EFAVIRENZ-INDUCED GYNAECOMASTIA IN HIV INFECTED MALES: A REPORT OF 2 CASES

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ABSTRACT

Highly Active Antiretroviral Therapy (HAART) has been a major leap in the treatment of HIV. HAART has improved both morbidity and mortality in HIV patients. Of late, the cases of gynaecomastia are increasing secondary to initiation of ART. Efavirenz-induced gynaecomastia still remains underreported.

CASE PRESENTATION

We hereby report two cases of Efavirenz-induced Gynaecomastia in young males with median duration of 12 months on Efavirenz after valid written consent.

CONCLUSION

Efavirenz is being used as a first line regimen drug for ART initiation and also when patient has tuberculosis as opportunistic infection. Hence, the side effects of Efavirenz should be addressed and proper guidelines should be framed to manage the same.

KEYWORDS

Efavirenz, Gynaecomastia, HIV, HAART.

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INTRODUCTION: Highly active antiretroviral therapy (HAART) has revolutionised the treatment of HIV infected individuals, with reductions in morbidity and mortality. However, multiple adverse effects have been described and serious limitations concerning tolerability and adherence to these drugs exist. There is a broad agreement on the principles of first-line antiretroviral treatment. It should combine at least two nucleoside (or nucleotide) inhibitors of HIV reverse transcriptase and one non-nucleoside inhibitor, or at least one HIV protease inhibitor. Comparative studies have now identified the most effective combinations in terms of virological efficacy and tolerability. The combination should be chosen according to its established efficacy, adverse effects, risks of interactions, and convenience. There is no reference combination suitable for all patients. Gynaecomastia is benign enlargement of male breast tissue caused by proliferation of glandular breast tissue.[1] Drug-induced gynaecomastia is very rare. Efavirenz-induced gynaecomastia still remains an underreported fact. There is lack of enough evidence and exact mechanism is still unknown. The incidence of Efavirenz-induced gynaecomastia in few case reports was 0.8/100 patients/year with prevalence of 2.8 in those on ART for 2 years. (Piroth et al 2001).[2]

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CASE REPORT 1: A 28-year-old male came with history of swelling of bilateral breasts since 5 months, insidious in onset started in right breast followed by left breast within 15 days. Swelling was associated with pain. There was no history of fever, sexual dysfunction, discharge from nipples. Patient was reassured that there was no underlying malignancy. Patient was a known case of HIV since 2010, initially started on SLN (d4T/3TC/NVP) regimen later changed to ZLN (AZT/3TC/NVP) due to non-availability of drugs. He was recently started on TLE (TDF/3TC/EFV) regimen in Jan 2016. The above symptoms started after starting the above drugs. Clinically, patient was well built and nourished with oral candidiasis. He had bilateral breast swellings measuring 10 x 14 cm on right side and 8 x 10 cm on left side with well-defined margins, firm in consistency and freely mobile (Fig 1). Clinical diagnosis of Drug-induced gynaecomastia probably secondary to Efavirenz was made. Serum biochemistry, haematological profile was normal. Serum hormonal levels were normal. Ultrasonography of breast showed hypertrophy of breast glandular parenchyma with discrete hypoechoic mass bilaterally (Fig 2). FNAC of breast showed benign ductal epithelial cells in clusters. Diagnosis of Efavirenz-induced gynaecomastia was made and the regimen was changed. Patient was followed up after 6 weeks. The pain decreased and size of the swelling decreased significantly.

CASE REPORT 2: A 35-year-old male came with history of swelling of bilateral breasts since 3 months; insidious in onset started in both breasts, progressed from 1 cm to 10 cm in size over 3 months.

Swelling was associated with pain but no discharge. No history of fever, sexual dysfunction, discharge from nipples. Patient was a known case of HIV since 2009, initially started on ZLN (AZT/3TC/NVP) regimen, but was changed to TLE regimen since he had developed anaemia and tuberculosis. He was on TLE (TDF/3TC/EFV) regimen since one and half year. The above symptoms started after initiation of new drugs. Clinically, patient was well built and nourished.

He had bilateral breast swellings measuring 12 x 14 cm on right side and 13 x 10 cm on left side with well-defined margins, firm in consistency and freely mobile. (Fig 3). USG breast showed Hypoechoic subareolar-ill-defined soft tissue lesions suggestive of Gynaecomastia (Fig 4). Clinical diagnosis of Drug-induced gynaecomastia probably secondary to Efavirenz was made and the drug was stopped. Patient reviewed after 6 weeks and had decreased size and symptoms had subsided. (Fig 5).

Parameter	Patient 1	Patient 2
Age	28 yrs.	35 yrs.
Date of diagnosis	Aug 2010	Oct 2008
Date of Initiation of ART	Aug 2010	Feb 2009
Compliance	Good	Good
Alcoholism	Yes, Occasional	No
ART regimen and period	SLN (Aug 2010 to May 2013) ZLN (May 2013 to Jan 2016) TLE (Jan 2016 to May 2016)	SLN (Feb 2009 to May 2009) ZLN (May 2009 to Nov 2009) TLN (Dec 2009 to Jan 2013) TLE (Nov 2014 to May 2016)
Mean CD4 count	154 cells/microlitre	310 cells/microlitre
Clinical and Immunological Failure	Yes	No
Opportunistic infections	Tuberculosis 2 yrs. back	Tuberculosis one and half years back
USG breast	Hypoechoic subareolar ill-defined soft tissue lesions-Gynaecomastia Rt. 5.3 x 4.9 cm Lt. 4.9 x 4.1 cm	Hypoechoic subareolar ill-defined soft tissue lesions-Gynaecomastia Rt. 6.4 x 3.9 cm Lt. 5.4 x 2.1 cm
FNAC breast	Benign ductal cells in clusters-suggestive of Gynaecomastia	Benign ductal epithelial cells in sheets with bare nuclei in background-Gynaecomastia
Serum biochemistry	LFT-normal RFT-normal	LFT-normal RFT-normal
Hormone levels FSH LH Prolactin Testosterone Thyroid profile	 6.27 mIU/mL (1.4-18.7) 8.07 mIU/mL (1.5-9.3) 8.7 mIU/mL (2.1-17.7) 217 ng/dL (241-827) Euthyroid	 4.87 mIU/mL (1.4-18.7) 7.86 mIU/mL (1.5-9.3) 10.1 mIU/mL (2.1-17.7) 391 ng/dL (241-827) Euthyroid
Followup after drug stoppage USG (After 6 weeks)	Reduced in size Rt. 4.3 x 2.8 cm Lt. 3.4 x 3.1 cm	Reduced in size Rt. 3.3 x 2.9 cm Lt. 3.4 x 1.1 cm

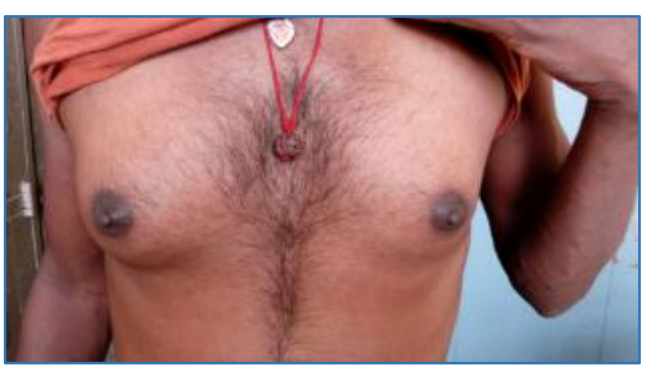

Fig. 1: At Presentation

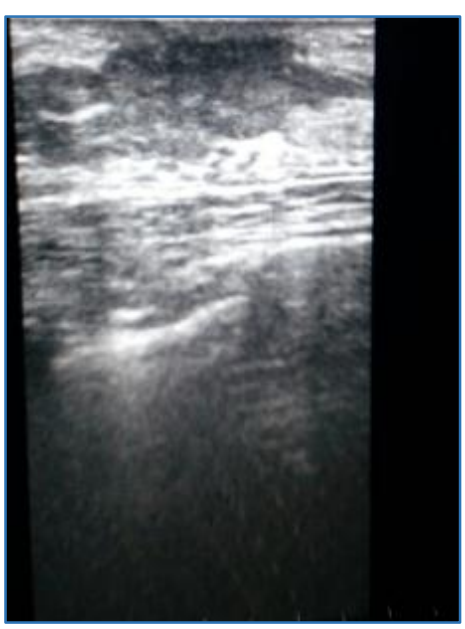

Fig. 2: USG Breast Showing Hypoechoic Mass

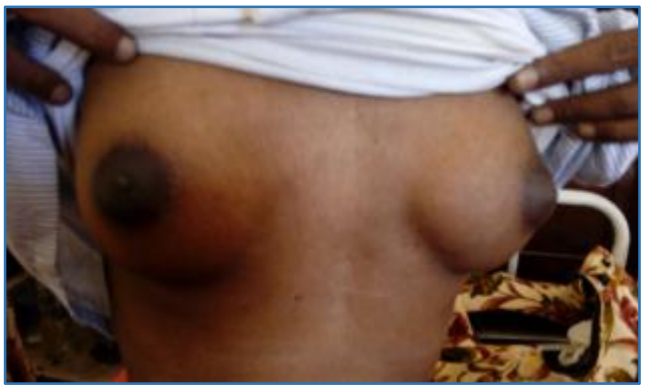

Fig. 3

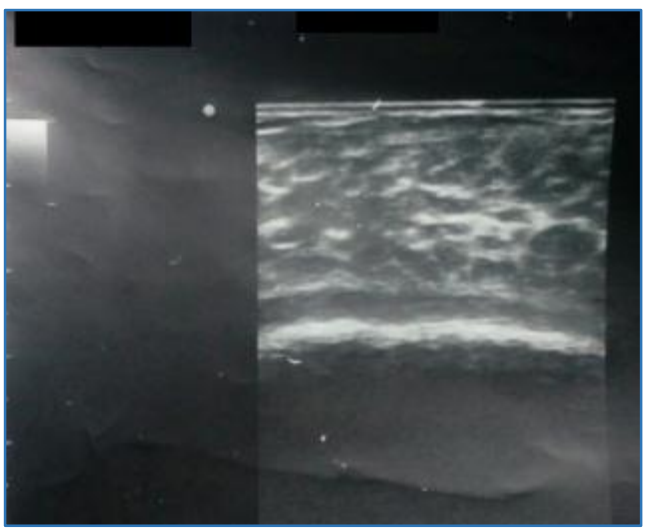

Fig. 4

Figure 3 & Figure 4 at Presentation

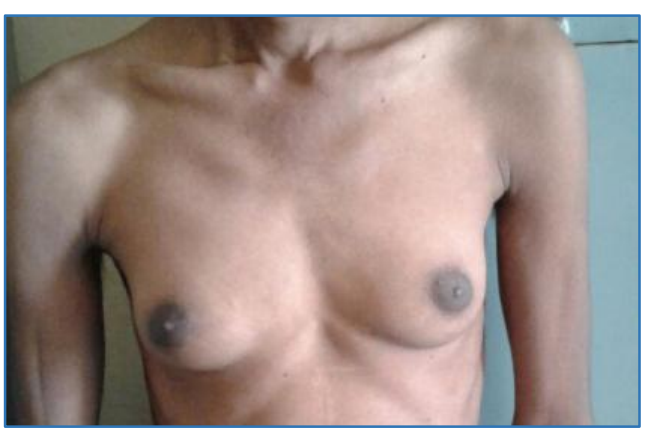

Fig. 5: After Drug Withdrawal

DISCUSSION: Reports show that 1.8–8.4% of male patients develop gynaecomastia with efavirenz treatment. Gynaecomastia is not uncommon in HIV-infected men undergoing HAART and it is usually transient. Efavirenz and didanosine treatment are associated with the emergence of gynaecomastia. An underlying hypoandrogenism seems to contribute to the emergence of this disorder in these patients.[3-9] The exact mechanism of Efavirenz-induced Gynaecomastia is not clearly known. It may be attributable to direct oestrogenic effects in breast tissues.

Decreased oestrogen metabolism, displacement from oestrogen-binding globulin, and diminished testosterone biosynthesis has also been postulated as possible mechanisms leading to gynaecomastia. Efavirenz directly modulates the oestrogen receptor and induces breast cancer cell growth in experimental models. MJ Sikora et al[10] demonstrated that efavirenz-induced growth of the oestrogen-dependent, ER-positive breast cancer cell lines MCF-7 and ZR-75-1 and that this effect was completely reversed by the anti-oestrogen ICI 182,780. They also provided evidence that efavirenz binds directly to ER-alpha.

These data provide evidence that Efavirenz-induced breast hypertrophy and gynaecomastia may be attributable in part to the ability of the drug to directly activate the ER. HIV is a chronic systemic disease that can cause Androgen deficiency. Gynaecomastia has also been linked to Protease inhibitor (PI) containing HAART as well as some nucleoside analogues (Donovan et al., 1999); giving rise to the hypothesis that gynaecomastia in patients receiving HAART may occur as part of the lipodystrophy syndrome. Antiretroviral agents inhibit cytochrome P-450 which may elevate the oestrogen-androgen ratio. Decreased oestrogen metabolism, displacement from oestrogen-binding globulin, and diminished testosterone biosynthesis has also been postulated as possible mechanisms leading to gynaecomastia. HAART also may cause lipohypertrophy and fat accumulation in breast (pseudogynaecomastia) and efavirenz has estrogenic activity. In our study, there was regression of symptoms in both patients after drug withdrawal.

CONCLUSION: Efavirenz-induced gynaecomastia is a common but rarely noticed side effect. The patient also has agony to reveal his symptoms. Identification and management of same will promote better drug compliance.

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