

Gigantomastia in perinatally HIV-infected female adolescent on efavirenz including antiretroviral treatment.

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Abstract

At present antiretroviral treatment has become a standard practice in treating HIV-infected individuals worldwide. With the need for a lifelong treatment, long term side effect of antiretroviral agents is an emergent issue of concern. We describe a perinatally HIV-infected adolescent female patient who developed gigantomastia while receiving efavirenz-based antiretroviral regimen. The diagnosis was confirmed by ultrasonography and mammography. The increase breast size interfered with her quality of life. Moreover, it did not improve after treatment modification (replacement of efavirenz with nevirapine) following by hormonal therapy (anti-estrogen). Breast reduction was performed. Although it is rare, physicians should be aware of this condition so that a timely diagnosis can be made. In most cases, only conservative treatment is sufficient, but in severe cases surgical intervention might be required.

Keywords: Therapy, Children, HIV.

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Background

Highly Active Antiretroviral Therapy (ART) has been available in Thailand since the year 1997; the natural history of people infected with HIV virus was changed since then [1]. Under Thai national program supported by Thai government since 2002, HIV-infected adults and children could survive longer; perinatally HIV-infected children could grow-up entering adolescent years and adulthood. However, when many have been placed on treatment, increasing number of individuals with adverse effects from long term use of ART was reported. Metabolic disorders including dyslipidemia, lipodystrophy, and impaired glucose tolerance were observed [2]. Breast hypertrophy or abnormal breast enlargement could be due to accumulation of fat tissue known as macromastia or lipomastia, and may be a part of lipodystrophy syndrome seen in HIV-infected patients on ART [3]. Another condition is a change in physical characteristic, breast enlargement in HIV-infected individuals treated with ART has been reported from several countries [4-8]. Gynecomastia, proliferation of glandular breast tissue, is the term used to describe abnormal breast enlargement usually in males. Similar condition in female is called breast hypertrophy,

or gigantomastia in case of extreme breast enlargement. The patient can present with neck, shoulder, or back pain, skin irritation or intertrigo resulting from breast size [9]. Emotional disturbance and effects on health-related quality of life were also reported [10]. The differential diagnoses include effect of external hormones or other concomitant drugs used, estrogen-androgen imbalance in adolescents and benign or malignant breast diseases.

Case Presentation

A 15 year and 2 month old girl with perinatally HIV-infection presented with bilateral breast enlargement. She was diagnosed as having HIV infection in early childhood when blood test during health check-up was performed. Without history of opportunistic infections or any HIV-related diseases, she has been initiated on ART at the age of 8 years. The girl was also diagnosed as having intellectual disability and attention deficit hyperactivity disorder. She has attended special educational school for several years. Later she quitted school as her grandmother decided that she should better be reared up at home. Her recent ART regimen which composed of lamivudine, zidovudine and efavirenz has been taken for 4 years. Other concomitant medications included risperidone and clonazepam.

When the girl was 15 years old, her mother noticed her exaggerated breast growth. She observed it for a few months before reporting to the HIV pediatrician. No pain or tenderness was noted. Physical examination revealed that the breasts were generalized increase in size without palpable mass. There were no other signs of lipodystrophy. Ultrasonography and mammogram demonstrated no evidence of solid mass or cystic lesion. A clinical diagnosis of medication-induced gynecomastia was considered. The pediatrician modified her ART regimen by replacing efavirenz with rilpivirine. Three months later when the girl came back for her scheduled follow-up visit, the breast size did not decrease. Moreover the girl felt much worried and anxious about her breast appearance. She talked less and denied food intake due to the fear that it might make her breast size become even larger. Adult HIV specialist and psychologist have been consulted, and her ART regimen was then modified to tenofovir, lamivudine and rilpivirine.

A month after the revision of her ART regimen and withdrawal of EFV, there was no regression in the size of her breast leading to persistence of her depression. She began to keep isolation in the house and denied any social interaction. Her mother requested for surgery. Thus, she was transferred to the tertiary care hospital for evaluation and management plan.

Physical examination revealed a female adolescent with intellectual disability. Her body weight was 45 kilograms (weight-for-age z-score -0.6) and height 146 cm (height-for-age z-score -2.1), body mass index 21.1 kg/m². The affected part was symmetrical pendula-shape breasts, sternal notch to nipple-areolar complex distance (SN-NAC) 28 cm, normal overlying skin, no striae (Figures 1 and 2). Other systems were unremarkable.

Her blood hormone levels revealed follicle stimulating hormone (FSH) 4.17 IU/L (normal range in women in follicular phase 3.5-12.5 IU/L); luteinizing hormone (LH) 15.75 IU/L (normal range in women in follicular phase 2.4-12.6 IU/L); and estradiol 329.50 pg/mL (normal range in women in follicular phase 12.5-166 pg/mL). The CD4 cell count was 559 cells/mm³ (19%); viral load was <40 copies/mL.

Hormonal treatment was prescribed; tamoxifen 20 mg/day was given orally. On the 3 month follow-up visit, the breast consistency was softer but did not decrease in size. After 6 months on hormonal therapy, surgical reduction was advised by endocrinologist and plastic surgeon that have been consulted and followed her condition. However, after the first counselling session with her caregivers, an agreement about surgical procedure could not be reached. They had fear of wound care after surgery and were afraid of other potential post-operative complications. The surgeon advised withholding the operation until they were ready. Thus, the girl remained on tamoxifen for other few months. Finally the caregivers came up and gave their consent for the surgery. Reduction mammoplasty with free nipple graft was eventually conducted. There were two specimens obtained, one was from right mastectomy, measuring 25.5 × 19 × 5 cm with 23 × 6 cm skin and 20 ×

14 × 3 cm separated soft adipose tissue. Another specimen was from left mastectomy, measuring 26 × 17 × 5.5 cm with 21 × 14 cm skin and 16 × 8 × 2 cm separated soft adipose tissue. Pathological results reported benign breast tissue with the presence of benign duct, rarely acini and increase fibrous stroma. No malignancy seen. There were no post-operative complications. When she came to a follow-up visit a month after hospital discharge, she recovered with good wound healing. Only minimal scar was observed (Figure 3).

Discussion

We report a case of gynecomastia in a perinatally HIV-infected adolescent girl while receiving efavirenz-based ART. Efavirenz, as well as protease inhibitors was consistently reported as associated with this anatomical change; it is suspected to have direct estradiol-like effects which can trigger the growth of breast tissue by binding



Figure 1. The anterior view symmetrical pendula shape breasts



Figure 2. The pendula-shape breast with normal overlying skin (lateral view)

to estrogen-receptor-alpha in the breast resulting in breast hypertrophy or gynecomastia, as well as modulation of estrogen receptor [11-13]. Moreover, similar to protease-inhibitors, effect of efavirenz on cytochrome P-450 inhibition might lead to an increase in estradiol concentration [14]. In this patient, we found high LH and estradiol levels, but normal FSH. Treatment with pharmacotherapeutic approach to control breast size has been attempted; Tamoxifen which was an anti-estrogen was prescribed. However, it did not seem to be effective. Apart from antiretroviral agents, other possible causes of gynecomastia include other medications, tumors, certain genetic syndromes, obesity, hyperthyroidism, chronic renal and liver diseases [4]. They are needed to be ruled out by history taking, clinical finding, or investigations. In this patient no evidence of such conditions found.

Regarding the effect of ART on breast, there were many case reports among HIV-infected adults from previous literature reviews. A case series of 6 patients from France in 2001 reported an increase in breast size among 4 men and 2 women aged 43-55 years being treated with efavirenz as a part of ART for HIV infection. The breast enlargement was not progressive and abated overtime even if the drug was continued without change [5]. The Spanish report included 5 HIV-infected male and female adults aged range from 30-47 years who received efavirenz for the duration of 4-15 months had gynecomastia. Efavirenz was withdrawn after diagnosis confirmed with ultrasonography, mammography and hormonal tests; regression in breast size was observed in the mean duration of 5 months after replacement [6].

The prevalence of breast hypertrophy in children and adolescents was supposed to be lower than adults as pediatric reports were rather scarce. According to the report from Ugandan pediatric ART study, breast hypertrophy was seen in one of 162 children initiated on efavirenz-based regimen at 52 weeks after treatment initiation [7]. A case report from South Africa was a 7 year old girl who has been on efavirenz for 10-12 weeks when presented with breast hypertrophy without other signs of puberty. Blood test confirmed all hormone levels were within normal range, switching from efavirenz to nevirapine was made. The breast enlargement was completely resolved in 4 weeks [8]. Another report from the UK was a 15 year old HIV-infected Kenyan boy treated with efavirenz-including regimen for 2 years. Bilateral breast enlargement was observed, and treatment with percutaneous hormonal cream was tried following by ART regimen modification. The conservative treatment attempts did not result in improvement and the boy had depressive symptoms (homebound and separated from his peers); he finally underwent bilateral mastectomy and true gynecomastia was confirmed by pathologic report which revealed proliferation of breast ducts without lobular unit [10]. The latter was quite similar to ours, except that our patient was a female. Breast hypertrophy was needed to be distinguished from pseudogynecomastia or lipomastia which was a characteristic of lipodystrophy syndrome and might be accompanying with other lipodystrophic

features. Ultrasonography and mammography are useful either to confirm diagnosis and to rule out mass or cystic lesions. They are non-invasive and can be performed in most clinical care settings. Next, blood hormone levels might help in determining whether there is an increase in estrogen or other related hormone levels. In our patient, despite of increase in serum estradiol level, treatment with anti-estrogen was not found to be effective. Part of it might be due to the fact that the diagnosis and treatment was delayed as the girl had pre-existing mental problem which inhibited her from telling her caregivers about the change in breast size. When recognized, it was much larger beyond the reversible point. Early developed gynecomastia can resolve when the causes were removed, i.e., drug withdrawn. However, it might not possible in a long term gynecomastia with the presence of fibrotic tissue [11,12]. However, the change in breast consistency confirmed effect of estrogen. In severe case like our patient, the abnormal breast size brought her discomfort, difficulty in daily living and some signs of depression. Surgical management was considered in order to retain optimal quality of life which was crucial especially for HIV-infected adolescents. In this case there was low risk of recurrence since the most likely drug related to gigantomastia has been discontinued.

Currently efavirenz is a part of the first-line ART for most HIV-infected populations recommended by the World Health Organization (WHO); it is significant that physicians should be aware of this unusual side effect so that it can be recognized in a timely manner. Change in breast size can cause both physical limitations due to the



Figure 3. Post reduction mammoplasty with free nipple graft

weight of the breasts, as well as psychological/psychiatric problems. Treatment options include ART regimen modification, hormonal therapy or surgery depending on the discussion between physician and patient/caregivers on a case-by-case basis. Nevertheless, surgical treatment should only be reserved for cases of massive breast hypertrophy where quality of life is obviously affected.

Conclusion

Gigantomastia is one among adverse events from long term antiretroviral treatment, specifically efavirenz-based regimen. Change in breast size can affect both physical and mental health of adolescent. Although it is rare, appropriate and timely diagnosis can be made if physicians and/or health care providers are aware of this condition. Available treatment options include ART regimen modification, hormonal therapy and surgery which should only be reserved for severe cases.

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