatic breast cancer unless it is performed for palliative purposes [5]. Surgical complications can arise and lead to other treatment modalities (i.e., chemotherapy) being delayed. Prospective studies report varying results on the outcomes of patients who underwent resection of their primary tumor. In a study including stage IV breast cancer, patients who received locoregional surgical treatment had longer rates of survival and lower rates of locoregional progression/relapse than patients who had non-surgical systematic treatment [9]. However, resecting the primary tumor may result in the release of cancerous cells into the body and cause further metastases, and thus, cause formation of new tumors [10]. Additionally, further investigation is required to determine the optimal treatment plan for patients who refuse surgical resection or those who are deemed not surgical candidates for a multitude of reasons. Many new technologies may hold promise for new therapies, such as proteomics, which may assess the efficacy of cancer therapies at cellular level [11].

Cryoablation is a minimally invasive operation requiring local anesthesia and has low rates of surgical complications and patient discomfort [12]. There are limited clinical trials, meta-analyses/reviews, and case reports supporting the use of cryoablation for breast cancer (Table 1). Most recently, the ICE3 clinical trial reported that 103 of 104 patients with early-stage breast cancer have shown no recurrence over a three-year period [7,13]. Single or multiple probes can be used to percutaneously target the tumor using real time ultrasound imaging [13]. The cryoablation process involves freezing the tissue to temperatures below –40 °C, allowing the tissue to thaw, and then freezing the tissue a second time. The first freezing cycle causes cell dehydration due to extracellular water becoming frozen. The passive thaw phase, considered the most important aspect, allows osmosis to occur and fills the cell with water. Intracellular ice crystals form during the second phase, and the necrosis area is expanded further [13]. Ice balls are formed during the procedure, which spreads beyond the diameter of the tumor to fully encompass the cancerous tissue as much as possible. Ultrasound imaging is used to track the formation of the ice ball. Tumor cells are also damaged by ischemia, platelet aggregation, microthrombus formation, and endothelial cell dysfunction [11]. The operation conserves the breast, which is an important cosmetic consideration for many patients. However, fat necrosis and infection can occur from the ice balls created by the probe [11]. Furthermore, other consequences of the procedure such as breast pain, swelling, skin burns, and ecchymosis are adverse events that the patient may experience [14].

In addition to the local effects, cryoablation generates immunological responses that have the ability to target metastatic tissue away from the primary location. Cancer cells use CTLA-4 and PD-1 receptors to prevent recognition by the immune system and inhibit effector T-cells [15]. Residual antigenic tissue from cryoablation causes coagulative necrosis, which results in the release of nuclear proteins, cytokines, and antigens from tumor cells [16]. The immune system can potentially recognize these foreign antigens and form anti-tumor antibodies and direct T-cells to induce a cytokine response against malignant cells. For example, mismatch repair (MMR) deficiency has been shown to be a mechanism that results in the generation of tumor neoantigens as recognizable targets for immunotherapy [16,17]. Immunotherapy can be used in conjunction with cryoablation to enhance a targeted systemic immune response [18]. Similar to our case study, anti-tumor effects have been observed when cryoablation was combined with ipilimumab, resulting in reduction of metastases [19]. However, long-term effects of cryoablation with immunotherapy and other systemic treatments are unknown and require further in-depth investigation with larger numbers of patients.

Nonetheless, cryoablation is beginning to be tested more frequently in patients with metastatic breast cancer because the procedure is minimally invasive and there are promising signs of the immune system targeting tumor cells throughout the body. In a study of 17 patients with stable metastatic cancer who received cryoablation and systemic treatment, 2 patients had a recurrence within 12 months of the procedure, and none had any major complications [20]. In another study, 17 out of 20 patients with invasive ductal carcinoma benefited from cryoablation [21]. In cases where the tumor does not undergo complete necrosis, repeat cryoablation can be performed to target residual lesions [11].

In our case, cryoablation was used in conjunction with chemotherapy and immunotherapy modalities with improvement demonstrated on 6-month post-cryoablation PET-CT imaging, which supports the notion of the abscopal effect. This refers to the response of metastatic sites of cancer that were not the direct targets of local therapy [18]. With our patient, there was total resolution of multiple hypermetabolic foci in the left breast with minimal residual activity. Additionally, imaging demonstrated resolution of FDG uptake in both the liver and left axillary sites of disease, consistent with a positive radiographic treatment response (Fig. 2). It is uncertain whether this positive treatment response was solely due to cryoablation or if it could have been attributed to the multimodal treatment the patient received, which included both cryoablation and systemic agents, including the most recent TDM1. The interval increases in hypermetabolic activity seen on the initial 3–4-month post-cryoablation may have represented an inflammatory response as part of the abscopal effect. This may be valid as the subsequent 6–7-month post-cryoablation surveillance imaging showed a complete radiographic response. It should be noted that in our case, unfortunately, the patient did relapse at the metastatic sites after about 1 year. Thus, the abscopal effect may be limited. This may be due to other clonal variants within the sites of metastatic disease that escape immune surveillance or develop resistance to the other systemic treatments that our patient was receiving. Although response durability was limited, cryoablation may hold a promising alternative for patients with metastatic breast cancer and will require further investigation to determine its long-term effectiveness as a treatment option in patients with metastatic breast cancer and limited response to currently therapies.

4. Conclusions

In conclusion, while breast cancer is a common disease with many available treatment options, many patients still have limited responses, especially those with metastatic breast cancer. Cryoablation is a relatively non-invasive procedure that is being investigated for the effectiveness in this specific patient population. Patients with metastatic disease who are not surgical candidates that are candidates for cryoablation, such as the patient described in this report, may derive benefit through the generation of an abscopal effect.

Author Contributions

JLK completed the literature review, initial drafting, and editing of the case report. IT contributed to the literature review and writing of case report. EG provided the case information, editing, and final review of case report. SC supervised the case report, provided edits, and approved the final review.

Ethics Approval and Consent to Participate

Ethics approval was not required for this case report. The patient provided signed written consent allowing discussion of her case.

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Conflict of Interest

The authors declare no conflict of interest.

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