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Case Report

Treatment of testosterone-induced gynecomastia with the aromatase inhibitor, anastrozole

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Gynecomastia is an unusual side effect associated with testosterone replacement therapy (TRT) that has been traditionally treated with surgery, radiation, or discontinuation of testosterone supplementation. We report here our experience with two cases of gynecomastia in men undergoing TRT who were successfully treated with the aromatase inhibitor anastrozole.
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Introduction

Testosterone replacement therapy (TRT) in hypogonadal men has become more common as health care providers have become increasingly aware of andropause and the benefits of treatment. However, administration of exogenous testosterone can be associated with side effects that include effects on the prostate, hematocrit, fertility and the development of gynecomastia. Gynecomastia is believed to arise from peripheral conversion of testosterone to estradiol via the enzyme aromatase. The condition is embarrassing to men, and may cause discontinuation of testosterone treatment that has otherwise been successful.[1]

Classically, male gynecomastia has been treated with radiotherapy or surgical resection of the breast gland tissue.[2] The introduction of a new generation of aromatase inhibitors has created an opportunity to treat testosterone-induced gynecomastia with oral medications alone.

We report here our experience with the use of an aromatase inhibitor, anastrozole, in the treatment of gynecomastia in hypogonadal men receiving testosterone supplementation.

Case reports

Case 1

A 61-y-old man presented with a history of erectile dysfunction and reduction in libido, and difficulty achieving orgasm. Past medical history was notable for left gynecomastia in adolescence, which was treated surgically without further recurrence. The current physical examination was unremarkable. Blood tests showed FT of 0.8 ng/dl, TT of 295 ng/dl, luteinizing hormone (LH) of 3.4 mUI/l (normal: 2–18 mUI/l), follicle-stimulating hormone (FSH) of 3.4 mUI/l (normal: 2–18 mUI/l) and PSA of 1.5 ng/l (normal: 0–4 ng/l). Reduced peak rigidity was observed by NPTR. Intramuscular injections of testosterone enanthate 400 mg/3 weeks were started. The nadir total testosterone level was 287 ng/dl. The patient experienced significant symptomatic improvement with testosterone supplementation.

At 6 months after beginning treatment, the patient noted gynecomastia on the right side, which had not received earlier surgical treatment as an adolescent. TRT was discontinued and 1 month later the patient reported complete resolution of the gynecomastia. Testosterone supplementation was resumed at the same schedule as before, and anastrozole (Arimidex®, AstraZeneca, London, UK) 1 mg/day orally was started as well. After 3 y, the patient

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continues to have clinical benefits from TRT without recurrence of gynecomastia.

Case 2

A 30-y-old man presented with a history of erectile dysfunction, reduced libido and fatigue. Physical examination was normal except for moderate obesity and mild bilateral gynecomastia. Blood tests revealed TT of 220 ng/ml, FT 1.1 ng/ml, FSH 0.9 mUI/l, LH 3.7 mUI/l and prolactin (PRL) 8.2 ng/ml (2.1–17.7 ng/ml). Poor erections were noted on NPTR. Treatment with intramuscular injections of testosterone enanthate 200 mg/2 weeks was initiated. After 6 months, the patient reported worsening of his baseline bilateral breast enlargement and new nipple tenderness. Peak serum levels of FT were 4 ng/dl. Estradiol levels were elevated at 103 pg/ml (normal: 10–52 pg/ml). Testosterone replacement was discontinued and anastrozole (Arimidex®, AstraZeneca, London, UK) 1 mg/day was initiated. After 1 month, the patient reported decreased breast size and resolution of his nipple tenderness. TRT was then re-introduced. After 5 months, the patient reported significant improvement in his baseline symptoms without return of any breast changes.

Discussion

We report here our successful experience using medical therapy with the aromatase inhibitor anastrozole for the treatment of gynecomastia induced by TRT in hypogonadal men.

Aromatase is the enzyme responsible for converting androgens to estrogens, and is widely distributed in several tissues such as brain, liver and reproductive tissue.[1] In men, estrogen production occurs mainly by extratesticular aromatization of androstenedione to estrone and of testosterone to estradiol.[1]

Aromatase inhibitors have been used primarily in the adjuvant treatment of breast cancer by reducing estrogen levels and consequently causing reduced stimulation of estrogen receptors in this disease. Anastrozole is a fourth-generation nonsteroidal competitive aromatase inhibitor with potent suppression of serum estradiol levels. It was approved by the Food and Drug Administration in 1995 for the treatment of estrogen receptor-positive breast cancer in postmenopausal women in whom the disease has progressed despite tamoxifen treatment.[3] Serum estradiol was reduced by up to 80% in patients with breast cancer treated with this drug.[4] Other aromatase inhibitors, such as the first-generation aminoglutethimide, have limited use due to toxicity and lack of selectivity for the aromatase enzyme, necessitating concomitant corticosteroid supplementation in some cases.[5]

In men, aromatase inhibitors have been used in the treatment of male infertility, in the hopes of achieving an improved testosterone-to-estradiol ratio. Raman and Schlegel[3] noted significant improvement in sperm concentration, motility and morphology in a group of men treated with anastrozole. No benefit was noted in azoospermic individuals. Gillam *et al*[6] recently reported a case of a giant prolactinoma treated with bromocriptine and cabergoline. The associated hypogonadism was successfully managed with TRT and anastrozole. Herzog *et al*[7] reported beneficial effects on sexual function and control of seizures in men using the aromatase inhibitor testolactone with TRT.

Theoretical adverse effects of aromatase inhibition in men include effects on body composition, carbohydrate/lipid metabolism, muscle strength, bone density and infertility.[7,8] Estrogens have been shown to have important beneficial effects on bone density, even in males;[8] however, the long-term effects on bone density in men receiving both testosterone supplementation and an anti-estrogen such as anastrozole are uncertain. However, no large-scale studies of anastrozole have been performed in men, and so there is limited information regarding its side effects in this population. In a series of infertile men treated with anastrozole, an asymptomatic increase in serum liver enzymes was observed in 7.4% cases, which returned to baseline levels after discontinuation of the medication.[3]

The development of gynecomastia in hypogonadal men undergoing TRT can be very troubling to affected individuals, and may result in cessation of therapy. Since TRT is generally considered elective because it is administered for quality of life rather than for a life-threatening illness, both radiation therapy and surgical treatment are often regarded by patients and physicians alike as being too invasive a treatment for gynecomastia and, instead, testosterone treatment is often discontinued by patients if they are embarrassed by the breast enlargement. Successful treatment with an oral medication such as an aromatase inhibitor thus represents an attractive alternative therapy, and should be considered for symptomatic men.

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