CASE REPORT

A rare complication resulting in a rare disease: radiation-induced male breast cancer

Jamila Alazhri, Constantine Saclarides, Eli Avisar

Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, Miami, Florida, USA

Correspondence to
Dr Jamila Alazhri,
drjzhri@hotmail.com

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SUMMARY

The increase in survival after childhood radiation therapy for some blood malignancies has led to an increase in the diagnosis of radiation-induced secondary solid malignancies (SSM). We report a young man presenting with invasive breast cancer 19 years after receiving radiation therapy and bone marrow transplant for acute lymphocytic leukaemia in childhood. This latency period is longer than previously reported. Therefore, survivors of radiation-treated primary cancer should be closely monitored for SSM, including breast cancer, for the rest of their lives.

BACKGROUND

Male breast cancer (MBC) is a rare condition, accounting for approximately 1% of all breast cancers in men and women in 2014.¹ There are multiple risk factors for MBC reported in the literature, and like female breast cancer, some of these have a strong oestrogen influence; these risk factors include genetics, endocrine abnormalities, Klinefelter syndrome, gynaecomastia, obesity, occupational exposures and a history of radiation exposure.²

Diagnostic and therapeutic radiation is a known risk factor for malignancy. A recent study on second cancer risk after radiation treatment for Hodgkin's lymphoma reported a standardised incidence ratio of 4.6 (95% CI 4.3 to 4.9) in the study cohort as compared with the general population, and the risk was still elevated 35 years or more after treatment.³ Although rare, it has been demonstrated in the literature that diagnostic and therapeutic radiation is associated with breast cancer in women.⁴ The relative risk of breast cancer in patients treated with radiation therapy for Hodgkin's lymphoma is 1.4,⁵ indicating a low incidence of radiation-induced breast cancer in women. However, among the radiation-induced SSM, breast cancer appears to be the most common. In the after mentioned study,³ breast cancer represented 20.4% of the excess risk of any second cancer among men and women, and 40.5% among women in the cohort. Not surprisingly, there is a paucity of case reports in the literature describing radiation as a risk factor for cancer in men. We describe a young man who was treated with full body radiation for acute lymphocytic leukaemia (ALL) in his childhood, and subsequently developed invasive breast cancer as an adult.

CASE PRESENTATION**History**

The patient is a 23-year-old man who presented to his primary care provider (PCP) with left breast discomfort, nipple thickening and retraction for 2 months.

The patient has no family history of breast cancer or other organs cancer. However, he has a personal history of childhood T-cell ALL with no extramedullary disease that was diagnosed at 4 years of age. He was treated with radiotherapy on paediatric POG 9398 protocol.⁶ He sustained an isolated central nervous system (CNS) relapse of T-cell phenotype ALL after 9 months, and was treated with a 3 drug reinduction, followed by consolidation as per the paediatric POG 9110 protocol.^{7 8} He then had a 6 of 6 HLA matched allogeneic umbilical cord blood stem cell transplant in 1996. For the transplant, he received a conditioning regimen with cyclophosphamide and whole body radiation with cranial and testicular boosts. His radiation therapy included radiation to the chest wall as part of the protocol. Previous radiation records were not available. He was then on immunosuppressive therapy with cyclosporine A and methylprednisone, which was appropriately tapered in the following months to years. The patient has been in remission since then.

Clinical findings

Physical examination at presentation demonstrated a young man, 63 inches tall, who weighs 135 pounds. On physical examination of the breasts, there was mild bilateral gynaecomastia and a 2 cm palpable retroareolar left breast mass was appreciated but no erythema, warmth, oedema or nipple secretion, although there was left nipple retraction. There was no palpable axillary or supraclavicular lymphadenopathy.

The rest of the physical examination was within normal limits.

INVESTIGATIONS**Diagnostic workup**

Mammography was first ordered by the PCP and showed a BIRAD 4, left breast irregular mass involving the left nipple areola complex with associated pleomorphic calcifications. Ipsilateral partially imaged axillary adenopathy was also evident. There were no suspicious findings on the right side.

Breast ultrasound confirmed the presence of an irregular hypoechoic solid mass involving the nipple areola complex with associated vascularity

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and with ipsilateral morphologically abnormal left axillary lymph nodes.

MRI was performed and demonstrated an enhancing left breast mass that corresponds to mammogram and ultrasound.

An ultrasound-guided core biopsy of the breast mass and axillary lymph node was performed, and a metallic clip was placed in the breast mass and the axillary lymph node as markers for purposes of future surgical localisation.

A pathology report revealed infiltrating ductal carcinoma, grade 2–3, estrogen receptor (ER) 95% positive, progesterone receptor (PR) 60% positive, HER-2 Neu positive, and a Ki-67 level of 20%.

The left axillary lymph node revealed metastatic adenocarcinoma consistent with the breast primary.

Metastatic workup

The positron emission tomography-CT scan revealed increased uptake in the breast area at the site of the mass, as well as three hyper metabolic left axillary lymph nodes. No distant metastases were noted.

A brain MRI was obtained, showing a small 5 mm non-enhancing developmental cyst in the medial left temporal region, which was not concerning for metastatic disease.

The breast cancer was staged as T2N1M0.

Genetic testing

The patient reports an Ashkenazi and Sephardic Jewish ancestry in the paternal bloodline, which may suggest a carcinogenic inclination. However, with no family history of cancer, a genetic syndrome is less likely to explain ALL and breast cancer. The topic was discussed with the patient and his parents and they elected not to go for genetic testing.

TREATMENT

Neoadjuvant chemotherapy

Considering his positive HER2 Neu status, the patient was treated with six cycles (once every 21 days) of neoadjuvant chemotherapy (NCT) consisting of: Taxotere, Carboplatin, Herceptin and Perjeta via a Port-A-Cath. The treatment began on 30 March 2015 with Neulasta support.

Surgery

The surgical oncology team counselled the patient regarding surgical treatment options, and recommended left mastectomy with sentinel lymph node biopsy (SLNB), or modified radical mastectomy (MRM), depending on the axillary response to NCT.

Adjuvant radiation therapy

The radiation oncology team evaluated the patient regarding the possibility of postmastectomy adjuvant radiation therapy. The rationale for this is further elaborated in our discussion below.

Adjuvant systemic therapy

Considering his positive ER, PR, HER2 status, it is planned to continue postoperative adjuvant Herceptin for 1 year, as well as to recommend adjuvant tamoxifen for 5–10 years.

OUTCOME AND FOLLOW-UP

The patient received six cycles of NCT as detailed above. The treatment began on 30 March 2015 with Neulasta support. However, it was complicated by very severe diarrhoea, and therefore Perjeta was discontinued after the second cycle.

On follow-up physical examination, the left breast mass was no longer palpable after the second cycle of chemotherapy, with excellent clinical response.

A repeated ultrasound of the left axilla after completion of NCT showed no remaining suspicious lymph nodes.

The patient underwent left simple mastectomy with SLNB and no axillary dissection was performed because the SLNB was negative.

The postoperative pathology report showed complete pathological response, and hence postmastectomy radiation therapy (PMRT) was not delivered.

He is currently completing a year of Herceptin and also receiving tamoxifen with baby aspirin.

He is doing well on follow-up and has no evidence of recurrence to date.

DISCUSSION

Diagnostic and therapeutic radiation is a known risk factor for malignancy. It has been associated with increased risk of cancer of the thyroid, breast, CNS, skin and bone marrow.⁹ The use of ionising radiation in children is of particular concern to clinicians for two reasons: first, paediatric patients are more sensitive to radiation, and second, children have more time than adults to allow for early acquired radiation-induced genetic aberrancies to evolve in their malignant potential⁹. According to Curtis *et al*,¹⁰ the risk of developing solid malignancy after bone marrow transplant (BMT) increased overtime to 6.7% at 15 years and was highest in patients who were less than 10 years at the time of BMT, had acute leukaemia, compared to chronic leukaemia and lymphoma, and received pretransplant total body irradiation (TBI) (relative risk of 4.1).

There are limited case reports in the literature of men who developed breast cancer following radiotherapy for ALL. To the best of our knowledge, there are only two. The first case report describes a 29-year-old man with a history of ALL who developed an invasive left breast cancer 13 years after he was diagnosed with ALL and treated with total body radiation and BMT. The breast cancer was treated with MRM and irradiation of the left chest wall. The patient developed a malignant pleural effusion 17 months later and died secondary to cancer progression.¹¹

The second case report describes a 34-year-old man with a history of ALL who developed stage IIB node-positive breast cancer that developed 15 years after he was diagnosed with ALL and treated with TBI and allogeneic BMT. His breast cancer was positive for oestrogen, progesterone and Her2/neu receptors. It was treated with MRM followed by Herceptin-based adjuvant chemotherapy as well as tamoxifen.¹

Our patient developed a stage IIB node-positive breast cancer 19 years after exposure to therapeutic whole body radiation for ALL before BMT, which is a longer duration compared to the two cases reported earlier. The most common secondary solid malignancy (SSM) in the Childhood Cancer Survivor Study was breast cancer, with a relative risk of over 16 and a median time to malignancy of 15 years.¹² The current data indicate that radiation-induced breast cancer can still develop after a long latency period. Indeed, some scientists believe that for SSM, the latency period after irradiation may extend to 45 years or more.¹¹

As seen in sporadic MBC, the radiation-induced cancer can present with advanced stage and nodal involvement compared to female breast cancer. The rarity of disease in men and hence the low index of suspicion lead to delay in the diagnosis for up to 10 months,¹³ resulting in advanced-stage presentation.

Advanced stage at diagnosis and lymph node status are the most important prognostic indicators. Estimates for 5-year survival when grouped by stage at presentation are 75–100% for stage I disease, 50–80% for stage II disease, and falling to 30–60% for stage III disease.¹⁴

The standard of treatment for locally advanced breast cancer in women is NCT followed by surgery. Since data are limited in MBC, we followed the same treatment recommendations for female breast cancer.

Her 2/neu was overexpressed in our patient and in the previously reported case.¹ This is consistent with our previous findings, showing a 56% Her 2/neu overexpression in MBC.¹⁵ Recent data show overexpression of 15% in male metastatic disease.¹ Interestingly, a recent study has demonstrated that Her 2/neu gene amplification and chromosome 17 polysomy can be induced by irradiation in human breast cancer cell lines with a low basal level of HER-2/neu.¹⁶ The Her 2/neu overexpression allows for the use of Herceptin, which is associated with better clinical and pathological response. One randomised clinical trial indicated that adding Herceptin to the chemotherapy regimen in Her 2/neu positive breast cancer increased the pathological complete response (PCR) rate from 25% to 66.7%.¹⁷ Moreover, Her 2/neu overexpression adds the benefit of using pertuzumab (Perjeta) in addition to Herceptin in the neoadjuvant setting. A randomised phase 2 clinical trial showed that patients given pertuzumab and trastuzumab (Herceptin) plus docetaxel had a significantly improved PCR rate (49 of 107 patients; 45.8% (95% CI 36.1% to 55.7%)) compared with those given trastuzumab plus docetaxel (31 of 107; 29.0% (20.6% to 38.5%); $p=0.0141$).¹⁸ Although Perjeta was discontinued after the second cycle in our case, the patient still had PCR with Herceptin based NCT. Only one patient out of the two previously reported received chemotherapy (Herceptin based) which was in the adjuvant setting,¹ and it is not clear why the patient in the other paper did not receive chemotherapy.¹¹

Mastectomy is usually the preferred surgical procedure for male patients with breast cancer, because of the small size of the male breast and because the majority of the tumours are retroareolar. Both patients in the previously described case reports underwent mastectomy.

Postmastectomy radiation is often recommended for MBC because of the close proximity to the skin and chest wall. The use of radiotherapy in the treatment of breast cancer in patients with a history of therapeutic radiation exposure is controversial. There is concern about the possibly augmented carcinogenic effect, as was the case in our patient. In women treated with breast conserving surgery for a radiation-induced breast cancer, however, reradiation was proven safe when administered 10–29 years after the previous radiation treatment for Hodgkin lymphoma.¹⁹ In one case report, the patient received PMRT because the tumour was attached to the fascia of the pectoralis muscle.¹¹ In the other case report, although there was evidence of lymphovascular invasion and 3 of 41 axillary lymph nodes were positive for metastasis, the authors did not mention whether or not the patient received PMRT.¹

The decision regarding adjuvant radiation therapy for our patient was deferred until after surgery, to take into consideration the final pathology information, especially residual tumour margins, lymphovascular invasion and number of positive lymph nodes. Fortunately, our patient had complete pathological response and negative SLNB. Therefore, the decision was to avoid postmastectomy reradiation for the chest wall.

According to a population-based study, MBC is commonly hormone positive. ER and PR are overexpressed in 90% and

81% of MBC, respectively.²⁰ It seems that this is true for radiation-induced MBC as well. All the three reported patients, including our patient, had ER and PR positive tumours. One patient did not receive tamoxifen until after he developed recurrence in the form of pulmonary metastasis, and he died in 2 months despite starting palliative therapy with tamoxifen and chemotherapy.¹¹ The other patient, as well as our patient, received tamoxifen in the adjuvant setting.¹ Adjuvant trials in female breast cancer showed a 40–50% reduction in recurrence rate of hormone sensitive breast cancer with 5 years of tamoxifen.²¹ In the absence of similar trials in men, hormone sensitive MBC should be treated with adjuvant tamoxifen for at least 5 years.

Surveillance for the other breast and for other male patients who received radiation therapy is not well defined. In addition to clinical breast exams, female patients with a previous history of ionising radiation to the breast are followed with annual mammography and MRI starting 8 years after the radiation therapy but not before age 25.¹⁹ Although the use of mammography and breast ultrasound in the workup of a mass in the male breast is well established, the value of screening mammography and MRI in high-risk males is not well defined. Nevertheless, awareness of the cancer risk and clinical breast exams on a routine schedule is advisable. Additionally, there might be a benefit in the use of imaging studies for the surveillance of high-risk male patients, especially in the presence of gynaecomastia or overweight.

Learning points

- Radiation-induced male breast cancer should be considered in the differential diagnosis of breast-related symptoms, even with a very remote history of exposure.
- The younger the age of exposure, the more years the patient has at risk of breast cancer.
- The most important prognostic indicators are stage at diagnosis and lymph node status; therefore, it is important to attempt early detection in these patients before the disease progresses to an advanced stage.
- Yearly clinical breast examinations and selective imaging studies should probably be offered to the subgroup of male patients at higher risk including those with early age at exposure (younger than 10 years), and those getting total body irradiation for the treatment of acute lymphocytic leukaemia.

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