

Male Breast Cancer During Treatment With Leuprolide for Prostate Cancer

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Male breast cancer accounts for less than 1% of all cancers in men. Risk factors for male breast cancer include family history, Klinefelter syndrome, and radiation therapy.¹ *BRCA2* mutations are found in approximately 4% of all cases and in 15% of cases with a first-degree relative who has breast cancer.² Leuprolide is an effective treatment for prostate cancer and is useful in the prevention and treatment of hormone receptor–positive breast cancer.^{3–6} Therefore, it is unusual to diagnose male breast cancer in a patient receiving androgen deprivation therapy with leuprolide.

Case Presentation and Management

An 81-year-old white man with a prostate-specific antigen (PSA) level of 10.85 mg/dL was found to have a 20 gram prostate with a suspicious nodule at the left base. A biopsy of the prostate revealed adenocarcinoma (Gleason score, 5+4=9). He had several serious medical comorbidities, including depression, hypertension, osteoarthritis, and glaucoma. Family history was notable for a daughter with breast cancer at age 44. Neoadjuvant androgen deprivation was initiated with 1 month of bicalutamide 50 mg daily, overlapped after 2 weeks with leuprolide acetate 22.5 mg. He was subsequently treated with 76 Gy external-beam radiation concurrent with leuprolide; the latter was continued for 16 additional months.

Fifteen months after completion of radiation therapy, the patient's PSA remained undetectable but a new nontender mass in his left breast associated with nipple retraction was observed. Imaging demonstrated a 2.4 cm

subareolar mass and a 2 cm left axillary mass. A needle biopsy of the left breast mass revealed adenocarcinoma. Bone scans and computed tomography scans were negative for metastatic disease. He underwent a left modified radical mastectomy after sentinel lymph node mapping demonstrated metastatic nodal disease. Pathology revealed a 3 cm pG3T2N1aM0, Stage IIB invasive ductal carcinoma of the breast. Estrogen receptor status was positive, progesterone receptor and HER2 were negative.

Postoperatively, the patient declined adjuvant chemotherapy and anastrozole 1 mg daily was initiated. Genetic counseling revealed a rare *BRCA2* mutation (K1025E variant). *BRCA2* testing in his daughter was negative.

Discussion

To our knowledge, this is the first reported case of male breast cancer in a patient receiving leuprolide therapy for prostate cancer. Several large prospective randomized controlled trials have established the benefits of androgen-deprivation therapy in localized prostate cancer.^{3–5} In those studies examining the benefit of gonadotropin-releasing hormone (GnRH) agonists (leuprolide, goserelin), there were no reported cases of breast cancer. The risk of male breast cancer with long-term steroidal antiandrogens is well established. In one prospective randomized study, 1,554 patients with benign prostatic hyperplasia received finasteride 5 mg daily. With a median follow-up of 4.5 years, the risk of breast cancer while taking finasteride was 0.25%.⁷

Surgery remains the principal treatment for breast cancer in men. The rarity of male breast cancer precludes large prospective adjuvant trials. As most male breast cancers are strongly estrogen receptor–positive, hormonal therapy is commonly utilized as adjuvant therapy. Tamoxifen, megestrol acetate, aromatase inhibitors, and

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surgical castration have all been utilized. Leuprolide has been shown to be efficacious for men with breast cancer.¹ It is anticipated that androgen deprivation may decrease the risk of breast cancer in men, suggesting that in this case the breast cancer likely represents resistance to leuprolide. This case suggests that a new mass in the breast of a prostate cancer patient must be evaluated for carcinoma despite treatment with leuprolide.

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Review

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In 2007, an estimated 180,510 new cases of breast cancer will be diagnosed in the United States, of which 2,030 (1%) will be diagnosed in men.¹ Due to the rarity of the disease, demographic data and information on therapeutic intervention have largely been obtained from retrospective reviews of single-institution experiences and individual case reports. Yacoub and colleagues² describe a case of an 81-year-old *BRCA2* mutation-positive male patient with prostate cancer who developed Stage II hormone receptor-positive breast cancer while on long-term treatment with leuprolide acetate. This case is unusual because leuprolide is known to be an active therapy for hormone receptor-positive breast cancer; therefore, the development of a new primary while receiving treatment is unexpected. This case raises several important issues regarding male breast cancer.

First, the case described by Yacoub and colleagues illustrates the known association between *BRCA* mutations and male breast cancer. Although mutations in *BRCA1* do not appear to confer a marked increased risk,³ *BRCA2* mutations are associated with higher rates of male breast cancer. The prevalence of *BRCA2* mutations in families with female and male breast cancer cases has been reported to be as high as 60%,⁴ although most population-based estimates are approximately 5–15%.⁵⁻⁷ In addition to having a higher risk of breast cancer, *BRCA2* mutation carriers have been reported to have higher rates of prostate cancer.⁸ The patient described in the case report has a family history of breast cancer in a first-degree relative, as well as a personal history of male breast cancer and prostate cancer. This history is highly suggestive of a *BRCA2* mutation, and genetic testing was appropriate. National

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Comprehensive Cancer Network guidelines currently recommend that all patients with male breast cancer be referred to a cancer genetics professional for consideration of *BRCA* testing, particularly if there are other familial cases of breast or ovarian cancer.

This case also raises the related issue of the increased incidence of second primary cancers among men with breast cancer. In an analysis of data from the SEER registry, Auvinen and associates reported that men with breast cancer were more likely to have prostate cancer and melanoma.⁹ It is unclear whether this increase in risk is related to *BRCA* mutations or to a more general phenomenon. Men with breast cancer also have a marked increase in risk of a second breast cancer when compared to men in the general population.¹⁰ However, the absolute risk of contralateral breast cancer in a male patient is low, at less than 2%.

In the case described by Yacoub and colleagues, the patient presented with typical clinical features of male breast cancer with a painless mass that was estrogen receptor–positive and did not overexpress HER2/neu. Over 90% of male breast cancers are hormone receptor–positive,¹¹ but male breast cancer has lower rates of HER2/neu overexpression and gene amplification compared to female breast cancer.¹² As with female breast cancer patients, these features, together with histologic grade and tumor size, are prognostic factors. In addition, presence and number of involved lymph nodes are known to be a strong predictor of survival.¹³

Other aspects of the case illustrated by Yacoub and colleagues are intriguing. First, the patient developed breast cancer while receiving the GnRH analog leuprolide. With the presence of a *BRCA2* mutation and a positive family history, the patient was already at a higher risk of developing breast cancer. The administration of leuprolide stops production of testicular androgens but does not eliminate production of adrenal androgens, a known source of estrogens through peripheral aromatization. However, it is doubtful that leuprolide predisposed this patient to breast cancer as it is an active therapy for hormone receptor–positive breast cancer. As the authors note, it is important to recognize that a man can develop breast cancer even if on therapy with leuprolide.

The use of anastrozole in the adjuvant setting is also of interest. Although there are no prospective trials addressing the use of hormonal agents in men with breast cancer, several retrospective studies have compared outcomes of men treated with and without tamoxifen and have suggested a benefit of tamoxifen.¹⁴⁻¹⁶ There are several case reports showing efficacy of aromatase inhibitors, but the degree of activity in male breast cancer is not known. In a small preclinical study, healthy men who

were given aromatase inhibitors had a 50% decrease in estrogen levels but also had increases in testosterone.¹⁷ At present, more data regarding the effectiveness of aromatase inhibitors in male patients are clearly needed because ongoing controversy exists as to the optimal adjuvant hormonal regimen.

In summary, the case reported by Yacoub and colleagues illustrates several important issues regarding male breast cancer: the prevalence of *BRCA* mutations, the need for genetic counseling, the risk of second primaries, and the lack of data regarding hormonal therapies. More information on optimal clinical management is needed so that clinicians and patients can make informed decisions about therapy. We encourage additional research on this rare disease that is both similar to and different from that encountered in women.

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