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Original Research Paper

Medicine

EFAVIRENZ INDUCED GYNAECOMASTIA IN MALES: A REPORT OF 4 CASES

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ABSTRACT Gynaecomastia is clinical condition associated with the development of the breast tissue in males. It can be common clinical presentation that varies from benign presentations in stages of human development to hormonal pathology, mainly due to hepatic dysfunction, malignancy, and adverse pharmacologic effects. With the introduction of Highly Active Anti Retroviral Therapy gynaecomastia cases are being reported in HIV infected men and have been associated with Efavirenz based regimen as its uncommon adverse effect. We report 4 cases of efavirenz induced gynaecomastia in seropositive male patient.

KEYWORDS : Gynaecomastia, Antiretroviral therapy, Efavirenz , seropositive.

INTRODUCTION;

The clinical definition of gynecomastia is the presence of a rubbery or firm mass extending concentrically from the nipple of the breast, and the histological definition is the benign proliferation of glandular breast tissue and is thought to result from an imbalance between oestrogens and androgens.(1) Commonly breast enlargement is observed in different age groups such as in neonates, adolescents, and in older men.The prevalence of gynaecomastia in adults varies from 24 – 70% with presentation ranging between the ages of 50 – 80 year.(2) Gynaecomastia has been less commonly identified among HIV infected men and the studies available involving these population are of small case series with lack of detailed hormonal study workup.(3) However, with the introduction of HAART gynaecomastia cases were reported in HIV men with incidence of 0.8/100 patoent .(4). At present HAART regimen containing Efavirenz as non-nucleoside reverse transcriptase inhibitor are preferred in treatment naïve patients. The underlying mechanism of Efavirenz induced gynaecomastia is not completely understood and different hypothesis like induction of an immune response, direct estrogenic effect of drug or altered steroid hormone metabolism by cytochrome 450 enzymes exists in medical literature to explain the underlying mechanism.(5)

We repot four cases of efavirenz induced gynaecomastia which recovered after change of regimen.

CASE REPORT 1;

A 18 year-old male came with history of bilateral breasts enlargement since 2 months.which was painful .There was no history of fever, sexual dysfunction, discharge from nipples or any other medication intake . Patient was reassured that there was no underlying malignancy Patient was diagnosed to have retroviral disease (HIV) since 5 year with a CD4 count of 826 cells/mm3.He was started on ART tenofovir, lamivudine and efavirenz (TLE) April 2016 to December 2017, Which was changed in jan 2018 to tenofovir, lamivudine and Nevirapine (TLN) due to presenting side effect. Recently patient develop nevirapine induced rash so it is replaced with atazanavir.

On clinical examination.

SMR B4 P5
SPL = adult size
Testicular volume =1.5 cc b/l

Investigation-

FSH -10 mIU/Ml, LH-4.1mIU/mL, Testoterone -3.2 ng/dL & estrogen-18 pg/ml

A USG breast revealing branching sheets and clusters of benign looking ductal epithelial cells with fibromyxoid stroma cells indicating the presence of gynaecomastia.

Digital mammography; negative for malignancy
Rest of the clinical examination and laboratory investigation unremarkable.

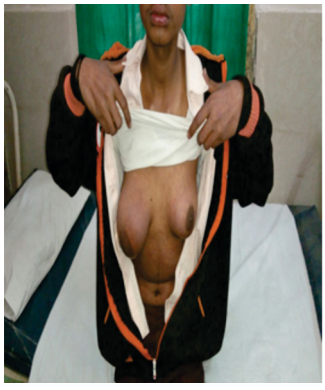

Figure no 1.

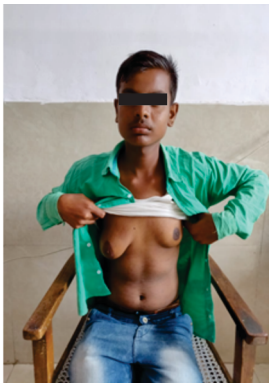

Figure no .2

A clinical diagnosis of medication-induced gynecomastia was considered and efavirenz was replaced with nevirapine in her ART regimen which was changed to atazanavir due to development of nevirapine induced rash. Patient follow up subsequently at the end of 6 month his gynecomastia reduced by 80% (figure no.2).

Our next three patient's data collected retrospectively which develop gynaecomastia secondary to efavirez.

Case report no. 2

A 18 year-old male had history of bilateral breasts enlargement since 3.5 months, which was painful. The patient was diagnosed to be positive for HIV 15 years back with a CD4 count of 286 cells/mm3 and initially was started on zidovudine, lamivudine and nevirapine (ZLN) therapy which was changed to tenofovir, lamivudine and zidovudine (TLN) due to zidovudine induced anemia till 2013. Later he had nevirapine induced rash for that nevirapine was replaced with efavirez. Patient develop gynaecomastia after 7 month of efavirenz therapy . Patient was evaluated for gynaecomastia with biochemicaly and ultrasonography (USG). Blood tests were performed for liver and kidney function results were within the normal range. USG depicted showed hypertrophy of breast glandular parenchyma with discrete hypoechoic mass bilaterally indicating the presence of gynaecomastia. Diagnosis of Efavirenz-induced gynaecomastia was made and the regimen was changed. Patient was followed up after 8 weeks, showing complete regression

of his gynaecomastia.

Case report no. 3

A 52 year-old male had history of bilateral breasts enlargement since 1 month, which was painful. The patient was diagnosed to be positive for HIV 10 years back with a CD4 count of 323 cells/mm3 and initiated was started on tenofovir, lamivudine and efavirenz (TLE), which was changed to to tenofovir, lamivudine and zidovudine (TLN).due to development of efavirenz induced gynaecomastia. Patient was evaluated for gynaecomstia with biochemicaly and ultrasonography (USG). Blood tests were performed for liver and kidney function results were within the normal range. USG Breast depicted hypo echoic areas with hyper echoic septae in the breast region with no areas of increased vascularity or dilated ducts bilaterally indicating the presence of gynaecomastia. Diagnosis of Efavirenz-induced gynaecomastia was made and the regimen was changed. Patient was followed up after 15 day,Showing complete regression of his gynaecomastia.

Case report no. 3

A 44 year-old male had history of bilateral breasts enlargement since 2 week, which was painful. The patient was diagnosed to be positive for HIV 11 years back with a CD4 count of 246 cells/mm3 and initially was started on stavudine , lamivudine and nevirapine (SLN), which was changed to tenofovir, lamivudine and efavirez (TLE) in 2013 due to change in treatment guideline for HIV but after 2 weeks patient developed gynaecomastia . Patient was evaluated for gynaecomstia biochemically and with ultrasonography (USG). Blood tests were performed for liver and kidney function results were within the normal range. USG Breast was performed but report not available with patient at present. Tentative diagnosis of Efavirenz-induced gynaecomastia was made and efavirez was replaced with nevirapine. Patient was followed up after 4 weeks, showing complete regression of his gynaecomastia.

Parameter	Case 1	Case 2	Case 3	Case 4
Age	18 year	18 year	52	44
Diagnosis date	2013	2003	2008	2007
Adherence to treatment	yes	Yes	yes	Yes
Mean CD4 Count	637	381	373	465
ART regimen and period	TLE (april 2016-Dec 2017) TLN (Jan 2018) TL+ Atazanavir (31/1/18)	ZLN TLN (24/6/13) TLE (17/2/14)	TLE (24/12/09 sept .15) TLN (11/9/15)	SLN (2008) TLE (21/1120 13) TLN(24/ 12/13)
Gyanecomasta developed after	2 year	7 month	5.6 year	1 month
Laboratory investigation	FSH -10,LH-4.1,Testostero ne -3.2 ,estrogen-18 pg/ml ,LFT & KFT- N	LFT & KFT-N	LFT & KFT-N	LFT & KFT- N
USG breast	subareolar ill defined soft tissue	Hypoechoic subareolar ill-defined soft tissue	Hypoechoic subareolar ill-defined soft tissue	-
Grade of Gynaecomastia	5	4	3	3
Follow up	Decreased by 80 % in 6 month	2 month	Regresss to normal after 15 day of change of ART	1 month

Discussion

We describe a case series of 4 patients with gynaecomastia on efavirenz-based ART. Efavirenz is the recommended NNRTI in the standard first-line ART regimen for adults.There has been increasing medical reports in the medical literature to associate use of HAART with the breast enlargement as its adverse effect.(6) In a study by PAM et al, analysis of fine needle aspiration (FNA) of breast masses in HIV infected patients revealed that 83% were diagnosed to have gynaecomastia, among them 40% were using HAART.(7)

It was previously proposed that EFV-induced gynaecomastia was mediated by either immune reconstitution or direct oestradiol-like effects, with mean clinical resolution at five months following removal of EFV.(8) A previous case series reported six patients from Nigeria who developed gynaecomastia on EFV therapy; in five of these cases, the gynaecomastia resolved upon discontinuation of EFV .(9)

We report three patient efavirez induced gynaecomastia. In our patient mean CD4 count varies from 637,381 , 373 and 465 cells/mm3 and duration of 2 year ,7 month, 5.6 year and 1 month while it regress after 6 month , 2 month , 15 day and 1month of discontinuation of efavirez respectively .it show that development of efavirez induced gynaecomastia does not depend upon CD 4 count and duration of efavirez intake. Similar cases reported previously Manfredi and colleagues reported stabilisation of breast development when efavirenz was continued [10]. Finally one study reported withdrawal of efavirenz as intervention with complete resolution of gynecomastia in all five patients in a mean period of five months [11]. Where it was quantified, the free testosterone & estrogen was normal in the one of our gynaecomastia cases but other three cases it is not possible to measure testostrerone & estrogen level due to limited resources. It was limitation of our study. In contrast, Biglia et al. reported an association between hypogonadism and gynaecomastia [12]. Typically, the hotline recommends that a free testosterone be done to exclude hypogonadism before switching efavirenz to nevirapine. Efavirenz among HAART have been recognized as a cause of gynaecomastia which when withdrawn have led to regression of symptoms [13] as seen in our case also where on stoppage of Efavirenz we found that the gynaecomastia regressed with alleviation of pain also. As there are multiple antiretroviral drugs available to treat HIV infection switching Efavirenz to alternative antiretroviral drug is one of the potential strategies to alleviate this adverse effect of Efavirenz. Other treatment modalities as use of Tamoxifen and other anti estrogenic drugs to treat Efavirenz induced gynaecomastia need further trials to validate its utility as definitive treatment in such cases. In refractory case we may need surgical intervention.

Conclusion

These case report shows that efavirenz may induce gynecomastia in HIV-infected patient on ART with complete resolution after withdrawal of efavirenz. Early recognition and differentiation from lipodystrophy are important to timely and correctly manage this side-effect in order to improve health, sustain adherence to ART and to reduce psychosocial stigma.

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