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Case Report

Gynecomastia Caused by Antiretroviral Therapy, Highly Suspected Efavirenz: A Case Report

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ABSTRACT

Gynecomastia is an enlargement of breasts in men. This disease is commonly found in patients with impaired liver function and patients on additional hormonal use. Approximately, 10% to 25% of gynecomastia instances are attributed to the use of pharmaceutical substances. This study presented the case of a 41-year-old male patient with complaints of breast enlargement for 2.5 years before the examination. Breast enlargement was felt slowly without any period of shrinking, and no complaints of breast pain hardening, or nipple discharge. The patient was diagnosed with Auto Immune Deficiency Syndrome (AIDS) in 2009 and taking a Fixed-Dose Combination (FDC) of Anti-Retroviral Therapy (ART) with the composition of tenofovir, lamivudine, and efavirenz once a day. History of hormonal uses, other drugs, and alcohol consumption was denied. According to the physical examination, the patient had an adequate nutritional status, a BMI of 20.8 kg/m^2, and enlargement of right and left breasts, the left breast was larger. According to the palpation, the enlarged breasts were firm and supple and there was no erosion or nipple discharge, or breast pain. The laboratory examination showed hepatitis marker, hormonal and thyroid levels are within normal limits. Medications are estimated to account for 10-25% of gynecomastia cases. Efavirenz decreases androgen activity through unknown factors. Several assumed mechanisms include the direct mammotropic effect of ARTs, and elevated IL-2 and IL-6 production due to T-helper cytokine response, thereby increasing the estrogen production which stimulates breast growth. Surgery can be done for cosmetic purposes.

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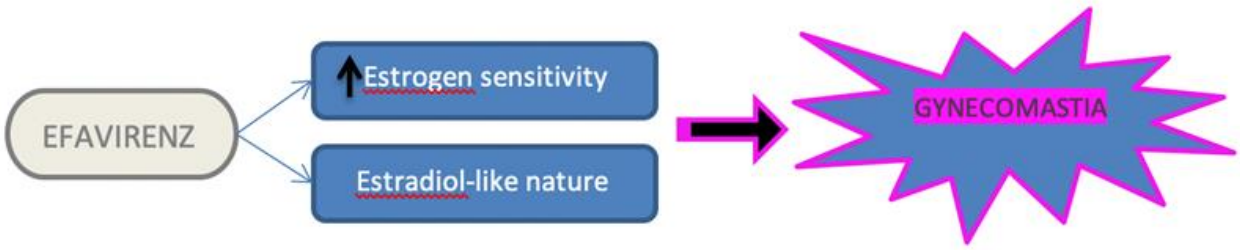
GRAPHICAL ABSTRACT



Introduction

Gynecomastia is characterized by the expansion of male breast tissue as a result of the proliferation of glandular and fatty tissue. This condition is not malignant and harmless, but can cause discomfort in physical conditions, trigger psychological stress, and adversely affect self-confidence [1]. Asymptomatic gynecomastia is observed in approximately 60% to 90% of neonates, 50% to 60% of adolescents, and can affect up to 70% of men between the ages of 50 and 69 [2]. The gynecomastia incidence is reported to increase with the development of the disease and the administration of drugs. Niewoehner's screening of 214 male hospitalized patients indicated that 65% of them had gynecomastia with various causes and varying sizes up to two centimeters in diameter with no specific complaints [3]. Nearly 66% of patients experience gynecomastia attributed to physiological factors (around 25%), with no underlying abnormalities detected (idiopathic, approximately 25%), or as a result of drug-induced breast development (up to 20%). The estimated frequencies of the remaining causes are as follows: cirrhosis at 8%; primary hypogonadism at 8%; testicular tumors at 3%; secondary hypogonadism at 2%; hyperthyroidism at 1.5%; and renal disease at 1%, as indicated in [4]. However, no specific data show the prevalence of gynecomastia in Indonesia. The primary reason for gynecomastia is the hormonal imbalance between estrogen and androgen within the breast tissue. Free testosterone and estrogen levels are influenced by binding globulin which can decrease in patients with long-term use of drugs such as the antiviral efavirenz for HIV [4]. The following section presents a case of a gynecomastia patient with a history of taking antiretroviral therapy (ART).

Case Illustration

A 41-year-old, unmarried man, domiciled in Surabaya, working as a grocery store owner, went to an endocrine polyclinic with complaints of enlargement of both breasts. Based on the anamnesis, the patient stated that both of his breasts had been enlarged for 2.5 years ago. The patient did not experience any significant impairment in his breasts, but due to the enlargement, the patient decided to consult the doctor. The enlargement was experienced slowly without any period of shrinking, with no complaints of breast pain and hardening, nipple discharge, or enlargement of the neck or armpit glands. The patient denied complaints of prolonged and severe headaches, a history of impaired consciousness or fainting, or visual impairment. The patient had undergone antiviral treatment since 2009, receiving ART with the composition of Tenofovir of 300 mg, Lamivudine of 150 mg, and Efavirenz of 600 mg once per day. He denied the administration of regular drugs and other herbs. Apart from complaints of breast enlargement, the patient did not experience any problems with his penis and testes, such as changes in size or function. The patient stated that he did not experience a decrease in libido.

The patient denied complaints of a lump in the neck, frequent palpitations, shaking, or rapid weight loss.

The patient also denied a history of alcohol consumption, surgery, administration of hormonal drugs, or injections to enlarge breasts. There was no history of liver, kidney, malignancy, or family history with similar complaints. The physical examination indicated that the patient had an adequate general condition with GCS 456, with a Glasgow Coma Scale (GCS) score of 456, blood pressure measuring 120/80 mmHg, a pulse rate of 80 beats per minute with a regular rhythm and normal amplitude, a respiratory rate of 20 breaths per minute, an axillary temperature of 37.5 ^{o}C, a body weight of 64 kg, and a height of 172 cm, resulting in a BMI of 21.6. There is no enlargement of the thyroid and lymph node glands. From the breast examination, there are enlargements on both breasts with the left breast slightly larger, the consistency was firm and springy, and no abnormal lumps, pain on touch, or skin and nipple abnormalities. The abdominal examination showed normal bowel sounds, and there was no organomegaly (Figure 1). The initial laboratory examination revealed the following results for the patient: a hemoglobin level of 15.9 g/dL, hematocrit measuring 45.9%, a leucocyte count of 4,300/mm^3, platelets at 223,000/mm^3, a neutrophil count of 64.8%, lymphocyte count at 26%, an erythrocyte sedimentation rate (ESR) of 5 mm per hour, a random blood glucose level of 116 mg/dL, serum blood urea nitrogen (BUN) of 10 mg/dL, creatinine level at 0.8 mg/dL, aspartate transaminase (AST) measuring 23 U/L, alanine transaminase (ALT) at 20 U/L, sodium (natrium) at 135 mmol/L, potassium (kalium) at 4.6 mmol/L, nonreactive HBsAg and anti-HCV, thyroid-stimulating hormone (TSH) level of 1.28 uIU/mL (within the normal range of 0.45-4.12 uIU/mL), and free thyroxine (FT4) at 1.16 ng/dL (within the normal range of 0.8-1.8). The subsequent laboratory examination revealed the following results: a fasting blood sugar level of 106 mg/dL, a 2-hour postprandial blood sugar level of 126 mg/dL, a prolactin level at 11.49 ng/mL (with a normal value below 20 ng/mL), an LH level of 12.7 mIU/mL (within the normal range of 1.42-15.4 mIU/mL), an FSH level of 4.49 mIU/mL (normal range for adult males: 1.5-12.4 mIU/mL), a morning cortisol level of 13.51 ug/dL (normal range: 5-25 ug/dL), a testosterone level measuring 365 ng/dL (normal range: 300-1,000 ng/dL), and a progesterone level of 0.6 ng/mL (with a normal value less than 1 ng/mL).

According to the data, the patient was then diagnosed with gynecomastia which was presumed to be related to ART with high suspicion caused by Efavirenz. The next section discussed the causes of gynecomastia in the patient by eliminating other possibilities.

Results and Discussion

Gynecomastia is a benign condition characterized by the development of breast enlargement in men, which occurs due to the proliferation of glandular and adipose tissues. It is divided into true gynecomastia and pseudo-gynecomastia.

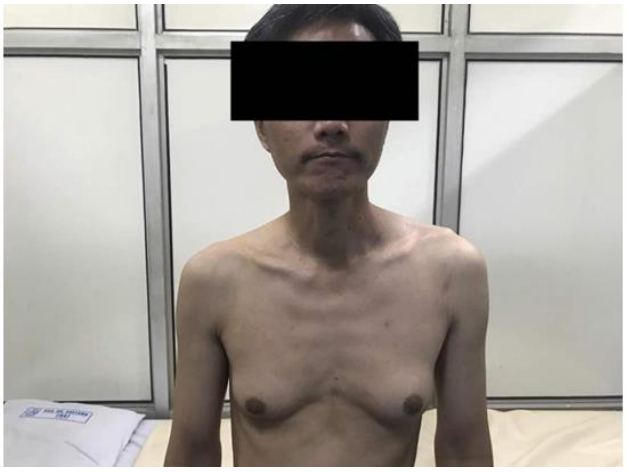


Figure 1: Patient's profile shows gynecomastia

Pseudo-gynecomastia can be found in men with excess body weight, resulting from lipomastia without glandular proliferation. This condition can also occur temporarily in neonates due to an environment with high estrogen levels while in the womb, and in elderlies due to relatively decreased testosterone production [1].

Breast tissue hypertrophy is caused by a temporary or permanent excess of estrogen hormone or a deficiency of the androgen hormone. It can result from changes in the function of adrenal or testicular tissue, conversion of estrogen in tissues such as fat, SHBG (sex hormone binding globulin) levels, or tissues that are specifically sensitive to hormonal stimulation. Breast tissue in men has both estrogen and androgen receptors. Estrogens are involved in promoting the proliferation of mammary ducts, while, in contrast, androgens act to suppress this process. The gynecomastia pathophysiology is rooted in the disruption of the balance between these two factors [1]. Gynecomastia is multifactorial and can be influenced by many conditions. Per Braunstein's findings, nearly 66% of patients experience gynecomastia due to physiological factors (around 25%), with no underlying abnormalities detected (referred to as idiopathic, approximately 25%), or as a result of drug-induced breast development (up to 20%). The estimated occurrence rates for the remaining causes are as follows: cirrhosis at 8%; primary hypogonadism at 8%; testicular tumors at 3%; secondary hypogonadism at 2%; hyperthyroidism at 1.5%; and renal disease at 1% [4]. Long-term exposure to estrogen due to environmental factors can trigger gynecomastia. Endocrine disorders caused by chemicals due to products consumed, air pollution, radiation, organochlorine pesticides, plastics, fuels, and polycyclic aromatic hydrocarbons also play a role. Damage to the liver causes disruption of estrogen degradation and increases SHBG so that estrogen levels in the blood increase. Individuals afflicted with alcohol-related liver disease face an elevated risk of developing gynecomastia, primarily due to the presence of phytoestrogens in alcohol and ethanol's direct interference with testosterone production, which further exacerbates the imbalance between estrogen and testosterone [5]. Gynecomastia can also occur in 10-40% of men with hyperthyroidism, although this is a rare clinical manifestation. After the patient reaches the euthyroid state, the gynecomastia will disappear on its own in one to two months [6]. Hormonal dysfunction a common occurrence in men with compromised kidney function, often resulting from the suppression of testosterone production or testicular damage induced by uremia. Malnutrition is observed in 40% of patients with renal failure, potentially contributing to the development of gynecomastia in men. While dialysis can alleviate the incidence of malnutrition-related gynecomastia, it is worth noting that only kidney transplants prove effective in rectifying hormonal damage and malnutrition in individuals with kidney failure [7]. The underlying pathophysiology of gynecomastia includes an absolute increase in free estrogen that can be caused by direct secretion from the pregnant woman's placenta, testes, and adrenal glands, extraglandular aromatization of androgens to estrogens, concentrations of SHBG, decreased metabolic rate, and the presence of exogenous estrogens. The imbalance between estrogen and androgen arises from various factors, including an elevation in free estrogen levels produced by either the testes or the adrenal glands, a reduction in endogenous production of free androgens, a decrease in estrogen degradation, an aromatization of extraglandular estrogen precursors, an increased ratio of free estrogens to free androgens, an insensitivity to androgens, exposure to estrogen-like substances or external estrogen sources, and the use of medications that can shift the binding of androgens to globulins. Other causes include drugs with estrogen-like effects and increased sensitivity of breast tissue [8, 9]. In adult males, the testes are responsible for generating approximately 95% of testosterone, 15% of estradiol, and less than 5% of estrone. The primary androgen hormone produced by the adrenal glands is androstenedione. The majority of estradiol and estrone are synthesized through the conversion of testosterone and androstenedione outside of the glands, taking place in various tissues,

including the liver, skin, fat, muscle, bone, and kidney, all of which contain the aromatase enzyme. Another pathway that also plays a role is the 17-hydroxysteroid dehydrogenase enzyme in extraglandular tissue which plays a role in the conversion of testosterone to androstenedione and estradiol to estrone [9]. Breast tissue in patients with gynecomastia has increased sensitivity to circulating estrogens despite normal androgen levels and concentrations. This reflects increased local aromatization of androgens to estrogens within the breast tissue itself. In addition, it is noteworthy that aromatase activity was observed to be elevated in genital skin fibroblasts among gynecomastia patients [10]. Several studies show the increase in body mass index (BMI) has a positive correlation to the diameter and incidence of gynecomastia in both adolescents and adults. Fat tissue in the breast contains the aromatase enzyme which converts testosterone and androstenedione to estradiol and estrone. Therefore, there is a hypothesis that the increase in breast fat tissue caused by weight gain results in an increase in estrogen production which continuously increases the stimulation of breast glands. Furthermore, the accumulation of adipose tissue in the breast area due to weight gain leads to pseudo-gynecomastia, a condition that may or may not be connected with pure gynecomastia [11]. The outlook for individuals with HIV disease has significantly improved following the introduction of highly active antiretroviral therapy (HAART), although there are some mild to severe side effects. Lipomastia (pseudogynecomastia) is the breasts enlargement associated with the fat accumulation in the center of the body due to the redistribution of fat tissue which is assumed to be associated with the side effects of HAART, especially protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). The pathogenesis of the cause is still unclear, but there are two possible mechanisms, namely the process of restoring the immune system and the effect of efavirenz which is similar to estradiol. Gynecomastia has been documented in individuals undergoing antiretroviral therapy (ART) while following a protease inhibitor (PI) regimen. Jover *et al.* reported that in five gynecomastia patients who were treated with efavirenz-containing regimens, gynecomastia occurred after a median of nine months (between 4-15 months). In addition, Piroth *et al.* documented five instances of gynecomastia associated with highly active antiretroviral therapy (HAART), with an annual incidence of 0.8 per 100 patients and a prevalence of 2.8% among individuals who had been on the treatment for over two years [12-14].

In 2001, Mercie reported the incidence of gynecomastia associated with efavirenz in patients experiencing lipodystrophy syndrome due to the use of highly active antiretroviral therapy (HAART), which included protease inhibitor (PI) regimens. In a cohort study, the occurrence of gynecomastia among patients receiving efavirenz was found to be 8.1% [15]. A case report by Caso found the incidence of gynecomastia in the absence of therapy-associated lipodystrophy due to efavirenz. In all three cases identified, the patients were treated without a PI regimen [16]. In 2002, Qazi *et al.* documented 15 cases of gynecomastia related to efavirenz, wherein the patients experienced complete resolution of the condition within a median period of two months after discontinuing efavirenz therapy [17]. Some assumed that the direct mammotropic effect of ART, which mimics the action of estrogen or progesterone on breast tissue receptors, is the cause. Qazi *et al.* stated that this could be due to the restoring process of the immune system. After initial HAART therapy, there will be an increase in helper T cells due to cytokine responses, notably an elevation in interleukin 2 (IL-2). It is worth noting that IL-2 has been shown to enhance the proliferation of carcinoma cells in laboratory experiments. Furthermore, IL-6 contributes to heightened estrogen availability and promotes breast growth. To sum up, an enhanced immune response results in an increased presence of estrogen within breast tissue [17-19].

The inhibition of cytochrome P-450 (CYP450) caused by HAART, especially the PI group, leads to an elevation in the estrogen-to-androgen ratio. This could be attributed to decreased estrogen metabolism [20], alterations in estrogen binding to globulins, and diminished testosterone

biosynthesis, among other potential underlying factors [21]. Efavirenz, which belongs to the NNRTI group, was found to have a 37% increase in the area under the curve (AUC) of circulating ethynyl estradiol, thereby affecting CYP450. A study conducted by Sinnico *et al.* revealed that blood samples from HIV patients treated with efavirenz showed elevated estradiol levels when assessed using enzyme-linked immunosorbent assay (ELISA), but on an examination by radioimmunoassay (RIA), estradiol values were found to be normal. It was concluded that efavirenz was associated with an ELISA which was sensitive to detecting estradiol [22]. Hence, it is plausible that efavirenz exerts an effect similar to estradiol within the human body, promoting the expansion of breast tissue and contributing to the development of gynecomastia [23-27].

Conclusion

To sum up, we presented a case of a 41-year-old man with complaints of breast enlargement 2.5 years before the examination and getting larger slowly without any period of shrinking. The patient denied a history of breast pain and hardening or nipple discharge. The patient felt that the breast enlargement did not cause significant impairments so he did not immediately seek treatment. The patient had no history of chronic disease. The patient has been regularly taking FDC ART with the composition of lamivudine, tenofovir, and efavirenz since 2009. Screening for various possible causes of gynecomastia had been performed and the results were normal. The gynecomastia is assumed to be caused by a side effect of taking efavirenz. The basic mechanism associated with the occurrence of gynecomastia is assumed to be an increase in the immune system followed by an increase in IL-2 and IL-6, thereby increasing estrogen sensitivity and the estradiol-like nature of efavirenz stimulates the growth of breast tissue. We had educated the patient to change the ART regimen, but he felt comfortable with it. Therefore, he chose to continue the same therapy. The patient is not ready to undergo surgical therapy for cosmetic purposes. The patient's prognosis is in good condition.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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