A CASE OF GYNECOMASTIA ASSOCIATED WITH EFAVIRENZ

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Abstract : We herein report on an HIV-infected patient with gynecomastia caused by efavirenz (EFV). A 57-year-old man was diagnosed with HIV-1 infection in 1994. He started therapy with zidovudine / lamivudine, didanosine, and EFV in December 2002. He felt painful breast hypertrophy after 5 months. There were firm, tender, unattached masses under the bilateral nipples, and ultrasonography showed benign enlargement of the breast without adipomastia. The blood levels of thyroid hormones, testosterone, estradiol, prolactin, and cortisol were normal. Therefore, we diagnosed him as having EFV-induced gynecomastia because of medication history and examinations. Although EFV was not stopped, his gynecomastia gradually improved.

Key words : human immunodeficiency virus infection, gynecomastia, efavirenz, adverse effect

INTRODUCTION

The prognosis of human immunodeficiency virus (HIV) infection has dramatically improved in the era of highly active antiretroviral therapy (HAART). However, HAART has been associated with the development of numerous acute and long-term adverse effects. Some morphologic changes are often observed as adverse effects of HAART[1]. There have been recent reports describing gynecomastia in HIV-infected men treated with HAART[2-5]. We describe herein an HIV-infected man with gynecomastia that developed after receiving efavirenz (EFV).

CASE REPORT

A 57-year-old homosexual man was diagnosed with HIV-1 infection at a public health office in December 1994. He commenced the antiretroviral therapy in October 1995, but often needed to change the regimen of antiretroviral therapy because of insufficient effects or adverse reactions. He received zidovudine (AZT) between October 1995 and July 1996, AZT and didanosine (ddI) between July 1996 and July 1997, AZT and lamivudine (3TC) between July 1997 and October 1997, AZT, 3TC and nelfinavir (NFV) between October 1997 and April 1998, stavudine (d4T), ddI and NFV between April 1998 and December 1998, d4T, ddI and indinavir (IDV) between December 1998 and August 2001, and d4T, ddI, IDV and ritonavir (RTV) between August 2001 and December 2002. He started the therapy with AZT/3TC, ddI and EFV in December 2002. EFV was the only agent administered for the first time. He had not received any other medications. His CD4 positive cell count was kept over 500/μl, and his

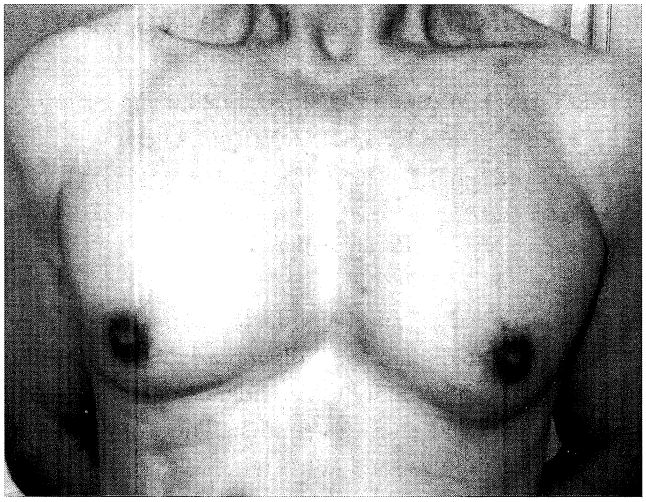

Fig. 1. Gynecomastia in this patient. The firm, tender, unattached masses were observed under his bilateral nipples

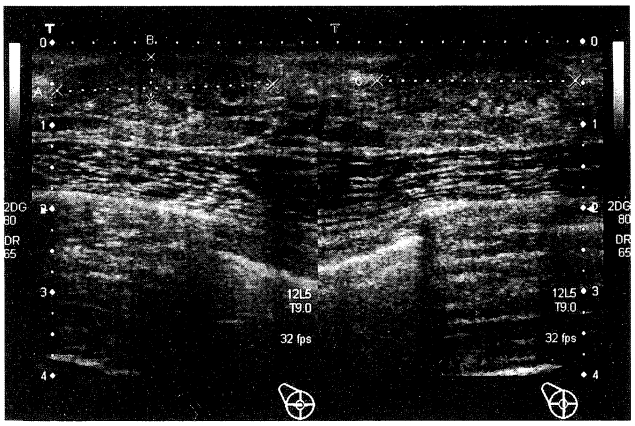

Fig. 2. Ultrasonography of the bilateral breasts showed ill-defined, heterogenous, echo-poor areas of nodularity deep to the nipple

plasma viral load was the limit of detection (<50 copies/ml). He felt painful breast hypertrophy at the end of May 2003. His height was 150.0 cm, and his weight was 47.6 kg. His blood pressure was 118/70 mmHg. There were firm, tender, unattached masses under the bilateral nipples (Fig. 1). His testicles were normal, and he showed no manifestations of lipodystrophy syndrome. Laboratory data showed a red blood cell count of $340\times10^4/\mu l$, serum aspartate aminotransferase of 36 IU/l, lactate dehydrogenase of 232 IU/l, γ-glutamyl transferase of 129 IU/l, creatinine of 1.2 mg/dl, triglycerides of 151 mg/dl, and total cholesterol of 268 mg/dl. The CD4 positive cell count was $591/\mu l$, and the HIV-RNA load remained undetectable. The blood levels of thyroid hormones, testosterone, estradiol,

Table 1. Table 1. Laboratory data

【Peripheral blood】			【Blood chemistry】			$CD4^+$	591 /μl
RBC	340×10⁴	/μl	AST	36	IU/l	$CD8^+$	929 /μl
Hb	13.8	g/dl	ALT	36	IU/l	【Virology】	
Ht	39.0		LDH	232	IU/l	HBsAg	−
WBC	5400	/μl	γ-GTP	129	IU/l	HCVAb	−
meta	1	%	UA	6.1	mg/dl	HIV-RNA	<50 copies/ml
st	1	%	BUN	20	mg/dl	【Endocrine】	
seg	60	%	Cre	1.2	mg/dl	TSH	1.97 μU/ml
ba	1	%	TG	151	mg/dl	T3	1.03 ng/ml
lym	31	%	T.cho	268	mg/dl	T4	6.4 μg/dl
mo	6	%	Glu	99	mg/dl	Cortisol	11.5 μg/dl
Plt	24.6×10⁴	/μl	【Serology/immunology】			PRL	8.6 ng/ml
			CRP	0.1	mg/dl	Estoradiol	36.5 pg/ml
						Teststerone	5.9 ng/ml

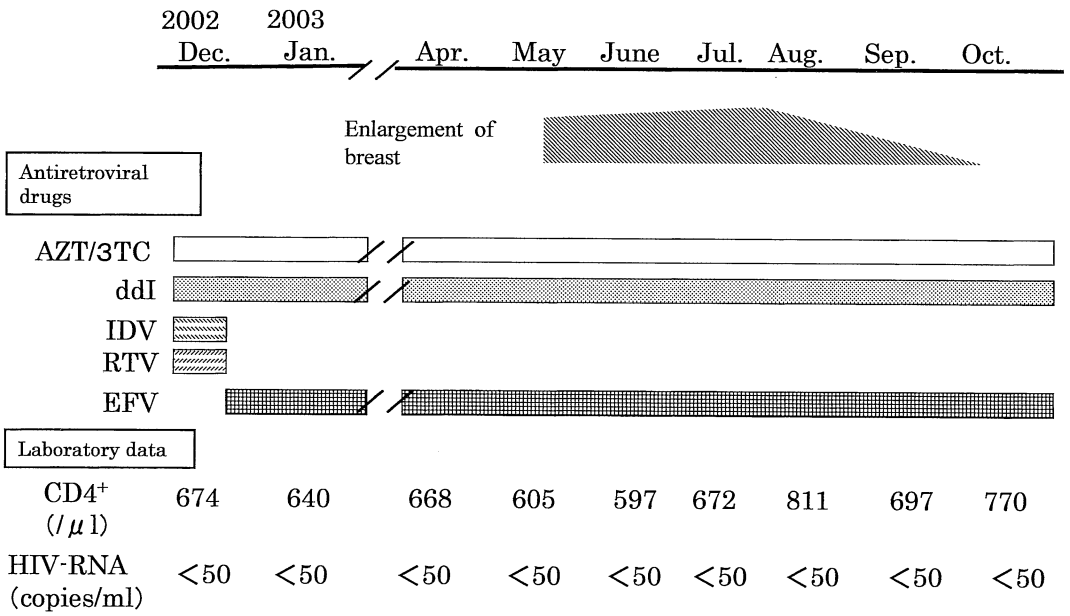

Fig. 3. Clinical course of this patient. AZT/3TC : zidovudine/lamivudine, ddI: didanosine, IDV: indinavir, RTV: ritonavir, EFV: efavirenz, CD4+: CD4 positive cell count.

prolactin and cortisol were normal (Table 1). Ultrasonography showed benign enlargement of the breast without adipomastia (Fig. 2).

We suspected gynecomastia associated with EFV because of the medication history and the results of examinations. We did not change the regimen of HAART because HAART was effective and his gynecomastia was mild. However, the size of his breasts regressed and they became no longer tender or painful after 5 months (Fig. 3).

DISCUSSION

Gynecomastia is defined as the development of prominent breast tissue in male. True gynecomastia is a condition in which there is an enlargement of the male breast due to an increase in the ductal tissue and periductal stroma[6]. On the other hand, lipomastia (pseudogynecomastia) is characterized by increased amounts of adipose tissue. Gynecomastia is recognized in 36–65% of normal men[7]. It is a normal physiologic al finding in 3 groups of males : newborns in whom it is transient due to exposure to maternal estrogens, adolescents who experience a transient gynecomastia in association with puberty, and elders in whom the androgenic activity decreases with aging. Gynecomastia has several etiologies, such as liver disease, hyperthyroidism, neoplasms of the testicles, pituitary tumors, adrenal tumors, and the use of drugs. Drugs can cause gynecomastia in several ways : acting as direct estrogen receptor agonists, increasing the estrogenic activity, enhancing the testicular estrogen secretion, interfering with the production of testosterone, or blocking the binding of testosterone to its receptor[8].

Our patient was not receiving other medications that could have caused gynecomastia, and this disorder appeared a few months after he began the HAART regimen including EFV that was the only agent received for the first time. He had no evidence of lipodystrophy syndrome. There were no biological or hormonal abnormalities that could explain gynecomastia in this case. These findings suggest that EFV can produce gynecomastia without lipodystrophy syndrome.

Gynecomastia has rarely been reported in HIV-infected men. However, gynecomastia has been increasingly reported in HIV-infected men taking several antiretroviral drugs since the introduction of HAART. At first, nucleoside reverse transcriptase inhibitors or protease inhibitors probably played a causal role[2-5]. Recently, there have been some reports on gynecomastia in HIV-infected men that was associated with EFV belonging to non-nucleoside reverse transcriptase inhibitors[9-11]. Therefore, we have to consider that gynecomastia may occur in HIV-infected men treated with several different classes of antiretroviral drugs.

The mechanisms underlying the development of EFV-associated gynecomastia remain unclear. Different hypotheses explaining this pathogenesis have been described in several reports. Qazi et al suggested that gynecomastia might represent a manifestation of immune restoration disease, because gynecomastia developed only in HIV-infected men who had excellent response to HAART[12]. The improvement of the helper T-cell cytokines response may influence the growth of breast tissue after commencement of an effective HAART. Besides, cytochrome P-450 inhibition induced by antiretroviral agents can elevate the

estrogen-androgen ratio. EFV was found to increase by 37% in the area under the curve (AUC) of coadministered ethynil estradiol, due to inhibition of cytochrome P-450[13]. Furthermore, EFV may have estradiol-like effects in the human body, triggering the growth of breast tissue. Sinicco et al found that blood samples from HIV-infected patients receiving EFV had unusually high levels of the female estradiol as measured by enzyme-linked immunosorbent assay (ELISA) method. Thus, EFV may bind to parts of the ELISA test that normally detect estradiol[14].

In conclusion, we report herein a case of gynecomastia associated with EFV. Our experience could explain the possible occurrence of gynecomastia in HIV-infected men receiving various antiretroviral drugs. Therefore, we should pay attention to gynecomastia in the long-term follow-up of HIV-infected men treated with HAART.

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