Original Article

A Case Series of Efavirenz Induced Gynaecomastia

Charu Jain[1], Neha Sharma[2], Uma Advani[3], Lokendra Sharma[4], Munesh Kumar[5], Monica Jain[6]

[1]Associate Professor, [2,3]Assistant Professor, [4,6]Senior Professor, Department of Pharmacology, SMS Medical College and Associated Group of Hospitals, Jaipur, [5]Assistant Professor, Department of Medicine, RUHS College of Medical Sciences and Associated Group of Hospitals, Jaipur, Rajasthan, India

DOI:10.37821/ruhsjhs.5.4.2020.352

ABSTRACT

Antiretroviral therapy (ART) has ameliorated the endurance of *human immunodeficiency virus* (*HIV*) patients. Nevertheless, antiretroviral drugs are extremely toxic and remain an important concern as they are linked with versatile adverse drug reactions. Gynaecomastia is consorted with exposure to antiretroviral therapy (ART), especially due to Efavirenz. We report a case series of three patients who presented with gynaecomastia. One patient had to undergo surgery and other two patients received pharmacotherapy.

Keywords: Antiretroviral therapy, Efavirenz, Gynaecomastia.

INTRODUCTION

An imbalance between oestrogens and androgens may lead to a benign development of glandular breast tissue in males known as gynaecomastia. Gynaecomastia is consorted with exposure to antiretroviral therapy (ART), specially due to Efavirenz. The figured prevalence of gynaecomastia in *human immunodeficiency virus* (*HIV*) infected men on antiretroviral therapy (ART) ranges from 1.8 to 2.9%.[1]

Most reports of ART-associated gynaecomastia come from resource-rich western countries, and there are few data from our country. This case series, describes the clinical characteristics of *HIV* infected patients with Efavirenz associated gynaecomastia and Nevirapine associated rash, reported to ART centre at a Government Medical College, Jaipur. Three cases were reported from the period of January 2020 to September 2020. Written informed consent was obtained from all the patients for publication of this case series and accompanying images.

CASE REPORT

Clinical vignette 1

A 23 year-old male was diagnosed with *HIV* infection and on treatment in accordance to the National AIDS Control Organization (NACO) guided regimen. He was started on Tenofovir 300 mg + Lamivudine 300 mg, and Efavirenz 600 mg as fixed dose combination once a day from 8 December 2017. After 3 years of starting highly active antiretroviral therapy (HAART), he presented with bilateral breast enlargement (Figure 1) and tenderness and had CD4 cell count of 689 cells/mm^3 with a viral load of 374 copies/ml on March 2020.

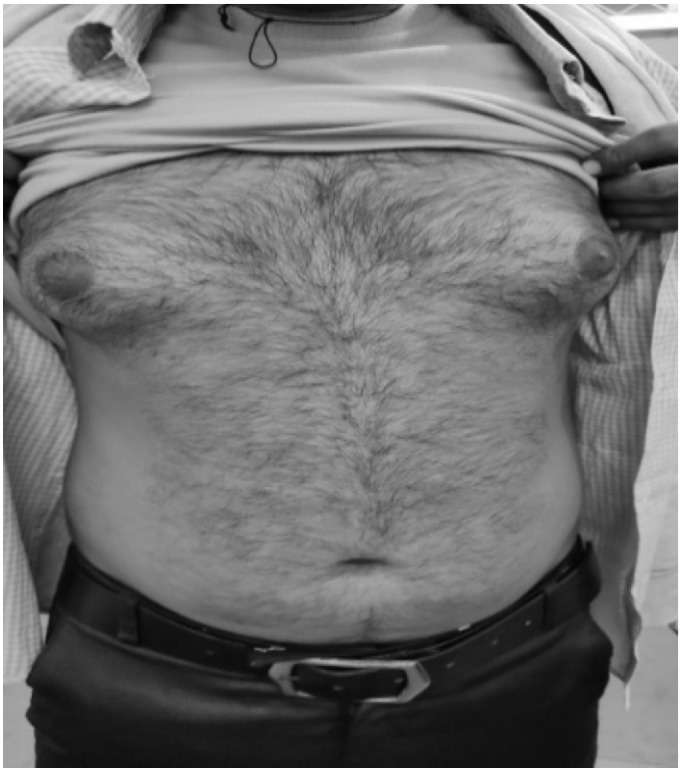

Figure 1: Bilateral enlargement of breast in patient on HAART.

Initially the patient was kept in observation and treated symptomatically without any change in HAART regimen. Patient was also taking anti tubercular therapy (ATT) for tuberculosis associated with *HIV*. He received three tablets of Isoniazid (H) 75 mg, Rifampicin (R)150 mg, Pyrazinamide (Z) 400 mg, and Ethambutol (E) 275 mg (HRZE) as a fixed dose combination in intensive phase and HRE in continuation phase for 6 months, for the treatment of category I sputum positive pulmonary tuberculosis associated with *HIV*. Later on patient developed nodule (2-3 cm) in left breast. No previous history of any endocrinological disorder was reported. Levels of serum testosterone, follicle stimulating hormone (FSH), leutinizing hormone (LH), serum prolactin, and alfa-feto protein were found within normal limits. High resolution computed tomography (HRCT) thorax was done for confirmation and nodular lesion of 1.7×2.1 cm in left breast in sub areolar region was found.

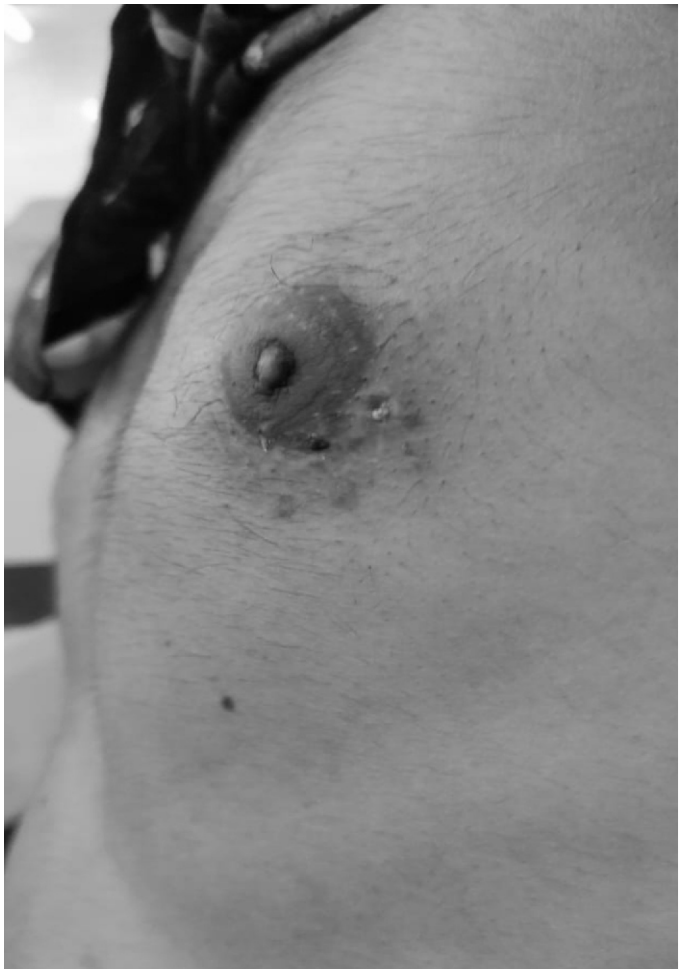

Figure 2: Postoperative image of patient showing regression of gynaecomastia.

The patient was referred to the Department of General Surgery from ART centre affiliated to NACO. Excision of breast nodule was done under general anesthesia and the mass was sent for biopsy. Microscopic report of the biopsy showed grayish white fibro fatty soft tissue pieces with pale brown cut surface. The ART regimen of Tenofovir (300 mg), Lamivudine (300 mg), and Efavirenz (600 mg) (TLE) was stopped and modified HAART regimen was started that included Nevirapine along with Tenofovir and Lamivudine (TLN regime) instead of Efavirenz. Anti-inflammatory and corticosteroids were advised after surgery. Breast size was regressed after the treatment (figure 2) which was also confirmed by ultrasonography (USG).

Clinical vignette 2

A 35 year old *HIV* positive man, resident of Dholpur referred to our centre with 3 months history of bilateral breast enlargement and tenderness. The patient was receiving TLE once a day since May, 2019 and then he developed symptoms one year after therapy. Ultrasonography was performed and prominent fibro glandular tissue was seen, measuring 13 mm right side and 15 mm left side. CD4 cell count was 380 cells/mm^3 and a viral load was termed as 'target not detected' (TND). Testosterone levels were found to be normal. TLE was stopped and patient was started on TLN. Patient was also prescribed vitamin E, multivitamins, and paracetamol. Regression of size of the breast was seen after the treatment.

Clinical vignette 3

Another HIV positive, 40 year old man, resident of Ajmer referred to our center with the history of bilateral breast enlargement and pain. He was initiated on TLE as combined antiretroviral therapy since September, 2018. Symptoms appeared two years after initiation of ART. CD4 cell count was 430 cells/mm^3 and a viral load was 1374 copies/ml. Testosterone level was normal in this patient. TLE was substituted to TLN for this adverse drug reaction. USG was performed to see reduced breast mass. Later, the patient came with generalized rash after four weeks of starting Nevirapine. The rashes were erythematous, maculopapular, confluent, and most prominent on the body and arms associated with pruritus as depicted in figure 3. In view of rash, Nevirapine was suspended and antihistaminic drugs were started till resolution of symptoms. Subsequently, same therapy was continued again.

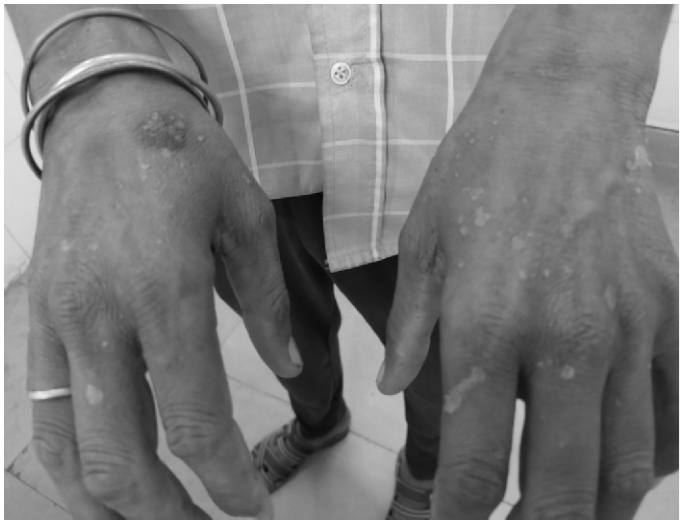

Figure 3: Erythematous, maculopapular, and confluent rashes induced by Nevirapine.

DISCUSSION

In this case series, we encountered Efavirenz induced gynaecomastia and Nevirapine induced rash. Among those that developed gynecomastia, the median baseline CD4 count was 318 cells/mm^3. All three cases of gynecomastia were bilateral and developed gynaecomastia within the first two years of starting an Efavirenz containing regimen. We observed that the onset of gynaecomastia was slow, occurring after a median of 15 months. Gynaecomastia resolved completely in all of these patients. Median time to improvement of gynaecomastia was 3 months. Free testosterone levels were estimated to exclude hypogonadism before switching Efavirenz to Nevirapine.[1]

In our case series, all cases recovered by replacing Efavirenz with Nevirapine. This was in concordance with other previously published studies. As authenticated in former studies, all our cases primarily presented with bilateral gynaecomastia.[1,2] The free testosterone level was found to be normal in our gynaecomastia cases in accordance with Njuguna et al.[1] This was in contradiction to a study which attested a connection between hypogonadism and gynaecomastia.[3] The proposed mechanism from in-vitro data is that Efavirenz mimics the effects of oestrogen on breast tissue. Two other hypothesized mechanisms suggested for ART associated gynaeco-mastia are that immune restoration may increase breast tissue oestrogen availability and Efavirenz has been shown to increase the area under the curve of ethinyl oestradiol by at least 37%, thereby elevating the oestrogen androgen ratio.[1,2]

It has been suggested in literature that discrete hepatic impairment in Efavirenz metabolism inflects oestrogenic activity, which may be enhanced by anti-tuberculosis therapy. One of our case also presented with concomitant tuberculosis.[4] Few anti TB drugs have been reported to cause gynaecomastia like Isoniazid, Thiacetazone, and Ethionamide, but these cases are very rare.[5] Like in only one of our case, the patient was administered HRZE, but the incidence of gynaecomastia with Isoniazid is very rare and he was not given Thioacetazone or Ethionamide, so the chance of getting gynecomastia due to anti- tubercular drug is excluded.

Surgery may be necessitated as treatment in some gynaecomastia patients. One of our cases had undergone excision of enlarged nodule from the breast. Antunes et al[6] reported bilateral mastectomy as the only successful treatment in a 46 year old male patient with gynecomastia secondary to ART in a low-income setting.

Limitations

We have presented a case series with limited number of cases. Gynecomastia in these patients was diagnosed after self reporting of enlarged breast by the patient himself, with no active screening done and therefore there is a possibility of under reporting. Prospective multicentric randomized controlled trials on large *HIV* population are warranted for validation of results. Had it been performed, it would have been possible to correlate these long term outcomes of ART.

CONCLUSION

The authors suggest that ART induced gynecomastia should be discerned at the earliest and timely modulation to a substitute ART regimen should be started to avert diminished adherence resulting from the perturbing side effect of gynecomastia. Though regress by its own on substitution of regime but some cases require definitive medical treatment or surgical treatment.

REFERENCES

1. Njuguna C, Swart A, Blockman M, Maartens G, Chisholm B, Stewart A et al. Cases of antiretroviral-associated gynaecomastia reported to the national HIV and

tuberculosis health care worker hotline in South Africa. *AIDS Res Ther*. 2016;13:40 .

2. 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. *J Med Med Sci*. 2011; 2:122-24.
3. Biglia A, Blanco JL, Martinez E, Domingo P, Casamitjana R, Sambeat M et al. Gynecomastia among HIV-infected patients is associated with hypogonadism: A case-control study. *Clin Infect Dis*. 2004; 39:1514-19.
4. Kratz JD, El Shazly AY, Mambuque SG, Demetria E, Veldkamp P, Anderson TS et al. Gynaecomastia in two men on stable antiretroviral therapy who commenced treatment for tuberculosis. *Malawi Med J*. 2016; 28(4):185-87. doi: 10.4314/mmj.v28i4.8.
5. Manjunatha Goud BK, Devi OS, Naya B, Devaki RN. A rare case of unilateral gynecomastia during antituberculous chemotherapy with Isoniazid. *Indian Journal of Pharmacology*. 2012: 44 (4); 521-22.
6. Antunes M, Marcella Schiavone M, Pizzol D, Di Gennaro F, Ludovico R, De Palma A. Bilateral mastectomy as radical treatment of gynecomastia secondary to antiretroviral therapy in a low-income setting: a case report. *Drug Saf -Case Rep.* 2018;5: 21 .

Corresponding Author

Dr Munesh Kumar, A-2, New Heera Bagh Flats, Near Kalyan Dharamshala, Jaipur, Rajasthan, India .

email: manuluvly@gmail.com