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Case Report

Partial breast irradiation in a patient with bilateral breast cancers and CREST syndrome

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ABSTRACT

PURPOSE: To describe the first documented use of partial breast irradiation (PBI) in a patient with calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias (CREST) syndrome.

METHODS AND MATERIALS: A 50-year-old woman with well-controlled CREST syndrome for 6 years was diagnosed with bilateral early-staged breast cancers. She underwent bilateral lumpectomies, sentinel lymph node biopsies, and PBI delivered via bilateral MammoSite catheters (Cytyc Corp., Marlborough, MA) followed by chemotherapy. She was monitored perioperatively, at 6 months and at 1 year for worsening of her CREST-related symptoms and complications associated with surgery and radiation therapy. Both surgeon and patient's opinion of her cosmetic outcome were also recorded at 1-year followup.

RESULTS: The patient experienced mild acute cellulitic changes in the perioperative period, which resolved with antibiotics. At 6 months, she exhibited a Grade 1 late toxicity, which has remained stable at 1-year followup. The patient and surgeon are very pleased with her cosmetic outcome.

CONCLUSIONS: Accelerated PBI was delivered safely to a patient with collagen vascular disease. By decreasing the surface area receiving radiation with accelerated PBI, we believe that the toxicity associated with the treatment was minimized. Future studies will be necessary to clarify the use of PBI in patients with collagen vascular disease.

Keywords: Accelerated breast irradiation; MammoSite catheter; Breast cancer; CREST syndrome

Introduction

For patients with breast cancer and collagen vascular disease (CVD), radiation therapy (RT) after breast conservation surgery is very controversial. Given the increased incidence of fibrosis, poor wound healing, and compromised cosmesis, many physicians consider RT to be contraindicated in patients with CVD (1–3). This leaves mastectomy as the only surgical option.

Several studies have shown that adjuvant accelerated partial breast irradiation (APBI) using the MammoSite (Cytyc Corp., Marlborough, MA) balloon catheter for early-staged breast cancer yields equivalent treatment efficacy, cosmesis, and toxicity to other forms of APBI and to whole breast radiation (4, 5). The use of APBI in patients with CVD has not yet been evaluated in the literature. We describe a patient with CREST syndrome and bilateral breast cancer. CREST syndrome is a collagen vascular disease in which the patient exhibits at least 2 of the following symptoms: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias. She was treated with breast conserving surgery and adjuvant APBI administered via bilateral MammoSite catheters.

Case report

A 50-year-old perimenopausal woman presented with a palpable left breast mass. Her medical history was

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significant for CREST syndrome and hypothyroidism. On physical examination, she had a 2-cm left breast mass at the 12 o'clock position, which correlated with suspicious findings on her mammogram and ultrasound. An ultrasound-guided breast biopsy revealed infiltrating ductal carcinoma, estrogen receptor/progesterone receptor positive, and Her2/neu oncogene negative. No other site of disease was found based on the above studies. Subsequent MRI detected two additional lesions in her right breast. Image-guided core needle biopsy of both right breast lesions demonstrated invasive ductal cancer (estrogen receptor/progesterone receptor positive and Her2/neu negative) in one lesion and benign findings in the other. As demonstrated on MRI in Fig. 1, the right breast cancer located in the 2:00 position measured 1.4 cm.

Our patient was diagnosed with CREST syndrome 6 years ago. She intermittently developed skin telangiectasias and Raynaud syndrome. She denied any additional signs or symptoms of the syndrome such as esophageal dysfunction, scleroderma, or calcinosis. She exhibited chronically elevated anticentromere antibodies. Although followed by a rheumatologist, she never required medical treatment and was otherwise very active and in good health.

Because of her history of CVD, we explained the controversy surrounding whole breast irradiation. Despite the limited nature of her autoimmune disease, her rheumatologist and radiation oncologist felt that she was at an increased risk of both acute and late toxicities. The patient strongly desired breast conserving treatment. We offered her the option of APBI, with the goal to minimize both the surface area receiving radiation and the volume of radiation delivered. We performed bilateral lumpectomies, sentinel lymph node biopsies, and placement of bilateral MammoSite catheters. She had an uneventful operative course.

Before initiation of radiation, final pathology was reviewed. Pathology of the left breast tumor revealed a 2-cm moderately differentiated invasive ductal cancer with three sentinel lymph nodes negative for metastatic disease. There was a minor component of ductal carcinoma *in situ*, no evidence of lymphovascular invasion, and the margins were negative for both invasive and *in situ* disease. The closest margin on the left breast was a 2-mm lateral margin. The right breast cancer was a 2.4-cm moderately differentiated invasive ductal carcinoma with one sentinel node negative for metastatic disease. There was no evidence of lymphovascular invasion in the tumor, and ductal carcinoma *in situ* comprises 10% of the tumor mass. The closest margin on the right breast was an 8-mm medial margin.

CT simulation revealed correct placement of the catheters with adequate spacing of the overlying skin. Minimum separation between balloon surface and overlying skin was 1.3 cm for the right breast and 1.0 cm for the left breast. Her treatment was initiated approximately 1 week postoperatively. She received bilateral breast MammoSite treatment for doses of 3400 cGy in 10 fractions over 1 week. The radiation was delivered twice a day with an interval of 6–7 h between the daily fractions. The maximum skin dose was 131% for the right breast and 107% for the left breast, based on a skin contour that placed the skin surface to a depth of 3 mm. The catheters were removed at the completion of the radiation without any difficulty (Fig. 2).

One week postoperatively, the patient exhibited mild acute radiation changes that presented as erythema on the superior aspect of both incisions. Cellulitis could not be ruled out, so she was treated with an oral course of antibiotics and the erythema resolved completely. Approximately 6 weeks after surgery, she was started on taxotere and cytoxan without adriamycin to avoid the risk of potential "radiation recall." Six months after the completion of her

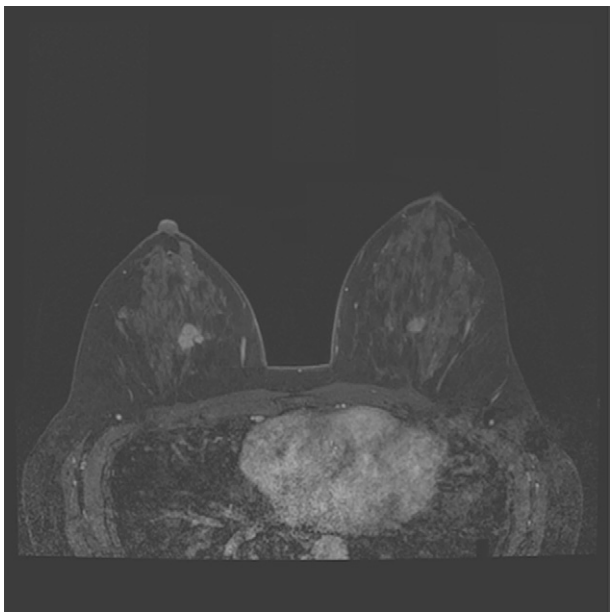

Fig. 1. MRI showing bilateral breast cancers.

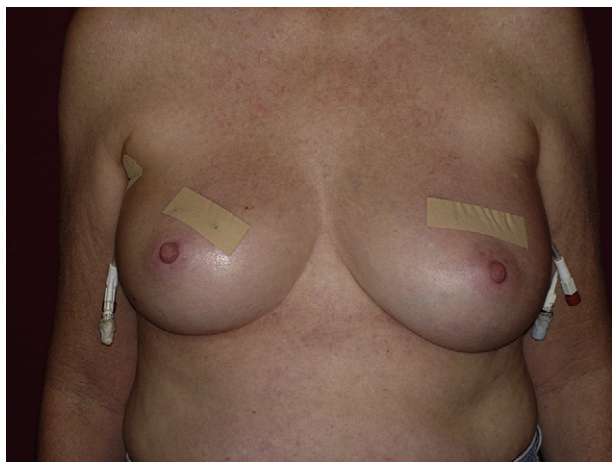

Fig. 2. Clinical appearance during radiation treatment.

surgery and radiation treatment, she complained of increased "hardness" in the area of the MammoSite cavities (Fig. 3). Her examination revealed induration along the left breast incision; her right breast showed a well-healed mature scar. She was closely monitored and after 2 weeks, the induration in the left breast was stable, but she developed erythematous changes with mild skin desquamation along the incision. Her right breast remained well healed. Ultrasound examination demonstrated seromas in both breasts without any evidence of underlying abscess. We treated the cellulitic changes with antibiotics and did not drain the seromas. The redness on her left breast resolved within 1 week. At her 1-year followup, she had some mild induration and telangiectasias along the incisions on both breasts; no evidence of any wound breakdown and otherwise has well-healed mature scars. She is very happy with her cosmetic outcome. Since the time of surgery and the initiation of her treatment, she denies any worsening of symptoms related to her CREST syndrome.

Discussion

CREST syndrome, a subset of systemic scleroderma, is an incurable, chronic, multisystem, and autoimmune disease. It has an annual incidence of 1–2 per 100,000 people in the United States with a peak onset occurring between the ages of 30s and 50s (6). More than half of the patients affected by the disease are women.

CREST syndrome is often referred to as "limited scleroderma." The diagnosis is made if the patient has at least two of the five following clinical features: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias. Determination of an antibody profile can be very helpful in confirming the diagnosis: elevation of serum anticentromere antibodies has a sensitivity of 57% and a specificity above 99.5% (7). The prognosis of scleroderma is dependent on the extent of major organ involvement and can be excellent in limited and stable disease. Medical management focuses on prevention and palliation of symptoms.

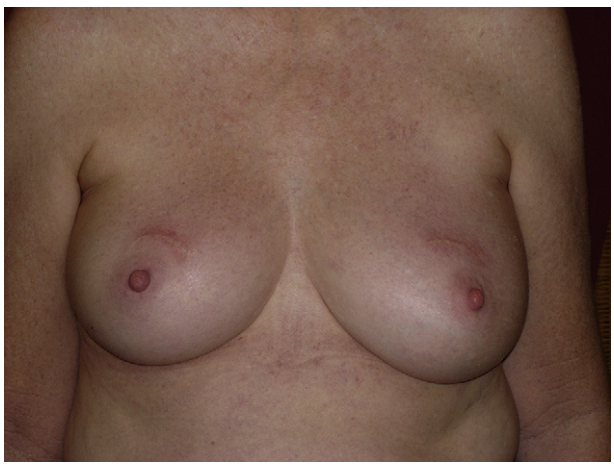

Fig. 3. Clinical appearance 6 months after treatment.

Given the heterogeneity of CVDs, the variation in radiotherapy dosing, and the additional effects of chemotherapy on the toxicity profile, the literature on the use of radiation in these patients is sparse and difficult to interpret.

A number of articles have documented that patients with scleroderma and other CVDs tolerate radiation poorly. These examples are primarily case reports and retrospective reviews (2, 3, 8, 9). Most commonly, the reports detail an increased incidence of severe complications, both acute with wound complications and skin desquamation and late (>90 days after treatment) with breast retraction and fibrosis.

In the largest retrospective study performed, Morris and Powell (10) studied the complication rate in 209 patients with CVD, who were treated with radiation. The authors found that patients with nonrheumatoid arthritis CVD had an increased rate of late toxicities at standard doses of 21% at 5 years. Activity of disease, medication use, and elevation of erythrocyte sedimentation rate did not correlate with increased toxicity of radiation. Late effects were further characterized according to treatment site; there was a 22% incidence of Grade 3+ late effects in nonrheumatoid arthritis patients with CVD, who underwent breast irradiation. In a meta-analysis performed by Chon and Loeffler (1), 13 of 15 articles reviewed showed a greater incidence of both acute and late toxicities in patients with CVD with a large range of 7–100%.

Most studies included in the meta-analysis consist of case reports with no control groups. Two separate matched-control studies evaluating patients with diverse malignancies and varied subtypes of CVD did not show a significant increase in radiation-induced complications in patients with CVD. Despite these encouraging results, important limitations to these studies exist (11, 12).

In one such analysis by Ross *et al.* of 61 patients (9), they reported an increased risk of late complications with rheumatoid arthritis (24% for patients with CVD vs. 5% for the matched control) and an increased incidence of acute complications with systemic lupus erythematosus. However, neither reached statistical significance. In their analysis by irradiated site, they report an increased incidence in late complications in patients treated with breast/chest wall irradiation; 2 of 6 patients had severe late toxicities, while the control group lacked any significant events. However, because of the small number of patients in this subgroup, statistical significance was not reached. Another limitation to this study is that almost half of the patients received palliative doses rather than therapeutic doses of radiation. In a similar matched-control analysis, Phan *et al.* (12) also found no overall increased incidence of acute or late complications in patients with CVD receiving RT. Although when performing a subset analysis of patients with scleroderma, they found a higher incidence of acute and late complications.

In the largest matched-control study of 72,263 patients, Lin *et al.* (13) reported that patients with CVD had an increased risk of any late toxicity (29.1% vs. 14%; $p = 0.001$), with a trend toward an increased rate of severe toxicity. Concurrent infusional chemotherapy was the only medication significantly associated with an increased risk of severe acute toxicity ($p = 0.0022$). Eight patients received breast/chest wall radiation, and the only documented complication in this subgroup was a severe acute skin desquamation in 2 patients, with none occurring in the matched-control group. As with some of the other matched-control studies, this study also found that patients with scleroderma were at the highest risk of severe acute and late complications after RT.

The Mayo clinic published their experience of 20 patients with scleroderma requiring external beam radiation for a heterogenous group of malignancies (14). Only 2 patients received chest wall irradiation for breast cancer although there were 9 patients with CREST syndrome included in this study. Five of 20 patients exhibited a severe radiation-induced complication, 3 patients acute, 2 patients chronic, and 1 patient both. Three of these 5 patients had CREST syndrome. Most patients experienced either a mild acute toxicity (60%) or a mild chronic toxicity (75%). Univariate analysis showed a statistically significant correlation between the development of an acute radiation-induced toxicity and the severity of the underlying scleroderma.

As described above, a wide variation of tolerance to toxicities exists among patients with CVDs receiving radiation. In addition to examining clinical characteristics of their underlying condition, diagnostic assays may provide additional information in these high-risk patients. An assay analyzing radiation-induced T-lymphocyte apoptosis is useful in predicting late toxicity in these patients (15). There are compelling data that this assay could serve as a rapid screen test in evaluating patients hypersensitive to radiation. This assay is not routinely used in clinical practice, and was not used in our patient, but may have an increased role in the future in determining the risk of late toxicities in patients with CVD.

Our patient required chemotherapy, which is known to promote an inflammatory skin reaction within the previously irradiated field. This phenomenon is known as radiation recall dermatitis (16). In patients with CVDs, it is unclear which agents can be administered with the least amount of toxicity because many agents can trigger this reaction. To date, the most common antineoplastic drug resulting in radiation recall dermatitis is adriamycin. In a trial examining the effects of radiation recall on 148 patients receiving APBI, adriamycin was administered in >75% of cases and radiation recall occurred in 11.5% of all patients (17). Other studies have suggested that taxanes can also result in this inflammatory reaction in as great as 6% of patients (18, 19). Given the clear benefit of systemic treatment in this patient, we opted to administer taxotere and cytoxan despite the potential risk of radiation recall. Adriamycin though was held from her treatment.

APBI was offered to our patient because we felt that it would be better tolerated than whole chest wall radiation. In comparison to whole breast radiation, APBI delivers a decreased volume of radiation to only the tumor bed and spares most of the normal breast tissue. Because the tumor bed has an increased rate of breast cancer recurrence, APBI is considered as an effective treatment modality. By decreasing both the surface area receiving the radiation and the volume of radiation administered, toxicity is minimized. Thus, we believe that APBI may be safer than whole chest radiation in patients at high risk for toxicities. Other techniques for administering PBI, such as multicatheter brachytherapy and three-dimensional conformal external beam radiation, should also be explored in patients with CVDs.

Our case report is the first documented use of MammoSite catheter APBI in a patient with CVD. Our patient tolerated the treatment well with only mild radiation changes to the MammoSite cavities. Because at least a minor component of soft tissue fibrosis could not be excluded, we considered these findings of induration and telangiectasias on her bilateral breast examination to be a Grade 1 late toxicity (20). Our patient has had only 1-year followup, and we recognize that the potential for late complications such as severe fibrosis can occur in 3–4 years after treatment (16). Though, we are able to document there were no severe acute or late toxicities within the first year after her treatment.

Overall, she has had an excellent cosmetic result. We can assume that the findings of induration and mild skin desquamation would be more severe with whole chest wall radiation. As summarized above, the literature lacks a decisive treatment algorithm for administering radiation to these patients, although an increased risk of toxicity exists, particularly in patients with scleroderma. As we continue in our endeavors to determine the patients with CVD who are at greatest risk for toxicity, we assert that APBI should be considered as a treatment option. We believe that by decreasing the volume of radiation delivered and the surface area receiving radiation, toxicity can be minimized. Future studies are required to clarify the use of APBI in patients with CVD.

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