

54-Year-Old Man With Breast Cancer After Prolonged Testosterone Therapy

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A 54-year-old man underwent a right simple mastectomy and sentinel lymph node biopsy for a 2.2-cm, grade III/III, sentinel lymph node–negative, estrogen receptor (ER)–positive, progesterone receptor (PR)–positive, and human estrogen receptor (HER)-2–nonoverexpressing infiltrating ductal carcinoma. There was lymphovascular invasion. The patient has been receiving testosterone enanthate (200 mg intramuscularly every 3 weeks) for the last 10 years for primary hypogonadism due to bilateral undescended testicles. There is no family history of breast or ovarian cancer. His postoperative examination was remarkable for moderate left-sided gynecomastia. Staging chest/abdomen/pelvis computed tomography scan and bone scan were normal. Chemistries and complete blood counts were normal. Serum testosterone levels were 781 ng/dL 3 days after his last testosterone injection (normal range: 230–750 ng/dL) and 36 ng/dL just prior to his next planned injection.

Male breast cancer (MBC) may become a more common diagnosis in this country as more of the population becomes overweight, given the association between weight gain in adulthood and breast cancer risk.¹ Also, the increased use of testosterone therapy for “male menopause” could contribute to an increased risk.^{2,3} Several questions arose in considering recommendations for this patient regarding adjuvant therapy and ongoing care.

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First, with the advent and now established role of aromatase inhibitors as standard adjuvant therapy for ER- or PR-positive tumors in postmenopausal woman, are there clinical, laboratory, or other considerations favoring tamoxifen over aromatase inhibitors for ER- or PR-positive MBC? Is the choice age-dependent?

Next, is it likely that the testosterone injections this patient received increased his risk for developing breast cancer, and should they be discontinued because they could increase either recurrence risk or the risk of developing a new primary breast cancer? Higher testosterone levels have been associated with increased risk in postmenopausal woman² and androgens are normally metabolized to estrogens.³

Finally, can the estimates of absolute reduction in recurrence risk for a woman receiving chemotherapy preceded by hormonal therapy, compared to hormonal therapy alone, be applied to this patient? Also, is the role for adjuvant radiation therapy for MBC patients different from that for women with breast cancer?

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Review

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A case of MBC in a hypogonadal male who was supplemented with testosterone enanthate 200 mg every 3 weeks is reported. Pathologically, the tumor presented as an ER(+) ductal carcinoma, similar to more than 70% of MBC cases.¹ The report poses a number of questions, including whether the occurrence of the disease indicates an association with testosterone supplementation or whether this is merely a coincidence.

Although there are arguments for the role of androgens in female breast cancer (FBC), an increase of MBC risk may be attributed rather to increased estrogen or an imbalance of androgen and estrogen: first-born males had a higher risk than the following siblings²; 60% of MBC patients have a history of a medical condition known to cause gynecomastia³; and men with Klinefelter's syndrome have a 50-fold increased lifetime risk of developing MBC.⁴ MBC was also described following estrogen therapy for prostate cancer.⁵ However, there is no association between these 2 cancers: neither is the incidence of prostate cancer increased in men with MBC,⁶ nor have patients with prostate cancer an increased incidence of MBC.⁷

It is also unlikely that changes in the androgen receptor gene substantially contribute to MBC risk. In general, a higher percentage of MBC than FBC is positive for estrogen and gestagen receptors. Neither mutations in the androgen receptor gene, which induce partial androgen insensitivity in the male,⁸ nor the length of CAG repeats enhance the susceptibility for MBC.⁹

The suggestion that high testosterone levels contribute to the risk of MBC similarly to the induction of FBC by estrogens is thus questionable. No case control studies concerning testosterone supplementation in hypogonadism and the occurrence of MBC are available in the literature.

More than endocrine factors, mutations of distinct genes appear to be of importance. They are estimated to account for up to roughly 10% of MBC. The combination of *BRCA1* and *BRCA2* gene mutations is responsible for approximately 80% of hereditary breast cancers,¹⁰

but *BRCA2* mutation seems to be more important as a risk factor for MBC. Men who inherit a mutation in the *BRCA2* gene carry a 6% risk of developing breast cancer by the age of 70.¹¹

A random association is more likely. Hypogonadism affects an estimated 2–4 million men in the United States, of which only 5% receive treatment (ie, 100,000 men).¹² In 2002, more than 1.75 million prescriptions were written for testosterone,¹³ which corresponds to a mean number of applications of 17.5 per patient per year.

The incidence of MBC is low. Rudan et al gave a figure of 0.83/100,000 per year,¹⁴ meaning that 1 MBC case per year should be expected among men being treated with testosterone.

Nevertheless, this case report may increase awareness of the possible risks of testosterone supplementation in the aging male, and it may support the advisability of excluding men with MBC from testosterone treatment studies.

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