Gigantomastia Bilateral Induced Efavirenz: A Case Report

Amos Pongbulaan[1], Erwin Astha Triyono[2]

[1]Resident, Department of Internal Medicine, [2]Doctor at Division of Tropical and Infection, Department of Internal Medicine, Dr. Soetomo Hospital – Faculty of Medicine Airlangga University, Surabaya Indonesia

Abstract

The prognosis of HIV-infection has improved dramatically since the introduction of Highly Active Antiretroviral Therapy (HAART). With the need for a lifelong treatment, the longterm side effect of antiretroviral agents is an emergent issue of concern. Gigantomastia is a rare condition characterized by excessive breast growth. It may occur spontaneously, during puberty or pregnancy, or while taking certain medications. HAART medications which probably associated with gigantomastia is efavirenz. A 25-year-old woman with HIV-infection who developed bilateral gigantomastia while receiving efavirenz-based HAART regimens. The diagnosis was made after other possible causes of disease-induced gigantomastia were exclude and confirmed by mammography. Surgical treatment has been considered after failure of medical treatment. Although it is rare, physicians should be aware so that a timely diagnosis can be made. In most cases, only conservative treatment is sufficient, but in severe cases surgical intervention might be required.

Keywords: *Gigantomastia, Efavirenz, HIV, HAART*

Introduction

The introduction of HAART multi-drug combination regimens has considerably improved prognosis of patients infected with HIV by reducing

AIDS-related morbidity and mortality. However, chronic treatment with these regimens is associated with multiple adverse effects, nonadherence, and eventually therapy failure. Treatment regimens containing efavirenz are preferred in treatment-naive patients and are widely used in other settings. While efavirenz is generally well tolerated, concentration-dependent side effects that impact drug adherence and promote resistance. Common adverse effects of efavirenz include central nervous system symptoms (up to 50% of patients), but other less common adverse effects have also been reported. An increasing number of reports suggest that the use of HAART (efavirenz-based-therapy), is associated with breast hypertrophy or gynecomastia due to benign and malignant mammary diseases.(1),(2),(3)

Gigantomastia is a particular weight of excess breast tissue and rare condition characterized by excessive breast growth. Symptoms of gigantomastia may include mastalgia, ulceration/infection, posture problems, back pain.(4) Gigantomastia is classified etiologically into three main groups: idiopathic, imbalance in endogenous hormone production, and drug-induced.(5) Treatment is aimed at improving the clinical and psychological symptoms and reducing the treatment side effects; however, the best therapeutic option varies from case to case.(6),(7)

We report rare case of gigantomastia bilateral associated with efavirenz-based HAART regimens.

Case Description

A 25-year-old woman with HIV-infection came to the outpatient clinic (July 2019) at Soetomo Hospital complained of an enlargement of both breasts for six

Corresponding author:
Amos Pongbulaan
Departement of Internal Medicine, Faculty of Medicine, Airlangga University, Jl.Mayjen Prof. Dr.Moestopo 47, Surabaya, East Java, Indonesia Phone: +6231-5020251
Email: amospongbulaan1985@gmail.com
Orcid ID: 0000-0001-6313-5402

months after start of the new regimen ART (Tenofovir, Lamivudin, Efavirenz). The patient complained of mastalgia and back pain. She did not experience milky discharge from the nipple. Except for the breast enlargement, she felt well and did not have any other complaints. She had one child, the first child was born when she was 23 years old. During her pregnancy, no significant enlargement of the breasts was noted. Her husband also with HIV and got Duviral and Neviral therapy. She had normal menstrual cycles (not pregnant) and the last pregnancy was 2 years ago. She did not excess weight gain. Family history was negative for breast hypertrophy.

On July 2017, she was diagnosed as having HIV infection and was taking a regimen of Duviral and Neviral. In April 2018, she was diagnosed pulmonary tuberculosis and received anti-tuberculosis drug therapy and during anti-tuberculosis drug therapy, patients experienced Drug-Induced Liver Injury, and to reduce liver function disorders, we changed the ART (antiretroviral therapy) regimen to tenofovir, lamivudine, and efavirenz. Then, she completed pulmonary tuberculosis treatment in March 2019 and was declared cured. She did not take any drugs of abuse or medication other than ART.

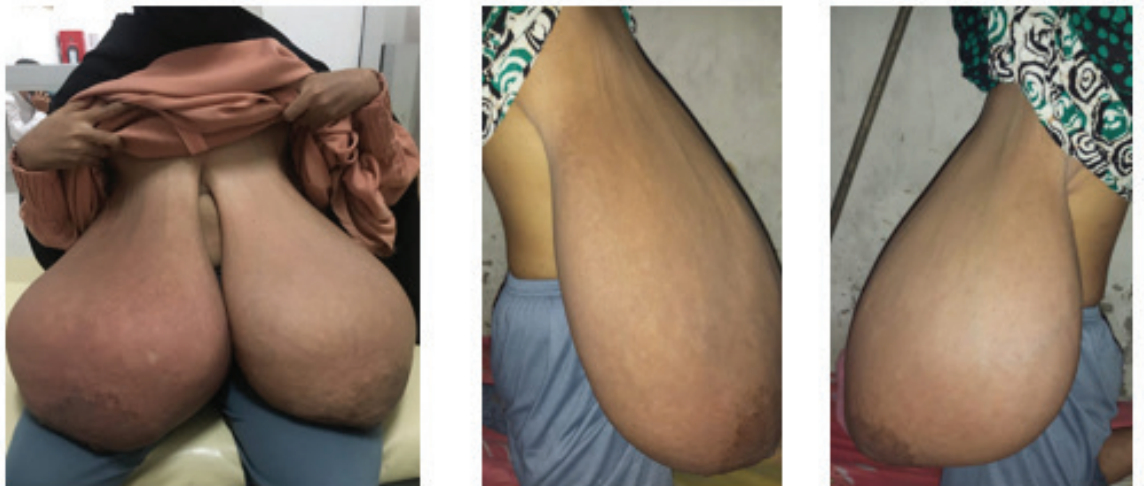

Figure 1: Gigantomastia in first arrival

On physical examination, body-weight 63 kg, body-height 153 cm, BMI 26.9 kg/m^2. Blood pressure 110/70 mmHg, heart rate 80 bpm, breathing 20x/minutes, axillary temperature 36.5^{0}C, oxygen saturation 99% room air. No enlargement of a lymph node, anemia, icterus and cyanosis.. Examination of heart, lung, abdomen, and extremities were normal. Breast examination, enormously hypertrophic breasts reaching below the waistline (Figure I). There was not any erythema, warmth, or ulceration on breast skin. There was no discharge observed from the nipple and no find any mass.

Laboratory finding: hemoglobin 10.5 g/dL, hematocrit 33.3%, MCV 78.7 fL, MCH 24.8 pg, MCHC 31.5 gr/dL, leucocyte 8.04x10^3/uL, thrombocyte 531x10^3/uL, HbsAg and Anti-HCV non-reactive. CEA <0.5 ng/ml, CA15-3 6.2 U/ml, CA19-9 18.62 U/ml, TSH 2.0889 iu/ml, FSH <5.48 iu/ml, LH 6.25, Prolactin 10.71 ug/l, AST 39 u/l, ALT 36 u/l, BUN/creatinine 7/0.57 mg/dl, CD4 612 cell/uL, Viral load undetected. Chest-X-Ray, mammography and breast ultrasound were normal. She was diagnosed HIV with gigantomastia bilateral induced efavirenz and switched ART regimen from efavirenz to nevirapine and administration of tamoxifen 20 mg/day.

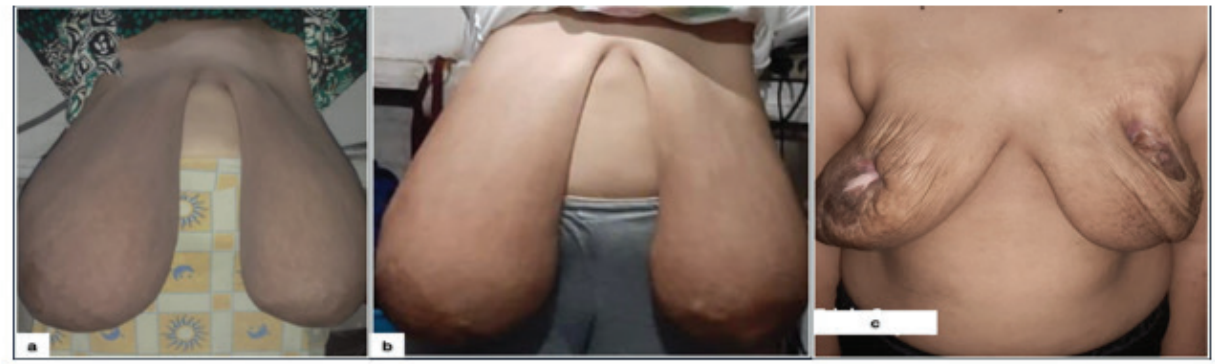

Figure 2: (a) one month follow up, (b) eight months follow up, (c) three months post-surgery

On 1 month follow-up, the breast consistency was softer but did not decrease in size. After 10 months on hormonal therapy, surgical therapy as a best optional treatment. Reduction mammoplasty was eventually conducted. When she came to a follow-up visit a month after mammoplasty, she recovered with good wound healing. Only minimal scar was observed.

Discussion

The incidence of breast enlargment in patients treated with HAART for more than 2 years is 2.8%. The mean delay of gigantomastia appearance following initiation of HAART is 9 months. It can be unilateral or bilateral.[2] Gigantomastia is breast enlargement that requires a reduction of over 1,500 g per breast.[8],[9] Gigantomastia is classified etiologically into three groups: idiopathic (Group 1), imbalance in endogenous hormone production (Group 2), and drug-induced (Group 3). Group 1 is further divided into two: Group 1a, obese patients (BMI >30 mg/m^2) and Group 1b, nonobese patients (BMI <30 mg/m^2). Gigantomastia cases related to the pubertal period and pregnancy are classified as Group 2a and Group 2b, respectively. Idiopathic gigantomastia has an unknown etiology and insidious onset. Mechanism of Group 2a are increased estrogen receptors in mammary gland and hypersensitivity of receptors to estrogen and progesterone. These patients have sudden disease onset, unilateral/bilateral gigantomastia, and family history. In Group 2b, a possible mechanism is increased sensitivity to prolactin in mammary gland.[7],[8],[5]

The etiology of gigantomastia remains unknown; many mechanisms have been implicated including hormonal abnormalities, hormone receptor hypersensitivity, malignancy, drug induction, genetics, and autoimmunity.[10] Breast hypertrophy was needed to be distinguished from pseudogynecomastia or lipomastia which was a characteristic of lipodystrophy syndrome and might be accompanied by other lipodystrophic features. Ultrasonography and mammography are useful either to confirm a diagnosis and to rule out mass or cystic lesions. Next, blood hormone levels might help in determining whether there is an increase in estrogen or other related hormone levels.[11] There has been reports in literature that breast enlargement could present as a side effect of HAART.[12] Medications probably associated with gynecomastia include risperidone, verapamil, nifedipine, omeprazole, efavirenz, steroids, alcohol, and opioids.[13]

The mechanisms of underlying efavirenz-induced-gigantomastia are not well understood. Firstly, a direct oestrogenic effect (trigger the growth of breast tissue by binding to estrogen-receptor-alpha in breast resulting in breast hypertrophy/gynecomastia). Secondly, induction of an immune response (increased of IL-2 and IL-6 were associated with proliferation of human carcinoma cells of the breast *in vitro* and involved in elevating aromatase activity resulting in an increase in estrogen levels of breast tissue leading to the development of breast masses). Thirdly, altered steroid hormone metabolism by cytochrome P450 inhibition might lead to an increase in estradiol concentration.[3],[11],[14] From the above criteria, her clinical symptoms, physical examination and laboratory or radiography, the patient was diagnosed with bilateral gigantomastia caused by efavirens-induced

and entered into group 3.

There is no standard treatment for gigantomastia. Treatment is first aimed at treating any infections, ulcers, pain, and other complications. However, in most cases, surgery is considered to reduce the size of the breasts. The effect of drug therapy on gigantomastia is limited, so surgical treatment is an option as first-line treatment.[4],[15] Losing weight in Group 1a and withdrawal of medicine in Group 3 are the first treatment steps before surgery. Breast reduction surgery is the most frequently used surgical approach. However, recurrent surgery is required in most cases due to spontaneously continuing breast enlargement or hormonal impulses like pregnancy. In this situation, total mastectomy might be an option. Hormonal treatment like bromocriptine, medroxyprogesterone, dydrogesterone, tamoxifen, and danazol are generally applied before surgery, but not as a standard option. Bromocriptine is effective in Group 2b, while tamoxifen, medroxyprogesterone, and dydrogesterone are used in Group 2a.[5]

Drug-induced gigantomastia occurs after taking medications.[4] Switching from efavirenz to alternative drugs may be one potential strategy to alleviate this adverse effect. However, multiple factors need to be considered before switching to alternative therapy. Based on literature, tamoxifen and other anti-estrogens may be useful in the treatment of efavirenz-induced gynaecomastia.[3] Surgical treatment has been considered after failure of medical treatment or upfront especially in idiopathic and drug-induced forms.[16] In this case, therapy was switching ART regimen from efavirenz to nevirapine and administration of tamoxifen 20 mg/day. Then, surgical treatment has been considered after failure of medical treatment.

Conclusion

A woman 25-year-old HIV infection with bilateral gigantomastia associated with efavirenz-based HAART. The available treatment options include ART regimen modification, hormonal therapy and surgical treatment has been considered after failure of medical treatment. Early recognition is important to timely and correctly manage this side effect in order to improve health sustain adherence to ART.

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Ethical Clearance: Not required for a case report.

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References

1. Jover F, Cuadrado JM, Roig P, Rodríguez M, Andreu L, Merino J. Efavirenz-Associated Gynecomastia:Report of Five Cases and Review of the Literature. 2004;10(3):244–6.
2. Meerkotter D. Gynaecomastia associated with highly active antiretroviral therapy (HAART). J Radiol Case Rep. 2015;4:34–40.
3. Sikora MJ, Rae JM, Desta Z. Efavirenz directly modulates the oestrogen receptor and induces breast cancer cell growth. 2010;603–7.
4. Al-Assaf SM, Al-Assaf M. Manuscript Info Abstract Introduction:ISSN:2320-5407. Int J Adv Res. 2018;6(12):781–4.
5. Dellal FD, Ozdemir D, Aydin C, Kaya G, Ersoy R, Cakir B. Case Report Gigantomastia and Macroprolactinemia Responding to Cabergoline Treatment:A Case Report and Minireview of the Literature. 2016;2016.
6. Moazzami B, Chaichian S, Farahvash MR, Taheri S, Ahmadi SA. Case Report A Rare Case of Gestational Gigantomastia with Hypercalcemia:The Challenges of Management and Follow up. 2016;17(1):243–6.
7. Dancey A, Khan M, Dawson J, Peart F. Gigantomastia e a classification and review of the literature. 2008;
8. Lanzon A, SV Navarra. CASE REPORT Gigantomastia in a patient with systemic lupus erythematosus successfully treated by reduction mammoplasty. sagepublications. 2009;18(January):1309–12.
9. Cho MJ, Yang J, Choi H, Kim WS, Yu Y, Park KS. An idiopathic gigantomastia. 2015;166–9.
10. Le E, McGirt L, Abuav R. http://lup.sagepub.com/. sagepublications. 2009;18:1015–8.
11. Aurpibul L, Oberdorfer P. Gigantomastia in perinatally HIV-infected female adolescent on efavirenz including antiretroviral treatment. 2016;20(1):309–12.
12. Agbaji OO, Agaba PA, Ekeh PN, Sule HM, Ojoh RO, Audu E, et al. Efavirenz-induced

gynaecomastia in HIV-infected Nigerian men:A report of six cases. 2011;2:1221–4.

13. Jayalakshmi MD, Torvi JR. IJBCP International Journal of Basic & Clinical Pharmacology Case Report Efavirinz induced gynecomastia:a case report. 2019;8(2):351–3.
14. Rukmangathen R, Brahmanapalli VD, Devulapalli M, Prasad D. A Case Report on Efavirenz Induced Gynaecomastia. 2017;10(3):223–6.
15. Moussaoui A, Kouach J, Ennouhi A, Babahabib A, Benabdejlil Y, Moussaoui D, et al. Idiopathic recurrent gigantomastia : A case report. 2014;2(4):54–7.
16. Benna M, Naser R Ben, Fertani Y, Ayadi MA, Bettaieb I, Chargui R, et al. Case Report Extreme Idiopathic gigantomastia. 2018;6(5):1808–11.