

## Gynecomastia and Galactorrhea in Male Older Patients: Distinguish Between Drug Induced or Prolactinomas?

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### ABSTRACT

Finding the cause of gynecomastia and galactorrhea can be challenging, hence one of the most important cornerstones is detailed case history. Gynecomastia is an enlargement of the breast in males due to hyperplasia of the glandular tissue. Gynecomastia can be caused by physiological (20%), pathological (30%), drugs (10–20%), and idiopathic (25%). We report a case of gynecomastia with prolactin disorder and previous use of antihypertensive medication. A 68 year old man, with hypertensive heart disease, controlled on medication (low dose spironolactone 25mg/day, digoxin 0.25mg/day and diltiazem 30 mg three times a day), for the last 12 months; presented with painful swelling and discharge of bilateral breasts for the last 14 days; on examination of both breasts a firm, mobile lump was palpated under the right nipple; blood tests: blood urea nitrogen (BUN) 12 mg/dL; creatinine 1.1 mg/dL; thyroid stimulating hormone (TSH) 0.57  $\mu$ U/mL; luteinizing hormone (LH) 12,0 IU/mL; testosterone 6,41 ng/mL; estradiol 111,8 pmol/L; prolactin 87.5 ng/mL. Head magnetic resonance imaging (MRI) was performed; multiple chronic lacunar infarcts, intrasellar and suprasellar were normal and no mass or infection was visible. The probable cause was attributed to spironolactone and digoxin, the medications were stopped; the patient's pain and swelling improved and returned to normal after 2 months of discontinuation, prolactin was assessed at 0.193 ng/mL. Gynecomastia due to spironolactone has many mechanisms: blockade of androgen receptors, prevent binding of testosterone and dihydrotestosterone; decrease testosterone production from testes, increase estrogens by enhancing peripheral conversion of testosterone to estradiol. It has been suggested that digoxin binds to the estrogens receptor and may directly stimulate breast tissue proliferation, inducing gynecomastia. Spironolactone is known to cause gynecomastia, but there are very few case reports of digoxin-induced gynecomastia. No other evidence of prolactinoma in this case. It is important for the clinician to keep this in mind; although low doses combination between spironolactone and digoxin may cause gynecomastia.

**Keywords:** Gynecomastia, galactorrhea, spironolactone, prolactin, digoxin

## INTRODUCTION

Finding the cause of gynecomastia and galactorrhoea can be challenging, hence one of the most important cornerstones is detailed case history. Gynecomastia is very common. Up to 70% of all boys develop pubertal gynecomastia and up to two-thirds of all adult men might have palpable breast tissue on examination.<sup>1</sup> Gynecomastia can be caused by physiological (20%), pathological (30%), drugs (10–20%), and idiopathic (25%).<sup>2</sup> It is a clinically significant phenomenon commonly observed in males during adolescence. While physiological or pubertal gynecomastia is the most frequently encountered cause during this period, other potential etiologies are uncommon but may arise from various pathological conditions, such as obesity, aromatase excess syndrome (AES), primary or secondary hypogonadism, congenital adrenal hyperplasia, Klinefelter syndrome (KS), testicular feminization syndrome, adrenal and testicular tumor, hyperthyroidism, liver and renal diseases, and malnutrition. Additionally, certain medications have been shown to induce proliferation of male breast tissue.<sup>3</sup> Drugs are causative in approximately 20% of men presenting with gynecomastia.<sup>4</sup> Spironolactone, an aldosterone antagonist, is associated with gynecomastia. Digoxin, which can also cause gynecomastia.<sup>5</sup> Prolactinomas represent the most common secretory tumor of the pituitary gland. Clinical presentation may be due to prolactin over-secretion, localized mass effect, or a combination of both.<sup>6</sup> In men, the main complaint is usually associated with hypogonadism, namely decreased libido, erectile dysfunction, and gynecomastia.<sup>7</sup> The challenge facing endocrinologists lies in their ability to distinguish between drug induced and prolactinoma causes of gynecomastia and galactorrhoea.

## CASE ILLUSTRATION

We present a case of a 68 year old man with gynecomastia and galactorrhoea. He also had symptoms suggesting hypertensive heart disease and the diagnosis was confirmed by physical examination, chest X ray and

electrocardiogram in the previous hospital. Therapy with spironolactone 25 mg/day, digoxin 0.25mg/ day and diltiazem 30 mg three times a day (tid) was prescribed earlier by his internist already in 1 year.

He was admitted with bilateral breast tenderness with discharges, pain and symmetrical enlargement, occurring 2 weeks before the present hospital admission. He also noted decreased sexual desire and became impotent during spironolactone administration. No complaints about vision and other conditions. Physical examination of his breasts was consistent with the diagnosis of bilateral gynecomastia and galactorrhea. On examination, there was no ulceration, nipple retraction or skin color changed and discharge was expressed from the nipple. The size was about 3 cm on both breasts. Normal scrotal on examination. Imaging by breast ultrasound was not performed. Routine biochemical test included blood urea nitrogen (BUN) 12 mg/dL; creatinine 1.1 mg/dL; thyroid-stimulating hormone (TSH) 0.57  $\mu$ IU/ml; luteinizing hormone (LH) 12.0 IU/mL; testosterone 6.41 ng/mL; estradiol 111.8 pmol/L; levels of serum prolactin; 87.5 ng/mL and we conducted a head magnetic resonance imaging (MRI) without contrast. The result was multiple chronic lacunar infarcts, intrasellar and suprasellar were normal and no mass or infection was visible. The probable cause was attributed to spironolactone and digoxin. The medications were stopped; and replaced with candesartan 16 mg/ day, diltiazem 100 mg/day and initiated bromocriptine 2.5 mg/ day. The patient's pain and swelling improved and returned to normal after 2 months of discontinuation bromocriptine stopped while known prolactin level was at 0.193 ng/mL, and dual therapy antihypertensives still continuing to control hypertensive heart disease.

## PATHOGENESIS

Receptors for androgens, estrogens, progesterone, and prolactin are found in the male breast. It has been shown that estrogens stimulate breast tissue proliferation, whereas androgens inhibit this process. It is believed that

most cases of gynecomastia are caused by an imbalance of these two influences, with estrogens induced stimulation predominating. Such an imbalance may occur with increased estrogens action on the breast, decreased androgen action, or a combination of the two. This may be due to an increase in circulating or tissue levels of estrogens, a decrease in circulating or tissue levels of androgen, increased responsiveness of the breast to estrogens (e.g. increased numbers of estrogens receptors), or decreased breast responsiveness to androgens (e.g. androgen insensitivity due to receptor mutations or drugs).<sup>8</sup>

Other hormones might also be involved in the development of gynecomastia; prolactin, progesterone, insulin-like growth factor (IGF) 1, IGF 2 and luteinizing hormone (LH and/or human chorionic gonadotropin (hCG) have been found in male breast tissue.<sup>1</sup> Hyperprolactinemia has been associated with gynecomastia, but it probably plays an indirect role by causing hypogonadism although prolactin receptors are expressed in gynecomastia. Only some men with hyperprolactinemia develop gynecomastia, and many men with gynecomastia do not have hyperprolactinemia. It is not clear how prolactin and progesterone might regulate each other in men.<sup>4</sup> Aging is often accompanied by increased adiposity, leading to increased aromatization of androgens to estrogens. Also, serum sex hormone binding globulin (SHBG) levels rise with increasing age, further decreasing the free and bioavailable testosterone. Additionally, older men often have multiple medical problems and require multiple medications, some of which may contribute to gynecomastia.<sup>1</sup>

## DISCUSSION

Various medications and conditions are associated with gynecomastia.<sup>9</sup> It is well known that spironolactone can cause gynecomastia and was described several times in the literature.<sup>10</sup> Spironolactone may increase peripheral conversion of testosterone to estradiol and displace testosterone from SHBG. It is also suggested to bind to peripheral androgen receptors to competitively inhibit

testosterone and dihydrotestosterone.<sup>4</sup> Deepender and Braunstein wrote some expert opinion about spironolactone association with gynecomastia, this medicine level is good quality evidence for gynecomastia. Among 1663 heart failure patients receiving 25mg/day of spironolactone develop gynecomastia in 10% population follow up in 24 months.<sup>11</sup> Digoxin has been suggested to binds to the estrogen receptor and may directly stimulate breast tissue proliferation, inducing gynecomastia.<sup>4</sup> Deepinder and Braunstein also wrote that one of the drugs that can cause gynaecomastia is digoxin, although it is not know if it is dose dependent or not. The time of occurrence after taking this medicine is around 2 months with low quality evidence of associations.<sup>11</sup> The most frequent cause of non tumoral hyperprolactinemia is medications. Neuroleptics or antipsychotic agents are the ones most commonly causing hyperprolactinemia. Medication induced hyperprolactinemia is usually associated with prolactin levels ranging from 25 to 100 µg/L. In this case result levels of serum prolactin of 87.5 ng/mL. Some patients with medication induced hyperprolactinemia remain asymptomatic, and men may present with low libido and erectile dysfunction.<sup>12</sup> Although patients came to the polyclinic with bilateral breast tenderness, pain and symmetrical enlargement, occurring in 2 weeks before. We obtained a pituitary magnetic resonance imaging (MRI) to differentiate between medication induced gynecomastia and symptomatic gynecomastia with hyperprolactinemia due to a pituitary or hypothalamic mass (prolactinoma). The head MRI without contrast imaged was multiple chronic lacunar infarcts, intrasellar and suprasellar were normal and no mass or infection was visible. It is thought that gynecomastia is caused by a medication or recreational drug. Withdrawal from this agent should result in at least some improvement over a period of a few months.<sup>8</sup> The patient was no longer taking spironolactone and digoxin, as at the preferred hospital, only diltiazem 30 mg tid was being administered. At the endocrinology polyclinic, the medication

was replaced to candesartan 16 mg/day and diltiazem CD 100 mg/day.

## CONCLUSION

In conclusion, no causal factors other than the administration of medication could be identified in the present case; these changes regressed upon the discontinuation of spironolactone and digoxin. In patients presenting with symptomatic gynecomastia and galactorrhoea, careful history and physical examination are essential. Appropriate screening laboratory tests must be conducted to identify underlying disorders and inform the subsequent therapeutic approach. The underlying causes of the condition should be addressed and corrected. Further follow-up is required to rule out other potential causes. Further examination and laboratory testing are required to ascertain whether an additional causative disorder or disease is present in this case, to gain a fuller understanding of the underlying pathology.

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