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High dose and long-term use of spironolactone induce gynecomastia in an elderly man with chronic heart failure: a case report



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ABSTRACT

Introduction: Gynecomastia is caused by an imbalance of estrogen and androgen in the male breast tissue. It can be divided into three causes, physiological, drug-induced, and idiopathic. Spironolactone is a potassium-sparing diuretic that has known to pose an antiandrogen effect and can cause gynecomastia.

Case Description: A 75 years old man came for a regular cardiac examination at the hospital. He complained of tenderness and pain at his right breast for the last six months and only getting worse since the previous two weeks. He had a regular appointment with a cardiologist after diagnosed with Chronic Heart Failure Functional Class III, Suspected as Coronary Artery Disease, Hypertensive Heart Disease since January 2017. The patient regularly takes Furosemide

40 mg once a day, Clopidogrel 75 mg once a day, Valsartan 10 mg once a day, Bisoprolol 1.25 mg once a day, and Spironolactone 100 mg once a day. On physical examination, tenderness was felt on the right breast. Fine-needle aspiration cytology examination of the right breast was conducted, the finding was compatible with gynecomastia.

Conclusion: Gynecomastia is a breast enlargement in men that occurred due to hormonal imbalance and most often caused by the side effect of a high-dose and long-term use of Spironolactone. Discontinuation of the spironolactone treatment or switching to other therapy is recommended. However, gynecomastia should not be used as a reason for not prescribing Spironolactone to patients with severe heart failure.

Keywords: chronic heart failure, gynecomastia, spironolactone.

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INTRODUCTION

Gynecomastia is a benign condition of breast enlargement that happens to men, caused by the proliferation of glandular tissue and local fat accumulation. Gynecomastia can make patients feel uncomfortable, cause psychological stress, and harms self-confidence. Meanwhile, pseudo-gynecomastia frequently occurred in men with obesity, without glandular proliferation.¹ Proliferation on breast tissue can occur at any age and can be unilateral or bilateral. Gynecomastia can occur in 36% of young adult men aged 17 to 58 years old, and 50% can be found in men age above 44 years old.²

Gynecomastia can happen because of a physiological process or pathological conditions such as induced by drugs,

endocrine diseases such as a testicular, adrenocortical, pituitary tumor, hyperthyroid, and non-endocrine causes such as cirrhosis, stress, and renal failure.³ Around 20%-25% of new cases of gynecomastia are triggered by drugs. One of the drugs that quite often cause gynecomastia is spironolactone diuretic. Spironolactone mainly works as an aldosterone antagonist. Spironolactone also inhibits testosterone production in the testicle, increases the process of aromatization of testosterone to estradiol, and binds with androgen receptors at some tissues. Thus, spironolactone also works as an anti-androgenic substance.¹ Spironolactone is one of the therapies that must be considered for all patients with ejection fraction less than 35% and severe symptomatic heart failure functional

class III and IV. It was also used when the optimal dose of beta-blocker and ACEI or ARB had been reached, but the patient still symptomatic.⁴

CASE

A 75-year-old man came to the cardiologist for routine examination with a chief complaint of pain on the right side of his chest. The chest also felt tender and heavy for the previous six months, and it is getting worse for the last two weeks before his routine visit to the clinic. The patient routinely checks himself to a cardiologist every month. On examination, complaints such as pain in the left chest that penetrates the back, being crushed, cold sweat were absent. The only complaint was shortness of breath that exaggerated

when the patients do moderate to heavy activity. The patient usually sleeps with three pillows. Urination and defecation frequency was within normal limits. This patient has been diagnosed with chronic heart failure functional class III, coronary artery disease, and hypertensive heart disease since 2017. Since then, he has been prescribed the following medication, furosemide 40 mg once a day, clopidogrel 75 mg once a day, valsartan 10 mg once a day, bisoprolol 1.25 mg once a day and spironolactone 100 mg per day.

The patient appeared to be in full awareness (*compos mentis*) and moderate pain from the physical examination. Blood pressure was 100/80 mmHg, pulse frequency of 84 times per minute, respiratory rate of 22 times per minute, the body temperature of 37°C. The general examination found that eye within normal limits, with no sign of anemia or icterus. From inspection of the chest, it was found that the chest looks symmetric, with slight size differences of the right breast (figure 1). Chest auscultation revealed vesicular breathing on both sides of lung fields. The right breast felt more tender from breast palpation than the left, and the patient complained of pain when the right breast was pressed. From extremities examination, it was warm, and no edema was present. From echocardiography examination, it was found that the patient had coronary heart disease, left heart hypertrophy, with an ejection fraction of 76.74%.

Regarding the breast-related complaint, the patient was consulted with a surgeon. The patient did the fine-needle aspiration cytology examination. The cytology examination from the sample taken from the right breast was compatible with gynecomastia's cells.

Based on these data, the patient was diagnosed with gynecomastia induced by spironolactone. The cardiologist gives the patient furosemide 40 mg once per day, clopidogrel 75 mg once per day, valsartan 10 mg once per day, bisoprolol 1.25 mg per day, and the spironolactone treatment had to be stopped for a month. The surgeon prescribed a treatment of Lanturo^l™ 400 mg once per day and meloxicam 15 mg once per day.

DISCUSSION

Gynecomastia is referred to as a condition where one or both of the men's breasts enlarged.⁵ To differentiate between the true gynecomastia with pseudo-gynecomastia or another kind of breast tumor, proper physical examination through inspection and palpation had to be done. In true Gynecomastia, the tissue will feel tender, concentric around the nipple and areola. Meanwhile, patients with pseudo-gynecomastia do not show a consistency such as a tender mound and do not pose a strong bond with surrounding tissues.¹ This is consistent with what was found in this patient. From chest examination, it was found that the right breast looked slightly larger than the left breast, and on palpation, it was tender.

Gynecomastia is caused by benign hyperplasia from the glandular, fibrous, and adipose tissue that occurred because of the imbalance of estrogen and androgen that affects these breast tissue. Gynecomastia can occur because of many pathological conditions. One of the most common triggering factors is drugs which affect the hormonal balance. It is estimated that drugs, including spironolactone, caused around 10-20% of the gynecomastia.⁵

Spironolactone work as aldosterone antagonist. Spironolactone also inhibits testosterone production in the testicle, increases the process of testosterone aromatization to estradiol, and spironolactone also binds to the androgen receptor in several tissues.¹ Spironolactone inhibits the androgen receptor and prevents the receptor from binding with testosterone



Figure 1. Swelling on the right breast.

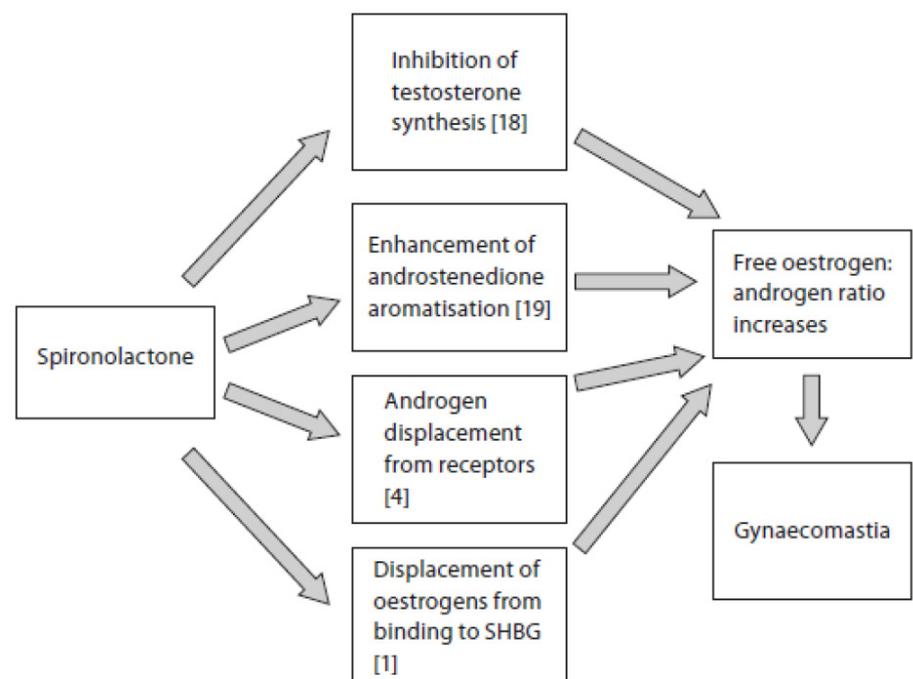


Figure 2. The mechanism of spironolactone involvement in the development of gynecomastia.⁵

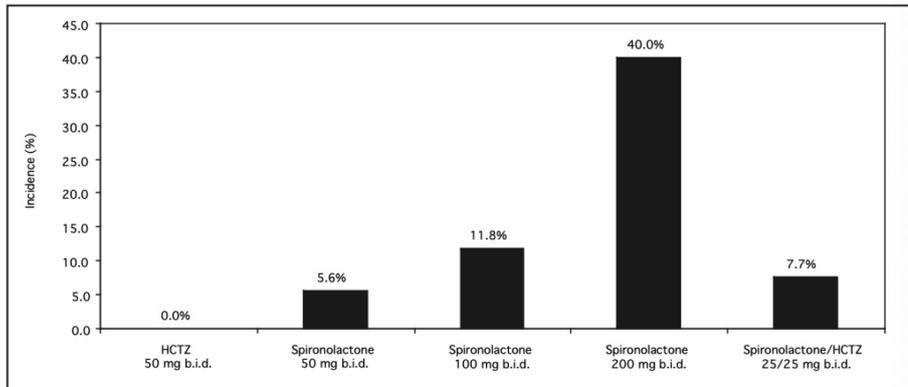


Figure 3. Prevalence of gynecomastia in a double-blinded study of 79 adult men. HCTZ = Hydrochlorothiazide.⁶

and dihydrotestosterone. This substance decreases testosterone production by a testicle and inhibits the 17-alpha-hydroxylase and 17,20-desmolase enzyme. Furthermore, spironolactone replaces testosterone binding with SHBG (sex hormone-binding globulin) and increases the metabolic cleaning of Testosterone. This will escalate the estrogen level by increasing the peripheral testosterone conversion into estradiol (Figure 2). This mechanism augments the level of estradiol in the blood that leads to gynecomastia. However, the involvement of spironolactone with gynecomastia is heavily influenced by its dose and duration of use.^{3,5}

A previous report from the Boston Collaborative Drug Surveillance reported that out of 788 patients with gynecomastia hospitalized, 20.8% of them had a history of using Spironolactone for therapy. Among 79 gynecomastia males with spironolactone therapy, it was found that 5.69% of these patients were on 50 mg of spironolactone twice per day, 11.8% on 100 mg of spironolactone twice per day, 40.4% patients on 200 mg of spironolactone twice per day (Figure 3). The prevalence of gynecomastia increases with the increasing dose of spironolactone consumed.⁶ Another study in France involving 182 patients reported gynecomastia incidence also related to the Spironolactone dose, about 7.0% among the patients who consumed a 25-50 mg spironolactone, 16.7% for 75-100 mg, and 52.2% for 150-300 mg.⁷ In this case, the patient was known to consume spironolactone since 2017. The dose was

100 mg once per day, and he started to feel chest tenderness and pain in June 2019.

Another research by Chapman et al. showed that out of 1790 participants who consumed Spironolactone, gynecomastia occurred in 114 male participants and led to discontinued use in 52 participants.⁸ In a case-control study by Nuttall et al., among the 16 subjects studied, all subjects that received spironolactone and had complaints of swelling on the breast without any pain or tenderness. They also found that the testosterone levels in their blood were significantly decreased while their blood estradiol level increased. This suggests that spironolactone alters the peripheral testosterone metabolism in some men and causes testosterone ratio changes to estradiol. The gynecomastia disappears after they discontinued the spironolactone.²

In this patient, the spironolactone treatment was stopped. He was given another additional therapy by the surgeon, LanturoTM 400 mg per day and Meloxicam 15 mg per day. Discontinuation of spironolactone treatment or replacement with other drugs with similar function is recommended. For example, the canreonate, one of the two spironolactone metabolites, shows a similar therapeutic effect to spironolactone but without the side effects from any other metabolite such as 17-alpha-hydroxyspironolactone, which is responsible for gynecomastia. Eplerenone can also be used as a replacement for spironolactone.⁵ Eplerenone has a lower affinity to androgen and progesterone receptors than spironolactone, thereby minimizing

the risk gynecomastia. However, gynecomastia's risk should not be used as a barrier to prescribing Spironolactone to a man with severe heart failure, as it could significantly decrease the risk of morbidity and mortality.⁹

CONCLUSION

Gynecomastia is breast enlargement in men that can make the patients feel uncomfortable and psychologically stressed. One of the most common causes of gynecomastia is the side effect of prolonged, high doses of spironolactone medication. Spironolactone can cause gynecomastia through several mechanisms that disrupt the balance of estradiol and testosterone level in the blood. The clinician can remind the patient of spironolactone's side effects to prevent drug usage due to their own will, misunderstanding, and anxiety due to side effects. Discontinuation of spironolactone or changing to another therapy with a similar therapeutic function such as Canreonate or Eplerenone is recommended. Side effects such as gynecomastia should not be used as an obstacle for giving spironolactone to patients with severe heart failure, considering that spironolactone can reduce morbidity and mortality risk in patients with heart failure.

DISCLOSURE

Current report has been previously presented in Bali Cardiology Update 2019 as a poster presentation without any prior publication on the event.

ETHICAL CONSIDERATION

The authors had gained consent from the patients to publish his case in an academic journal without revealing any personal identity and solely for academic purposes.

CONFLICT OF INTEREST

The authors stated that there is no conflict of interest in writing this article.

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AUTHOR CONTRIBUTION

IGAS was responsible for the patient management and oversight of the pharmacotherapy of the patient. PGABP and NF were responsible for writing the report and conducting follow-up examinations in collaboration with IGAS.

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