

**Efavirin z induced gynecomastia: a case report****Jayalakshmi M. D.\*, Janaki R. Torvi**

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**Received:** 02 December 2018**Accepted:** 28 December 2018**\*Correspondence to:**

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**ABSTRACT**

Gynecomastia is swelling of the breast tissue in men, caused by an imbalance of the hormones, estrogen and testosterone. Drugs commonly implicated are spironolactone, cimetidine, ketoconazole, hGH, estrogens, hCG, anti-androgens, GnRH analogues and 5- $\alpha$  reductase inhibitors. Medications probably associated with gynecomastia include risperidone, verapamil, nifedipine, omeprazole, alkylating agents, HIV medications (efavirenz), anabolic steroids, alcohol and opioids. HIV infected patients who are treated with highly active antiretroviral therapy (HAART) can develop breast enlargement due to benign and malignant mammary diseases. We report here a case of gynecomastia due to efavirin z.

**Keywords:** Efavirin z, Gynecomastia, HAART**INTRODUCTION**

According to WHO, adverse drug reaction is defined as "Any response to drug which is noxious or unintended and occurs at a dose normally used in man for prophylaxis, diagnosis or treatment of diseases or for modification of physiological function".<sup>1</sup>

India has the third largest Human immunodeficiency virus (HIV) infection epidemic in the world. In 2016, HIV prevalence in India was estimated to be 0.3% which equates to 2.1 million patients living with HIV and 62000 people died due to AIDS related illness.<sup>2-3</sup> The introduction of HAART, a combination of different antiretroviral drugs has vastly improved the health states of HIV infected patients.<sup>4</sup> HIV infected patients who are treated with highly active antiretroviral therapy (HAART) can develop breast enlargement due to benign and malignant mammary diseases. Malignant diseases include

adenocarcinoma, lymphoma, Kaposi's sarcoma and metastasis. Benign disorders comprise infections and changes in the breast stroma, including pseudoangiomatous stromal hyperplasia, lipomastia and true gynaecomastia.<sup>5</sup> Gynaecomastia, a benign proliferation of glandular breast tissue in males is thought to result from an imbalance between oestrogens and androgens.<sup>6</sup> The estimated prevalence of gynecomastia in patients on HAART ranges from 1.8 to 2.9%.<sup>7</sup> Authors report here a case of gynecomastia due to efavirenz.

**CASE REPORT**

A 33-year-old adult on HAART presented with complaint of mass on the right breast of 4 months duration. He had HIV infection diagnosed 4 years back, had been treated with multiple antiretroviral regimens. Therapy was initiated with stavudine, lamivudine and nevirapine. Because of unavailability of stavudine, the regimen was modified 3 years later to zidovudine, lamivudine and

nevirapine. Then after 2 years regimen was changed to tenofovir, lamivudine and efavirenz (TLE) due to persistent decrease in CD4 count (<100). After 4 months of starting this regimen, patient noticed swelling of right breast associated with pain which was insidious in onset and gradually progressive. There was no history of diabetes or hypertension and use of other medications. Physical examination: Patient was moderately built, nourished, conscious, cooperative and was well oriented. On local examination, bilateral breast swelling was present, on inspection, 10\*14cm on right side and 8\*10cm on left side, well defined margins, no discharge or ulcerations and no dilated veins on the swelling. On palpation, inspeitory findings were confirmed, concentric swelling, firm in consistency, margins were well defined and was movable in all 4 directions. On auscultation there was no bruits. Systemic examination was normal.

Laboratory investigations included CD4 count- 157 cell/ $\mu$ l, HIV RNA- 271,274 copies, Hb- 11g%, LFT -total protein- 7.1g/dl, Albumin- 3.6g/dl, AST- 47IU/L, ALT- 57IU/L, alkaline phosphatase- 26IU/L, peripheral smear indicates macrocytic anaemia and HBsAg were negative. RFT and urine examinations were within normal limits.

USG was suggestive of hypertrophy of the breast glandular parenchyma bilaterally. FNAC - benign ductal cells in clusters, features consistent with gynecomastia.

Causality assessment was done using Naranjo's scale which showed that efavirenz is the possible cause of the adverse reaction in our case (score - 4) followed by using Modified Hartwig and Siegel scale (ADR severity assessment scale) that falls in moderate ADR (level 3).

The initial Serum creatinine value before undergoing surgery were 0.87 mg/dL and 0.86 mg/dL with a standard deviation of 0.172 and 0.184 in AM and GM group respectively.

## DISCUSSION

Gynecomastia results from alterations in the ratio of effective estrogen to testosterone, which may have many causes, including increases in the amount of estrogen (due to estrogen-secreting testicular tumors or ingested androgens), decreased testosterone levels (due to ketoconazole use or secondary hypogonadism), or both (due to liver disease, primary hypogonadism, or spironolactone use).<sup>8</sup>

Gynecomastia has to be distinguished from pseudogynecomastia and lipomastia, which are both forms of fat accumulation in the breasts. Breast palpation can help to distinguish fat accumulation in the breasts from true gynecomastia. In gynecomastia, typically a soft, elastic or firm disk-shaped mass, that is concentric with the nipple-areola, can be palpated with the patient lying flat on his back. Uncommonly, benign tumours and breast cancer can also cause breast enlargement in males. Once the presence

of gynecomastia is established, a differential diagnosis of its causes needs to be considered. There are two broad categories: physiological gynecomastia (common) and pathological gynecomastia (uncommon). Physiological gynecomastia is self-limiting and occurs in newborns, adolescents, and the elderly. The pathological causes can be further divided up into three subcategories, namely testosterone deficiency, increased oestrogen production, and drug-induced breast enlargement. Testosterone deficiency can occur in HIV infection. Causes of excess oestrogen include  $\beta$ -hCG-producing tumours (especially testicular cancers), chronic liver disease, and malnutrition.<sup>9</sup> The drugs definitely associated with the onset of gynecomastia are spironolactone, cimetidine, ketoconazole, hGH, estrogens, hCG, anti-androgens, GnRH analogues and 5- $\alpha$  reductase inhibitors. Medications probably associated with gynecomastia include risperidone, verapamil, nifedipine, omeprazole, alkylating agents, HIV medications (efavirenz), anabolic steroids, alcohol and opioids.<sup>10</sup>

Efavirenz is known to be associated with gynecomastia. The proposed mechanism from in vitro data is that efavirenz mimics the effects of oestrogen and through direct binding and modulation of the oestrogen receptor (ER).<sup>11</sup> Two other hypothesized mechanisms have been suggested for ART-associated gynecomastia: immune restoration may increase breast tissue oestrogen availability, and efavirenz has been shown to increase the area under the curve of ethinyloestradiol by at least 37%, thereby elevating the oestrogen-androgen ratio.<sup>12</sup>

The introduction of highly active antiretroviral therapy (HAART) in developed countries in the late 90s has been associated with a remarkable decrease in AIDS-related mortality. This decrease in mortality has changed the perspective of HIV infection from that of a rapidly fatal to a chronic manageable infection. ADRs have been one of the most important limiting factors to the success of HAART because they are responsible for new co-morbidities noticeable by the patients or their families and may result in decreased adherence to treatment which consequently might lead to virological failure and poor prognosis.<sup>13</sup>

Various authors have reported gynecomastia with efavirenz. A study done by Mira JA et al, concluded gynecomastia is not uncommon in HIV infected men undergoing HAART and it is usually transient and efavirenz and didanosine treatment are associated with the emergence of gynecomastia.<sup>14</sup> Mercié et al, have reported 6 cases of efavirenz-associated breast hypertrophy in HIV-infected patients.<sup>15</sup> Jover F et al, have reported 5 cases of efavirenz-associated gynecomastia.<sup>16</sup>

## CONCLUSION

Gynecomastia is a well-recognized adverse effect of efavirenz that has cosmetic and psychological consequences, also patients cite the fear of having a

malignancy as a reason for seeking evaluation. Appropriate counselling should be given to patients with gynecomastia to avoid ART interruptions and non-adherence.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

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**Cite this article as:** Jayalakshmi MD, Torvi JR. Efavirinz induced gynecomastia: a case report. *Int J Basic Clin Pharmacol* 2019;8:351-3.