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Case Report
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Breast Cancer Occurring after Childhood Total Body Irradiation as Conditioning for Allogeneic Stem Cell Transplantation: Case Report and Review of the Literature

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Abstract

Exposure to ionizing radiation during childhood and adolescence is well known to increase the risk of later malignancy, including leukemia and a variety of solid cancers. Radiation to the chest or mediastinum during treatment of Hodgkin Lymphoma or metastatic solid cancers in young females is well known to cause a substantial increased risk of later breast cancer. Less well known is the risk of breast cancer arising after Total Body Irradiation (TBI) in this age group as part of conditioning for Hematopoietic Stem Cell Transplantation (HSCT). This report presents a young woman who developed high-grade invasive breast cancer at age 27, sixteen years after childhood treatment for relapsed acute leukemia with TBI conditioned allogeneic stem cell transplantation. Female patients treated in childhood with TBI conditioning for HSCT should be educated about their breast cancer risk, and should have regular surveillance for breast cancer beginning at a much younger age than the general population. The recent finding of two possible genomic variants associated with increased breast cancer risk after childhood radiation may offer a future tool to identify patients who need particularly close surveillance.

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Introduction

The association between ionizing radiation exposure and malignancy has been the subject of investigation for many years, beginning with the long-term surveillance of the survivors of the Hiroshima and Nagasaki atomic bombs in 1945. Although thousands of people were killed by the bombs, there were thousands of survivors who were exposed to varying levels of radiation. Many of them were followed over the decades since the war, revealing much about the short-term and long-term effects of radiation exposure. Leukemia was the first malignancy observed in survivors, but over the subsequent years an increased risk of many other types of cancer has been described [1-3]. Many studies of solid tumors in atomic bomb survivors and in others exposed to non-therapeutic radiation have shown an excess of breast cancer in these individuals [4-7]. Because of the recent Fukushima Daiichi nuclear power plant accident in Japan and the 1986 Chernobyl accident in Ukraine, we are learning more about the risk of solid cancers after accidental radiation exposure [7,8].

Medical radiation for treatment of cancer and non-malignant conditions is also a well-established cause of secondary malignancies, e.g., after radiation treatment of a primary cancer, or radiation treatment of acne [9-11]. Many factors contribute to breast cancer carcinogenesis after therapeutic radiation for solid cancers, including radiation dose, age when treated, hormonal factors, and timing of radiation in relation to sexual development [11]. We have learned much from studying women treated for Hodgkin Lymphoma with mantle field radiation as children or young adults [12-15]. We have also learned that treating solid cancers in young girls with whole lung radiation is another risk factor for breast cancer [12,14].

Although much of our knowledge comes from childhood radiation for solid malignancies, acute leukemia is the most common childhood cancer. Children with acute leukemia are treated primarily with chemotherapy, but some undergo allogeneic HSCT for high risk or relapsed disease. A few of these children receive low dose TBI as part of the HSCT conditioning regimen prior to transplant.

Because it has been extensively studied, the risk of breast cancer after childhood or adolescent radiation for Hodgkin Lymphoma or solid tumors is widely recognized by physicians. However, many are unaware of the risk after treatment for childhood acute leukemia, particularly in patients treated with TBI conditioning for HSCT. Clinicians who are not cognizant of this risk may fail to

Table 1: Selected references examining the relationship of childhood radiation exposure from a variety of sources and subsequent development of secondary malignancies in general and breast cancer in particular. Radiation exposure data analyzed includes atomic bomb survivors, other environmental exposure (e.g., nuclear accidents), medical/therapeutic exposure, and total body irradiation for stem cell transplantation. Data bases searched include PubMed, online journal archives, other online bibliographies, and web-based search engines. Reference numbers are in brackets in each element of the table.

REPRESENTATIVE STUDIES	SECONDARY MALIGNANCIES	SECONDARY BREAST CANCER
Japanese Atomic Bomb Survivors	Reviews of solid cancer incidence and non-cancer mortality Refs [1-3]	Reviews of breast cancer risk in survivors Refs [4-6]
Environmental Radiation & Nuclear Accidents	Cancer risks after non-medical exposure Refs [7,8]	*No data*
Cancer Secondary to Therapeutic Radiation	Risk of secondary cancer from therapeutic radiation Refs [9-11]	Risk of secondary breast cancer from therapeutic radiation Refs [12-15]
Cancer Secondary to Childhood Radiation	Risk of cancer from childhood radiation [18-20]	Risk of breast cancer from childhood radiation [12-15,21]
Cancer Secondary to Total Body Irradiation	Risk of secondary cancer & late complications from total body radiation Refs [23-25,30,31,34]	Risk of cancers including breast from total body irradiation Refs [30,31]
Breast Cancer after Chemotherapy Without Radiation	*No data*	Breast cancer after childhood chemotherapy without radiation Refs [32,33]

consider appropriate surveillance for patients at risk.

The following case report describes a 27 year old woman who developed breast cancer 16 years after treatment for relapsed acute myelogenous leukemia with TBI-conditioned allogeneic HSCT. This report includes a brief literature review of secondary breast cancer in this clinical setting (Table 1).

Methods

A directed review of relevant literature was performed using several literature search tools, identifying reviews and compilations of patients with data pertinent to the questions raised in this case report. The literature data bases searched include PubMed, online journal archives, other online bibliographies, and web-based search engines.

Case Report

Acute leukemia history

In March, 2015, a 27-year-old gravida 0 para 0 woman was referred for treatment of newly diagnosed breast cancer. In 1998, at age 10, she was diagnosed with acute myeloid leukemia (AML - FAB M5a). Her bone marrow was 100% cellular with 80% blasts, 10% promyelocytes, 10% erythroid cells and scattered megakaryocytes. Flow cytometry confirmed AML with monocytic differentiation, and cytogenetics showed a 46, XX, t(9;11)(p22;q23) karyotype in 100% of cells. She received 6 months of chemotherapy on a Pediatric Oncology Group (POG) regimen with mitoxantrone, high-dose cytarabine, etoposide, and intrathecal cytarabine, achieving a complete remission.

In June, 1999, her AML relapsed. At that time, she was going through menarche with early breast development. She was treated with a POG salvage regimen of idarubicin and cladribine, achieving a second remission. She then underwent allogeneic HSCT with umbilical cord blood from a single male donor. Her conditioning regimen consisted of TBI (1,350 cGy in nine fractions over 4.5 days) followed by 60 mg/kg etoposide x one dose. Approximately 8.61 x 10^6 CD34 cells/kg and 7.83 x 10^6 CD3 cells/kg were infused, and she achieved 100% engraftment with donor cells. Post-HSCT immunosuppression consisted of cyclosporine and steroids, which were weaned off by day 180. Her leukemia remains in remission since then, and she has had no infectious complications other than shingles.

She has had several health issues since HSCT, including cutaneous graft versus host disease. Her other problems are likely due in part to radiation: cataracts, avascular necrosis of both femoral heads, nonalcoholic steatohepatitis, pancreatic exocrine insufficiency with diabetes, hypothyroidism, and hypogonadism. She was transplanted during menarche, stopping further sexual maturation and causing growth arrest secondary to ovarian failure. She has chronic xerostomia with chronic dental problems, and she is unable to sweat normally, interfering with thermal regulation.

Breast cancer history

In February 2015, she felt a mass in the lower inner quadrant of her right breast. Diagnostic mammography revealed a suspicious 1.3 cm mass, and she was referred to a breast surgeon. At that time, she had a 2 x 2 cm area of thickening in the right breast about 3 cm from the nipple. Ultrasound showed a 1.3 x 0.7 x 1.1 cm mass along the 2:30 axis 3 cm from the nipple, with branch extension into a dilated subareolar lactiferous sinus suspicious for intraductal cancer, and a 4 mm hypoechoic nodule along the 1:00 axis about 1 cm from the superior margin of the mass. No abnormal axillary nodes were seen.

Ultrasound-guided biopsy showed infiltrating and in situ ductal carcinoma of high grade (SBR grade 3) with the in situ component less than 5% of the tumor volume (Figure 1A and B). The prognostic profile showed negative estrogen and progesterone receptors. HER-2/neu was positive by FISH (HER-2/cep-17 ratio 4.7, average HER-2 spot count 21.0). Ki-67 was high at 54% (Figure 2).

PET/CT scan showed no evidence of metastatic disease. Breast MRI scan revealed the primary tumor mass, as well as abnormal linear enhancement extending from the lateral border of the mass

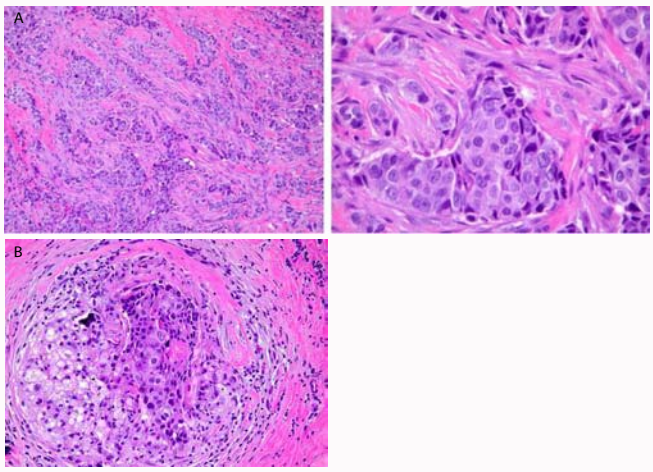

Figure 1A and 1B: Ultrasound directed biopsy of breast mass showing infiltrating and in situ ductal carcinoma, SBR grade 3. The intraductal component showed a solid growth pattern with comedonecrosis, and constituted less than 5% of the tumor volume. (Photomicrographs courtesy of Dr. Jo Ellen Krueger).

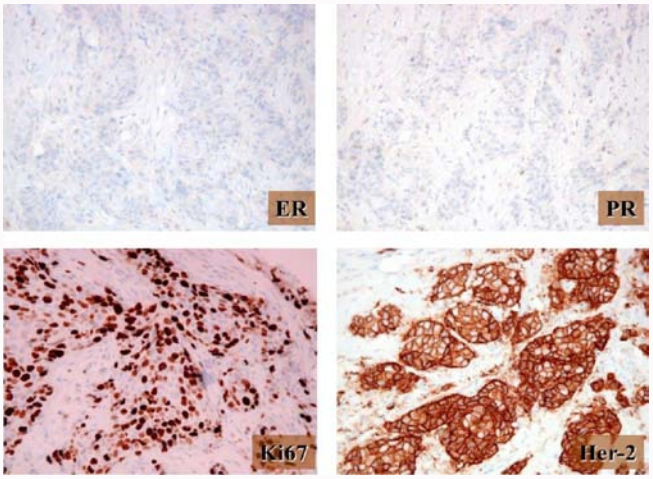

Figure 2: Prognostic profile by Immunohistochemical staining of the tumor tissue. Estrogen Receptor (ER) and Progesterone Receptor (PR) stains are both completely negative. Ki-67 is high, staining 3+ in 54% of cells, indicating a high proliferative rate. HER2/neu is strongly positive, staining 3+. HER2 by Fluorescence In Situ Hybridization (FISH) confirmed amplification of the HER2 gene, with a HER2/cep-17 ratio of 4.7 and HER2 spot count of 21.0. (Photomicrographs and immunohistochemical stains courtesy of Dr. Jo Ellen Krueger).

towards the base of the nipple. At least four additional well-defined, intensely enhancing masses up to 9 mm were located within the upper, inner, and anterior regions of the breast. These findings were highly suspicious for extensive multifocal malignancy spanning an area of 4.4 x 4.5 cm in her relatively small right breast.

Breast conservation was not an option. The extent of disease within her involved breast and her prior TBI effectively precluded postoperative breast radiation. In addition, the left breast was also considered at increased risk for breast cancer due to her prior radiation, and bilateral mastectomy was recommended. Finally, her MRI scan strongly suggested multifocal right breast cancer, raising concern that immediate mastectomy might leave positive surgical margins requiring post-operative radiation. Accordingly, she was treated with neoadjuvant chemotherapy prior to her surgery. The TCHP regimen, consisting of docetaxel, carboplatin, trastuzumab, and pertuzumab, was chosen for its high rate of pathologic complete remission in the neoadjuvant setting [16,17].

In August 2015, she underwent bilateral mastectomies following six cycles of TCHP. The final pathology showed no residual malignancy in the breast, and a sentinel lymph node was negative. There was no evidence of disease in the left breast. She did well postoperatively, completing a full year of adjuvant trastuzumab, and she remains disease free.

Discussion

Survivors of childhood cancer have long been known to have an increased risk of second malignancies later in life [2,3,12,14,15,18,19]. Radiation therapy for childhood cancer accounts for a significant element of this risk, with a particularly common group being patients treated with mantle field radiation for Hodgkin Lymphoma. Those treated before age 30 years face an ongoing risk of breast cancer beginning a few years after radiation, and extending even into the fifth and sixth decades of life [20]. Recognition of ionizing radiation in children and adolescents as a risk factor for cancer began with analytic studies of Japanese atomic bomb survivors, followed by many epidemiologic studies since that time [1,4,5,18]. With the increasing use of radiation to treat childhood cancer, the carcinogenic effects of therapeutic radiation have become progressively more obvious [7,9-13,14,18,20]. Mantle radiation in girls with Hodgkin lymphoma has long been accepted a specific risk factor for breast cancer [12-15].

Chemotherapy rather than radiation is the principal treatment for pediatric cancers. Acute leukemia is the most common cancer in children, accounting for about 30% of childhood malignancies. Acute Lymphoblastic Leukemia (ALL) is about five times more common in children than Acute Myelogenous Leukemia (AML), with around 2,500-3,500 new cases per year. The five-year survival rate for childhood ALL is about 85%, and for AML about 60-70%, and children free of recurrent leukemia for 5 years are probably cured [21]. For some acute leukemic children, particularly AML, the prognosis for long-term remission with chemotherapy is poor. For these patients and for those who relapse after standard chemotherapy, allogeneic HSCT may offer the best chance for cure. Relatively few children undergo allogeneic HSCT, however, and only some of them receive TBI in addition to chemotherapy as their conditioning regimen [22-24]. Consequently, many fewer girls are treated with TBI compared with the number treated with mediastinal radiation for Hodgkin Lymphoma. Additionally, several studies examining second malignancies after childhood TBI reported a variety of solid tumors, but did not report an increase in breast cancer [22,23]. For these reasons, physicians are less aware of the breast cancer risk from TBI than from mantle field radiation.

Possible contributory factors to our patient developing breast cancer at age 27 include chemotherapy, exposure to relatively low dose radiation, and possible immune compromise secondary to the cord blood transplant. While chemotherapy and radiation are known carcinogens, there is no reason to believe her immunologic status was an etiologic factor in her breast cancer. She was only on immunosuppressive medication for 180 days post-transplant, and her only significant infection throughout her entire course was an episode of shingles. In addition, several large studies of immunosuppression in solid organ transplant patients found no increase in the incidence of breast cancer, despite an overall increase in secondary malignancy. The largest of these was a cohort study linking the US Scientific Registry of Transplant Recipients to 13 state and regional cancer registries, including 175,732 solid organ transplant recipients. The incidence of breast cancer in this study was actually lower than predicted, with a Standardized Incidence Ratio (SIR) of 0.85. As shown in Table 2, similar results are reported in several other analytic studies, with SIRs approximating 1.00 in both transplant patients and HIV/AIDS patients [25-28].

Several recent large-scale investigations of the effects of HSCT on long-term health have shed considerable light on the problem of secondary breast cancer [29,30]. In 2008, Friedman et al. [29] evaluated 3,337 women followed by the Fred Hutchinson Cancer Research Center or by the European Bone Marrow Transplant Registry who survived at least 5 years after allogeneic HSCT before age thirty. The incidence of breast cancer was 26.6 cases per 10,000 patients per year. Three major breast cancer risk factors identified in this review were younger age at transplantation, disruption of ovarian function by alkylating agents, and exposure of breast tissue to radiation with TBI. The hazard ratios were 9.5 with transplantation under age 18, and 4.0 with TBI. Of these survivors, 1.6% developed breast cancer (median of 12.5 years after transplantation) with a 25-year

Table 2: Compilation of four analytic reports evaluating the risk of breast cancer in immune compromised subjects. These include reports of studies of solid organ transplant patients on long-term treatment with immunosuppressive drugs, as well as studies of patients with compromised immune systems due to HIV/AIDS. The studies reviewed in these reports did not demonstrate any substantial increase in breast cancer risk among patients with compromised immune systems.

Study Publication	*Type of Patients*	*Number of Patients*	*Number Developing Breast Cancer*	*Standardized Incidence Ratio SIR*
Stewart et al. [26]	Kidney & Heart Transplant	25, 914	86 (expected 113.8)	0.76
Grulich et al. [27]	HIV/AIDS Solid Organ Transplant	Not available	194 (6 studies) 156 (5 studies)	1.03 1.15
Engels et al. [28]	Solid Organ Transplant	175, 732 (all genders, organs)	481 (expected 567.9)	0.85
Chapman et al. [29]	Kidney Liver Heart Lung	Not available	Not available	0.9 – 1.3 0.8 – 1.3 0.5 – 1.1 0.3 – 0.8

cumulative incidence of 11%. In a 2011 study, investigators examined long-term health outcomes in childhood cancer survivors treated with HSCT, compared both with their siblings (N=4,020) and with control patients treated with conventional cancer therapy (N=7,207) [30]. The childhood allogeneic HSCT survivors were at highest risk for severe/life-threatening conditions, including second malignancy, compared to conventionally treated cancer patients and to the non-cancer siblings. Nearly half of the female transplanted patients developed gonadal failure compared to 4% of those conventionally treated, with more than double the incidence of second malignancies. Treatment with alkylating agents and anthracyclines may also be risk factors for breast cancer in childhood cancer survivors, in addition to the effects of chest radiation, [31]

Moskowitz et al. [32] reported on the cumulative risk of breast cancer in 1,230 female cancer survivors treated with radiation therapy [21]. They found treatment with a lower delivered dose of radiation (2 to 20 Gy) had a much higher risk of subsequent breast cancer (SIR 43.6), compared to the moderately high risk (SIR 24.2) after the higher delivered dose of mantle field radiation (40 Gy) for Hodgkin Lymphoma. The cumulative breast cancer was 30% by age 50, with breast cancer specific mortalities of 12% at 5 years and 19% at 10 years, showing a substantial risk for both breast cancer incidence and death among these survivors.

The incidence of secondary malignancy after childhood radiation continues to increase throughout adult life, extending at least into the fifth and sixth decades. Turcotte et al. [20] studied 14,364 childhood cancer survivors diagnosed between 1970 and 1986, of whom 3,171 were age 40 or older at last contact. They found that secondary malignant neoplasms including new breast cancers continue to occur after age 40 in these patients, at least to age 55. Among the 196 secondary malignancies (other than non-melanoma skin cancers) diagnosed after age 40, breast cancer had an SIR of 5.5, mostly in women who had childhood chest radiation.

These studies substantiate the considerable risk of breast cancer among women whose breast tissue was exposed to therapeutic radiation as children. There is a considerable body of evidence showing the risk with high dose radiation, both therapeutic (e.g., mantle field radiation) and environmental (e.g., atomic bomb survivors). Much less data is reported on the risk following low dose childhood radiation with TBI conditioning for stem cell transplantation. Nonetheless, it is clear that TBI in female children and adolescents is associated with a significant risk of breast cancer, continuing into adulthood and even into old age. Although a retrospective analysis by the Pediatric Blood and Marrow Transplant Consortium failed to show a survival advantage, TBI is still used in a small number of pediatric patients undergoing HSCT for childhood AML [33].

Given the data summarized here, it is apparent that women treated with childhood TBI need lifelong breast cancer screening. We do not yet have tools to select those at highest risk for whom even closer surveillance is appropriate. However, a recent study reported at the 2016 annual meeting of the American Association for Cancer Research offers hope that such tools may eventually become available [34]. Dr. L. M. Morton and colleagues at the National Cancer Institute looked for genomic variants in female patients who developed breast cancer after childhood chest radiotherapy. They found two variants at two genetic loci associated with an increased risk, one with a hazard ratio of 1.96, and the second with a hazard ratio of 3.71. While these are preliminary findings, they suggest that these or other genomic variants may define a population with an increased susceptibility of breast tissue to the carcinogenic effects of radiation, and in the future may help select patients for more intense surveillance. However, until we have such selective tools, *all* females exposed to chest or breast radiation in childhood or adolescence will require close surveillance as adults.

Conclusions

The studies cited in this report demonstrate clearly that exposure of female breast tissue to radiation from early menarche to young adulthood is associated with an increased risk of breast cancer, extending from young adulthood into at least the sixth decade of life. Oncologists have long been cognizant of the risk associated with mantle field and other high levels of radiation exposure. The reports of the substantial breast cancer risk following low-level total body radiation used before stem cell transplantation have heightened that awareness.

When these children become adults, their medical care falls mainly to primary care providers, who are less likely than oncologists to be aware of these risks. Because breast cancer surveillance is not prioritized in the care of young women, the opportunity for potentially life-saving early detection is diminished. Until such time as we can identify individuals who are at uniquely high risk based upon genomic profiling or other as yet unidentified factors, all young women with a history of chest wall or breast radiation exposure in childhood or early adulthood should be counseled about their breast cancer risk, and should undergo lifelong breast cancer surveillance.

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