Breast cancer and long-term hormonal treatment of male hypogonadism

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Summary

Breast cancer in men is rare and its etiology is multifactorial. Androgens may promote the development of breast carcinoma in men though data on the subject is scarce. We observed 45 men with hypergonadotropic hypogonadism (aged 18–57) who received 250 mg of testosterone esters (Omnadren 250, Jelfa, Poland) every 3–4 weeks for 5–26 years. Seventeen of them were treated for more than 10 years. During the observation period breast cancer was diagnosed in 2 subjects (11% of the followed men). In one case it occurred after 11 years and in the other after 15 years of the therapy. We point to a possible association between long-term androgen replacement and a risk of breast cancer in men.

Introduction

Breast carcinoma is infrequently found in men. It makes 0.2–1.5% of all malignant tumors in men and less than 1% of all breast neoplasms in both sexes [1–3]. Although breast cancer morbidity is higher in women than in men, the cure rate is considerably lower in men. In males the disease is usually diagnosed late, in more advanced stages, when therapeutic interventions are less effective [4].

Male breast carcinoma is promoted by genetic, environmental and hormonal factors [5–11]. A relationship between long-term androgen therapy and breast carcinoma in men is not sufficiently documented [12]. The issue appears important for hypogonadal men, also those who receive testosterone because of so called andropausal symptoms.

Material

The observed group comprised 45 men with primary hypogonadism (hypergonadotrophic) aged 18–57. They have been treated and subsequently followed by the same physician for 5–26 years (between 1979–2005). Within the group 17 patients received androgens for more than 10 years. The treatment consisted of an ampoule of testosterone esters (250 mg) administered intramuscularly every 3–4 weeks (Omnadren, Jelfa, Poland).

Patients were well informed on the necessity of long-term androgen treatment and they conformed to suggested terms of observation. Only once/twice a year they happened not to receive the planned dose of testosterone.

Results

Two cases of breast carcinoma occurred in the observed group. They made 5.6% of the whole group and 11.2% of the subgroup treated for more than 10 years. Breast carcinoma was not found in any of the men receiving androgens for less than 10 years.

Case 1 – received testosterone between 36 and 47 years of age (for 11 years)

Height 169 cm, body mass 79 kg, blood pressure within normal limits. Healthy in childhood and youth, no neoplasms in the family. Married, no children, working as a coal-miner. In 1992 he underwent subtotal thyroidectomy due to a polinodular goiter with trachea compression (intact thyroid function in the later course).

He was diagnosed with hypergonadal hypogonadism at the age of 35. Testicles were remarkably small (1.5 cm in diameter). At the same time mental and somatic features of hypoandrogenism were present. Hormonal results were: LH – 17.9 mIU/ml, FSH – 38 mIU/ml.
total testosterone 1.6 ng/ml and other parameters within normal limits. Caryotype 46, XY.

During a routine examination, a nodule (2 cm in diameter) in the left breast was revealed. One-sided mastectomy m. Halsted proved the presence of infiltrating ductal carcinoma (sirrhous type) with metastases to level II lymph nodes. Immunohistochemistry showed presence of progesterone (+) and estrogen (+) receptors. The patient was treated with adjuvant chemotherapy and radiotherapy. At present he is in a very good condition (5 years after oncologic treatment).

Case 2 – received testosterone between 21 and 36 years of age (for 15 years)

Height 177 cm, body mass 88 kg, blood pressure within normal limits. Medical history – healthy. Oncologic history in the family – absent. Married, no children, working as a sales representative.

Hypergonadal hypogonadism was diagnosed at the age of 21. Laboratory findings were: LH – 12.0 mIU/ml, FSH – 22.6 mIU/ml, total testosterone 1.81 ng/ml. Other parameters within normal limits. Caryotype 46, XY.

The patient noticed a painless nodule (1.5–2.0 cm in diameter) in the left breast. Lymph nodes were not involved. Post-operative examination revealed carcinoma scirrhosum with presence of estrogen receptors (+ + +). The treatment of this patient is carried in another medical centre – there is no further data available.

Discussion

Breast carcinoma is found more often in men over 60 years of age, in men of Black or Jewish origin and after radiotherapy of the chest [5,8,13]. There is no doubt that carcinogenesis within the male breast is influenced by genetic factors [7,10,11]. It has been also shown that diet rich in vegetables and high consumption of coffee decrease, while an excess of beta-carotene, vitamin E and calcium in food may increase the risk of breast cancer [7,14,15]. Results of several studies suggest that men with higher educational and socioeconomic status, without children, exposed to electromagnetic fields, high temperatures or polycyclic aromatic hydrocarbons are more prone to develop breast cancer [5,16–18]. It has been hypothesized that there is a relationship between male breast cancer and administration of serotonin reuptake inhibitors [19]. Another factor postulated in the pathogenesis of breast carcinoma in men is an excessive exposition to estrogens (of endogenous and exogenous origin) [20]. It includes hiperestrogenism in Klinefelter syndrome, estrogen/androgen imbalance in the diseases of the liver, kidney and circulatory system, in adiposity, alcohol abuse or during therapy with antiandrogens (spironolactone, cimetidine, finasteride) [7, 21–25].

All men in our observation had idiopathic hypergonadotropic hypogonadism and Klinefelter syndrome was excluded in each of them. Men from within the group did not suffer from any chronic illnesses and did not receive medications that could affect the observed outcomes. The group was homogenous as to the strategy of treatment, the same form of testosterone administered, one supervising physician and a regular follow-up (with high adherence to suggested control). Psychosomatic effects of the therapy were optimal, though bone density measurements suggested it was not enough intensive [26].

Seventeen subjects in our observation received testosterone for more than 10 years. In two of them (11.7%) breast carcinoma was diagnosed: in one case after 11 and in the other after 15 years of treatment. In both cases expression of estrogen receptors was found in tumor specimens.

To our knowledge, there is no evidence on an association between long-term androgen treatment and breast carcinoma in men. In MEDLINE database we have not found reports with a study group similar to the one followed by us.

Most of the exogenous androgens (especially testosterone esters) are converted to estradiol. The rate of conversion is dependent on the dose of androgens, their chemical structure and the local activity of aromatase [27]. Aromatase is the key part of an enzymatic complex responsible for the transformation of androgens to estrogens. Activity of aromatase is influenced by genetic factors, race, sex and age.

Locally synthesized estrogens seem to be crucial for breast carcinogenesis. Their synthesis is regulated by autocrine and/or paracrine (not endocrine) mechanisms. It has been showed that aromatase is an important autocrine tumor growth regulator in ER(+) breast cancer. Aromatase may suppress or stimulate promotor genes in reaction to intracellular growth factors. Genotoxic effects of aromatase consist of an increase of the number of mutations and a direct impact on the system of DNA repair [28].

Estrogens are transformed to catechol estrogens: 2-hydroxyestriadiol, 4-hydroxyestriadiol, 16-alpha-hydroxyestriadiol and 4-hydroxyestrone [29]. They may bind to estrogen receptors and cause their permanent activation. According to a popular model of cancerous process, catechol estrogens influence an oxidative damage of DNA in breast epithelium [30].

Essential mutations occur mainly due to interactions between DNA and 4-hydroksy metabolites of estrogens, while 2-hydroksy derivatives may inhibit cancerous cells proliferation [31,32].

In summary there are at least three mechanisms that are considered to be responsible for the carcinogenicity of estrogens: receptor-mediated hormonal activity; a cytochrome P450 (CYP)-mediated metabolic activation, which elicits direct genotoxic effects by increasing mutation rates; and the induction of aneuploidy by estrogen [33]. Estrogens increase the rate of cell proliferation by stimulating estrogen receptor-mediated transcription and thereby the number of errors occurring during DNA replication. An alternative hypothesis proposes that