EFAVIRENZ Induced Gynaecomastia in a HIV Male presenting with Immunological and Clinical failure on HAART: A Case Report

Dr Samir Kumar Rama [1] Dr Dipankar Chakraborty [2] Dr Asif Iqbal Nizami [3]

ABSTRACT

Background: With the introduction of Highly Active Anti Retroviral Therapy gynaecomastia case are being reported in HIV infected men and have been associated with Efavirenz based regimen as its uncommon adverse effect. The underlying mechanism for Efavirenz induced gynaecomastia is not completely understood.

Case presentation: We present a case of 40 years old HIV infected male who presented with unilateral (right sided) gynaecomastia after nine months on Efavirenz based Antiretroviral regimen when started on antitubercular treatment for disseminated tuberculosis.

Conclusion: With Efavirenz based regimen being used as the first line therapy for HIV naïve patients and also in other settings as when treating tuberculosis co infection with antitubercular drugs, gynaecomastia as a side effect need to be recognized and intervened early with substitution of different antiretroviral drug so as to sustain adherence to antiretroviral therapy.

Key Words: Efavirenz, gynaecomastia, HAART, HIV, Tuberculosis

[1, 2, 3] Chief Medical Officer, Department of Medicine and Infectious Diseases, Assam Rifles Composite Hospital,Sukhovi,Nagaland, India

Corresponding author mail: ramasamir20@yahoo.in

Conflict of interest: Nil

INTRODUCTION

True gynaecomastia in the general population is estimated to have low prevalence (1% of adult men).[1,2] Histologically it is the benign proliferation of glandular breast tissue and when the diameter of the glandular tissue exceeds 0.5 cm gynaecomastia is palpated clinically.[3,4] 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.[5,6]

However, with the introduction of HAART gynaecomastia cases were reported in HIV men.[7-10] The incidence of

gynaecomastia in this patient group was 0.8/100 patient/year. At present HAART regimen containing Efavirenz as non-nucleoside reverse transcriptase inhibitor are preferred in treatment naïve patients and also widely used in other settings like tuberculosis.[11] Common adverse effects of Efavirenz are related to central nervous system which occurs in up to 50% of patients [12] but there are also increasing reports of gynaecomastia associated with Efavirenz based therapy.[13,14]

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.

CASE REPORT

Past medical history:

A 40 years old male detected to be HIV positive in 2008 in WHO clinical stage 1.His CD4 count was found to be 156 cells/mm3 and was started on HAART consisting of AZT/3TC/NVP with cotrimoxazole prophylaxis. Thereafter he was followed up yearly and his subsequent CD4 counts were 166, 147, 148 cells/mm3 in 2009, 2010 and 2011 respectively. Due to persistently poor adherence to HAART despite repeated counseling, his CD4 count never improved from the base line value.

He never presented with clinical failure in any of the follow ups.For last three years he adhered to the prescribed HAART and maintained his CD4 count between 160 to 170 cells/mm3. In April 2014 he presented with fever and dry cough of four week duration with swelling on the left side of the neck. Historically he had stopped ART for last six months. On physical examination left sided cervical lymphadenopathy was present with multiple,nontender,matted enlarged lymph nodes . On abdominal examination hepatosplenomegaly was clinically evident and rest of the systemic examinations was unremarkable.

On investigations his CD4 count was 58 cells/mm3.FNAC lymph node (cervical) showed caseous necrosis with granuloma and AFB positive consistent with lymph node tuberculosis.USG (abdomen) revealed

bilateral pleural effusion with ascites. CECT Abdomen revealed mild ascites with multiple small abdominal nodes and mild omental thickening.Few hypoechoic foci were seen in the spleen suggestive of granuloma.Sputum examination did not reveal AFB positive mycobacteria.CXR did not show parenchyma opacity and bilateral pleural effusion was present. All other hematological and biochemical investigations were within normal limits except Hemoglobin of 6.2gm/dl and TLC of 2200 cells/mm3.

Due to immunological and clinical failure presenting with fall in CD4 count (due to self stoppage of ART)and disseminated tuberculosis(abdominal/lymph node/pleura) he was started on ATT regimen 1 with HRZE wef 6/4/14 and ART regimen of TDF/FTC/EFV along with daily cotrimoxazole prophylaxis and macrolide prophylaxis weekly. He developed ATT induced hepatitis after four weeks of treatment with LFT showing T.Bilirubin-3.5 mg/dl,SGOT - 482 U/L and SGPT- 446 U/L .His ATT was stopped and was started on hepatic friendly antitubercular drugs consisting of Inj.Streptomycin/Ethambutol/Ofloxacin.

Thereafter, in two weeks his transaminitis and bilirubin settled down with LFT showing T.Bilirubin-0.7mg/dl,SGOT-33 U/L and SGPT-35 U/L. He was restarted on ATT (HRZE) wef 20/5/14 with gradual introduction of drugs. Thereafter he had good tolerance to drugs but developed paradoxical swelling of cervical lymph nodes on the left side due to immune reconstitution which was managed conservatively. After two months of intensive phase of ATT, he was started on continuation phase with Rifampicin and Isoniazid till 6/1/15, completing nine months of ATT along with continuation of ART and OI prophylaxis. His CD4 count increased to 213cells/mm3 on 29/7/14 and 223 cells/mm3 on 3/12/14.

History of presenting illness:

He again presented to our ART centre in February 2015 with complaints of swelling and discharge from the left axilla for 20 days duration along with swelling of the right breast for the same duration. He also complained of persistent swelling on the left side of the cervical lymph nodes. On

physical examination multiple, matted,nontender enlarged cervical lymph nodes were present on the left side. Left sided axillary lymph nodes were also enlarged with active discharge due to superadded infection and adjacent cellulitis. Right sided breast was slightly tender and there was a presence of palpable rubbery mass extending concentrically from the nipple which was 3 cm in diameter. There was no discharge from nipple and left side breast examination was unremarkable. There was also no other evidence of lipodysrophy.

Ultrasonography of the breast(right) showed hypo echoic areas with hyper echoic septae in the breast region with no areas of increased vascularity or dilated ducts suggestive of gynaecomastia (Figure 1).Serological status of hepatitis B and hepatitis C was nonreactive.Labaratory parameters including free testosterone index, level of fasting triglyceride,cholesterol,prolactin,total testosterone,sex hormone binding globulin,17β estradiol,follicle stimulating hormone,leutinising hormone and thyroid stimulating hormone were normal.

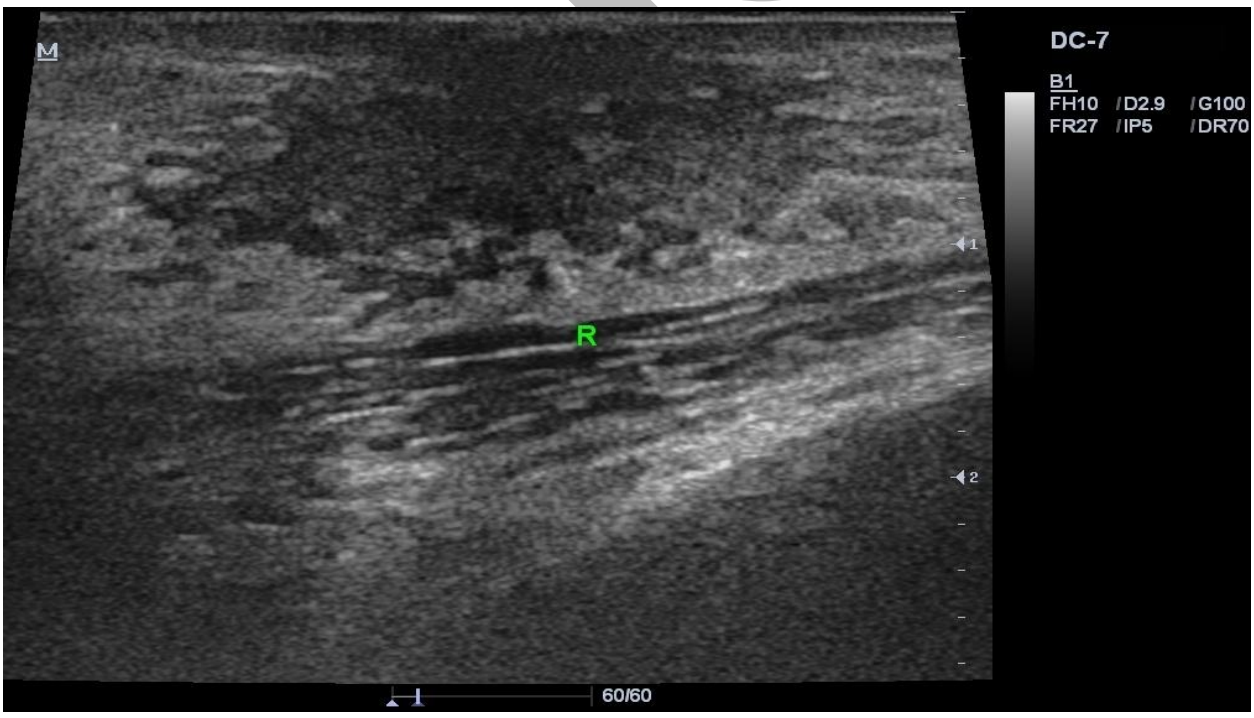

Figure 1: Ultra Sonography of breast (right side) suggestive of Gynaecomastia

FNAC of right side of the breast tissue was suggestive of glandular proliferation with fibro adipose tissue.

FNAC of left sided cervical lymph nodes suggestive of inflammatory exudates with persistent AFB stained positive mycobacterium seen.USG of left sided axilla suggestive of necrotic lymph nodes with negative AFB and Gram staining (Figure 2). Culture of the necrotic material from axilla did not showed any growth (including Mycobacteria).Other routine hematological and biochemical investigations were normal.

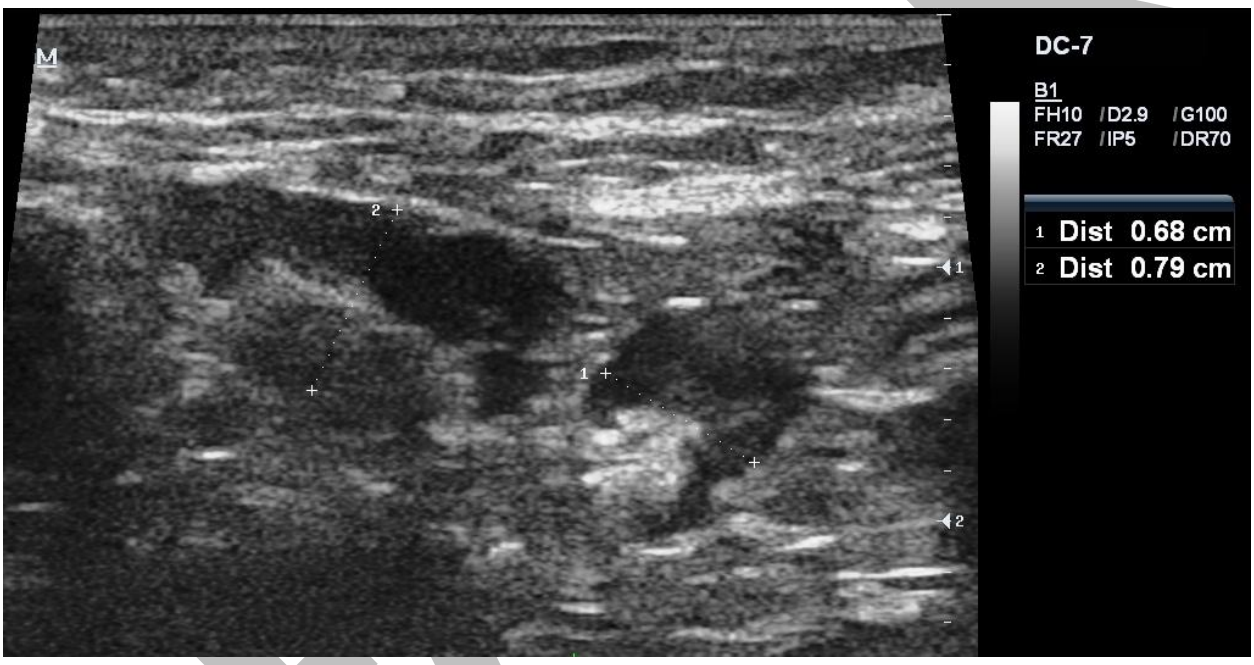

Figure 2: Ultrasonography of left axilla showing necrotic lymph nodes

As the individual had persistently enlarged lymph nodes with AFB positive we decided to continue the continuation phase of ATT for another six months (total ATT of 15 months).Left sided axillary swelling and abscess responded to the broad spectrum antibiotics after ten days. He was started on ART consisting of TDF/3TC/boosted PI (Lopinavir/Ritonavir) along with cotrimoxazole daily as OI prophylaxis with ATT consisting of Rifabutin(150 mg) daily with Isoniazid(300 mg).

After four weeks of stoppage of Efavirenz the size of the right sided breast

enlargement regressed clinically with abolition of the pain. The glandular size on palpation regressed from 3 cm size initially to 1 cm in size.

DISCUSSION

There has been increasing medical reports in the medical literature to associate use of HAART with the breast enlargement as its adverse effect.[15-18] In these patient group incidence of gynaecomastia was seen in 0.8/100 patient/year with prevalence of 2.8% in those treated for longer than 2 years in one study.[19] Reports have shown that 1.8% to 8.4% male HIV patients develop gynaecomastia on treatment with Efavirenz[13,14] even though the underlying mechanism of this adverse effect is not known. Other independent risk factors associated with gynaecomastia in HIV infected patients apart from HAART are chronic HCV infection[20], lipodystrophy linked to HAART containing protease inhibitors and some nucleoside reverse transcriptase inhibitors[21] and hypogonadism.[22]

In our case the individual did not had Hepatitis C infection and his hormonal assay were normal to rule out hypogonadism. The individual was on HAART containing AZT/3TC/NVP since 2008 and was changed to TDF/FTC/EFV in April 2014 when he was started on ATT for disseminated tuberculosis and developed anemia of chronic disease.

He developed unilateral (right sided) gynaecomastia after nine months on Efavirenz as also found in the study by Agbaji et al.[23] where delay in onset of gynaecomastia in patients on Efavirenz ranged from 8 to 16 months.

Among the hypothesis available in the medical literature to explain the underlying mechanism in development of HAART induced gynaecomastia, immune restoration with improvement in T cells cytokines particularly IL-2 response may increase the proliferation of the breast tissue. This can be an underlying contributory mechanism of gynaecomastia in our case also as when treated with ATT and ART for disseminated tuberculosis and immunological failure there was an increase in CD4 count from 58 cells/mm3 to 223 cells/mm3 in eight months with impressive immune restoration.

Also in addition direct estrogenic effect of Efavirenz in the breast tissues[24] might have contributed to the development of gynaecomastia in our case.

In our case Efavirenz was the most likely cause of gynaecomastia as we could not find any other cause of gynaecomastia through history, physical examination and laboratory tests.

Efavirenz among HAART have been recognized as a cause of gynaecomastia which when withdrawn have led to regression of symptoms[6,25] as seen in our case also where on stoppage of Efavirenz we found that the gynaecomastia (glandular enlargement) regressed from 3 cm diameter to 1 cm in four weeks time 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 and in our case also we have started protease inhibitor i.e Lopinavir/Ritonavir in the HAART in place of Efavirenz along with Rifabutin and Isoniazid as continuation phase of ATT.

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.

CONCLUSION

HIV infected men receiving Efavirenz based HAART can present with gynaecomastia as its adverse effect.Recognition of gynaecomastia as a side effect of Efavirenz is important to note as this drug is being used as a preferred component in the first line treatment of HIV infection worldwide.

REFERENCES

1. Braunstein GD. Gynecomastia. N Engl J Med 1993; 328:490–5.

2. Frantz AG, Wilson JD. Endocrine disorders of the breast. In: Williams RH, Foster DW, Kronenberg HM, Larsen PR, WilsonJM,eds.Williams textbook of endocrinology. 9th ed. Philadelphia: WB Saunders, 1998.

3. Echman A, Dobs A: Drug- induced gynaecomastia. Expert Opin Drug Sef 2008, 7: 691-702.

4. Ma NS, Geffner ME: Gynaecomastia in prepubertal and pubertal men. Curr Opin Pediatr 2008, 20: 465-470.

5. Melbourne KM, Brown SL, Silverblatt FJ.Gynecomastiawithstavudine treatment in an HIV-positive patient. Ann Pharmacother 1998; 32: 1108.

6. He`lene P, Jean-Marc M, Merle I, et al. Report of gynecomastia in five male patients during antiretroviral therapy for HIV infection. AIDS 1999; 13:2167.

7. Manfredi R, Calza L, Chiodo F (2001). Gynaecomastia associated with highly active antiretroviral therapy. Annals of Pharmacotherapy; 35:438-439

8. Paech J, Lorenzen T, von Krosigk A, Graefe K, Stoehr A, Plettenberg A (2002). Gynaecomastia in HIV-infected men: association with effects of antiretroviral therapy. AIDS; 16:1193-1194.

9. Arranz Caso JA, de Miguel Prieto J, Casas E, Sanz J (2001). Gynaecomastia without lipodystrophy syndrome in HIV-infected men treated with efavirenz. AIDS; 15:1447-1448.

10. Toma E, Therrien R (1998). Gynaecomastia during indinavir therapy in HIV infection. AIDS; 12:681-682.

11. Hammer SM, Eron JJ Jr, Reiss P et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. JAMA 2008; 300: 555–570.

12. Cespedes MS, Aberg JA. Neuropsychiatric complications of antiretroviral therapy. Drug Saf 2006; 29: 865–874.

13. Caso JA, Prieto Jde M, Casas E, Sanz J. Gynecomastia without lipodystrophy syndrome in HIV-infected men treated with efavirenz. AIDS 2001; 15: 1447–1448.

14. Mercie P, Viallard JF, Thiebaut R et al. Efavirenz-associated breast hypertrophy in HIV-infection patients. AIDS 2001; 15: 126–129.

15. Jover F, Cuadrado JM, Roig P, Rodrigeuz M, Andreu L, Merino J (2004). Efavirenz associated gynaecomastia: A report of five cases and a review of literature. Breast J. 10(3): 244-246.

16. Peyriere H, Mauboussin JM, Rouanet I, Merle C, Sotto A, Arnaud A, Hillaire-Buys D, Balmes P (1999). Report of gynecomastia in five male patients during antiretroviral therapy for HIV infection. AIDS; 13:2167-2168.

17. Schürmann D, Bergmann F, Ehrenstein T, Padberg J (1998). Gynecomastia in a male patient during protease inhibitor treatment for acute HIV disease. AIDS; 12:2232-2233.

18. Mastroianni A, Cancellieri C (2000). Gynecomastia associated with HAART. AIDS Read; 10:115–118.

19. Piroth L, Grappin M, Petit JM, Buisson M, Duong M, Chavanet P, Portier H (2001). Incidence of gynaecomastia in men infected with HIV and treated with highly active antiretroviral therapy. Scand. J. Infect. Dis. 3:559-560.

20. B Alejandra, B L Jose, M Esteban et al. Gynaecomastia among HIV- infected patients is associated with hypogonadism: A case- control study. HIV/AIDS.CID 2004: 1514-1519.

21. Donovan B, Bodsworth NJ, Mulhall BP, Allen D (1999). Gynaecomastia associated with saquinavir therapy. Int J STD AIDS; 10:49-50.

22. Collazos J, Martinez G, Mayo J, Ibarra S (2002). Sexual hormones in HIV- infected patients: influence of antiretroviral therapy. AIDS; 16:934-937.

23. A O Oche, A A Patricia, E N Peter et al. Efavirenz induced gynaecomastia in HIV-infected Nigerian men: A repore of six cases. J Med. Med. Sci. 2011: 1221-1224.

24. M J Sikora, J M Rae, M D Johnson, Z Desta. Efaviranz directly modulates the oestrogen receptor and induces breast cancer cell growth. HIV Med. 2010; 11: 603- 607.

25. Rietschel P, Corcoran C, Stanley T, Basgoz N, Klibanski A, Grinspoon S. Prevalence of hypogonadism among men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy. Clin Infect Dis 2000; 31:1240–4.