



Increased Risk of Male Breast Cancer with Prolactinoma: A Case Report

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Abstract

This case is reported of a 52 year-old male who, seventeen years after the treatment for a prolactinoma and over ten years after the onset of bilateral gynecomastia, developed left sided breast cancer. Ductal carcinoma in situ was found incidentally after he decided to have a left breast mass excised for symptomatic gynecomastia. Pathology reported a 1.0 cm, ductal carcinoma in situ, cribriform, grade 1, estrogen receptor (ER) positive, and progesterone receptor (PR) positive mass which later required a completion mastectomy. The patient was also consequently found to have a decrease in testosterone levels requiring high doses of testosterone replacement therapy. BRCA testing was recommended. In review of the patient's breast cancer family history, only a paternal aunt was identified. The patient was considered a candidate for contra lateral total mastectomy due to high levels of testosterone replacement and concerns with estrogen conversion. However, genetic testing was found to be negative and endocrine therapy (tamoxifen) was initiated as the patient requested to be treated conservatively.

Keywords: Male breast cancer; Breast cancer; Prolactinoma

Introduction

The pituitary is a small gland located at the base of the brain. It contains lactotroph cells that produce prolactin, a polypeptide hormone that stimulates lactation and influences fertility. Prolactin producing tumors develop when a normal lactotroph cell develops a mutation that permits the cell to divide continuously, resulting in the production of high levels of prolactin in the blood. Animal studies have reported that high levels of prolactin, through autocrine/paracrine signaling pathways, induce proliferation of breast tissue cells and enhance growth of mammary carcinoma in mice [1,2]. Cases of breast carcinomas in women and men with prolactinomas have been reported [3-5] raising the question of whether high prolactin levels increase risk of breast cancer in humans. Furthermore, elevated prolactin levels interfere with the function of sex organs in women and men resulting in diminished gonadal sex hormone production. Hormone replacement therapy is then typically sought after and initiated. While the beneficial effects of this therapy are seldom refuted and widely advertised, it has been recently suggested that testosterone replacement therapy may in fact increase one's chance of developing breast cancer [6].

Case Presentation

In 1999, a 35 year old obese man was treated with surgical excision of the pituitary gland for a tumor, however, his symptoms of gynecomastia, decreased libido, energy and strength progressed. On further investigation, it was discovered that his tumor had recurred requiring re-excision in 2010. The tumor was classified as a prolactinoma. At that time the serum prolactin level was 34.0 mg/ml (reference range 2.0-14.0). Five years later, the patient continued to complain of bilateral gynecomastia as well as a new onset subareolar pain of the left breast. Sonographic evaluation of the subareolar region revealed focal hypoechoic fibroglandular tissue that was reported to have the appearance of mild gynecomastia with no discrete mass identified. A left excisional biopsy was done. Histopathologic examination revealed ductal carcinoma in situ, cribriform pattern, nuclear grade I/III and gynecomastia. The receptor status was ER+ (100%) and PR+ (100%). After careful review of the pathology, a completion mastectomy was performed one month later. Histopathologic examination revealed a minute focus of residual DCIS. After these procedures, an MRI of the brain was also performed which reported the area of the pituitary gland as negative for any suspicious pathology. Hormonal investigation revealed below normal testosterone levels. Testosterone supplementation was started by his endocrinologist; however, concerns were raised regarding the conversion of testosterone to estrogen hormones with concerns that it could possibly lead to the

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Received Date: 24 May 2018

Accepted Date: 27 Jul 2018

Published Date: 05 Apr 2018

Citation:

Abghari M, Tamkus D, Bumpers H. Increased Risk of Male Breast Cancer with Prolactinoma: A Case Report. Clin Oncol. 2018; 3: 1454.

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development of contra lateral breast cancer. He was then evaluated by breast surgical oncology for evaluation for possible prophylactic total mastectomy. The patient requested to be treated conservatively. Tamoxifen therapy was initiated.

Discussion

Breast cancer is one of the rarest forms of cancer in men; however, the incidence is significantly increasing. According to Giordano et al, the incidence has significantly increased from 0.86 per 100,000 population to 1.08 per 100,000 population in the past 45 years [7]. This has led to a growing interest in searching for etiologic factors. Multiple variables have been found to increase the likelihood of breast cancer; the most important of these being prolactin and estrogen levels in the blood [8].

Prolactin and estrogen are important in normal mammary gland growth and development. The theory of prolactin as a causative factor in breast cancer was initially suggested over 4 decades ago based on data obtained from mice models [2]. The exact mechanism is not known, however, what has been suggested is that high circulating levels of prolactin increase synthesis and expression of prolactin receptors in malignant mammary tissue thus causing a prolactin induced increase in DNA synthesis in breast cancer cells [2].

Hyperprolactinemia in humans, in the majority of cases, is caused by a prolactinoma [9]. Symptoms associated with this condition typically present months to years later, resulting in continuous exposure of high levels of prolactin for extended periods of time. Interestingly, some antipsychotic agents have been shown to have the same effect. By blocking D2 receptors on lactotroph cells, the inhibition of prolactin secretion is put to a halt causing a two to ten-fold increase in prolactin levels in the blood [8]. A retrospective study comparing women who were exposed to prolactin-raising antipsychotics with women who were not revealed a small, but significant increased risk of breast cancer [8]. In contrast to the situation in mice models, the function of prolactin in the etiology and development of human breast cancer is not clear and requires further investigations with larger cohorts.

Estrogen is considered to play a major role in the production of both normal and abnormal breast tissue. Its role as a breast carcinogen has long been suspected and confirmed by multiple epidemiological studies [10].

Three major mechanisms are postulated to be involved;

- 1) Receptor mediated stimulation of cellular proliferation,
- 2) Cytochrome P450-mediated metabolic activation causing increased mutation rates,
- 3) The beginning of aneuploidy [10].

Thus, the role of estrogen in breast cancer has been deeply studied and is well known, however, the role of testosterone has yet to be described. One proposed theory is that excess circulating testosterone can be aromatized into estrogen which has been shown to increase human prolactin receptor gene expression within the peripheral tissues which in turn directly stimulate breast tumor cell proliferation [11,12]. When high blood prolactin concentration interferes with the function of the testicles the production of testosterone decreases, as was the case for our patient. This is done by prolactin-induced inhibition on the secretion of gnRH through prolactin receptors on hypothalamic dopaminergic neurons [13]. Low testosterone

levels place men in a hypogonadal state, causing decreased libido, energy, and strength, which eventually lead to adverse psychological events. Testosterone supplementation has become more common for treatment; however, exogenous administration does not come without its risks.

A suggested treatment route to alleviate this increased risk is endocrine therapy. Tamoxifen is an estrogen receptor antagonist used as adjuvant therapy in the treatment of ER positive breast cancer. Another mechanism of action recently discovered is its ability to block the prolactin receptors in mammary epithelial cells [14]. The decrease in prolactin levels seen with this treatment has been shown to dramatically decrease transformation and tumorigenic properties of such cells suggesting that tamoxifen may be clinically useful in the treatment of hyperprolactinemic breast cancer patients. However, further studies on hyperprolactinemia and hormone levels in men with breast cancer are warranted in order to increase our understanding of the optimal setting for breast cancer development and treatment.

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