Case Report
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Severe Lipodystrophy and Gynecomastia in a Male Patient on Lopinavir-based Second-line Antiretroviral Therapy

Şiddetli Lipodistrofi ve Jinekomastisi Olan Erkek Hastada Lopinavir Tabanlı İkinci Basamak Antiretroviral Tedavi

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Abstract

With the introduction of highly active antiretroviral therapy, there has been a dramatic improvement in the clinical course of patients with human immunodeficiency virus infection and acquired immune deficiency syndrome. However, the favorable virological, immunological, and clinical profile of highly active antiretroviral therapy comes at the cost of some common and, at times, severe metabolic adverse effects such as dyslipidemia, body fat dysregulation/lipodystrophy, insulin resistance, and diabetes mellitus. We describe a case of a male patient from North India who developed similar adverse effects including gynecomastia while on the protease inhibitor lopinavir; the mention of such case is rare in the existing literature.

Keywords: HIV-AIDS; HAART; dyslipidemia; metabolic syndrome; lipodystrophy; insulin resistance; gynecomastia

Özet

Yüksek etkinlikli antiretroviral tedavinin kullanıma girmesiyle birlikte insan immün yetmezlik virüs enfeksiyonu ve kazanılmış immün yetmezlik sendromu olan hastaların klinik seyirlerinde dramatik bir iyileşme olmuştur. Ancak, Yüksek etkinlikli antiretroviral tedavinin olumlu virolojik, immünolojik ve klinik profiline karşılık sık rastlanan ve kimi zaman da şiddetli olabilen dislipidemi, vücut yağ disregülasyonu/lipodistrofi, insülin direnci ve diabetes mellitus gibi bazı metabolik yan etkiler ortaya çıkmaktadır. Bu çalışmada, bir proteaz inhibitörü olan lopinavir ile tedavi edilmekte iken, jinekomasti de dâhil benzer advers etkiler gözlediğimiz kuzey Hindistanlı bir erkek hasta, güncel literatürde az rastlanmasından dolayı sunulmuştur.

Anahtar kelimeler: HIV-AIDS; YEART; dislipidemi; metabolik sendrom; lipodistrofi; insülin direnci; jinekomasti

Introduction

Since the beginning of the human immunodeficiency virus infection-acquired immune deficiency syndrome (HIV-AIDS) epidemic in the year 1980, more than 75 million people have been infected with HIV and more than 36 million have died of this dreaded disease. Although progress has been made on HIV-AIDS treatment, the global crisis of HIV-AIDS shows few signs of slowing down. The introduction of highly active antiretroviral therapy (HAART) has changed the natural history of the disease and led to a substantial decline in infection-related morbidity and mortality. However, these benefits come at the cost of significant toxicity on a long-term exposure, including metabolic adverse effects such as dyslipidemia, lipodystrophy, insulin resistance, hepatic steatosis, diabetes mellitus, increased cardiovascular risk, and lactic acidosis. Initially, the development of these effects was ascribed solely to protease inhibitor (PI) therapy, but it was later found to be related to certain nucleoside reverse transcriptase inhibitors as well. Lipodystrophy, or fat redistribution syndrome, is a term used to characterize the various changes in body fat composition. Various mechanisms for lipodystrophy in HIV have been suggested, including

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chronic HIV infection itself, mitochondrial dysfunction, cytokine alterations, direct toxicity of PIs, and other antiretroviral use.

Case Report

A 41-year-old male patient was detected with HIV infection in January 2004 and was initiated on antiretroviral therapy (ART) since then. He has been under follow-up in the Infectious Disease Clinic at our hospital, and the treatment details are outlined in Table 1.

On an outpatient visit in 2014, the patient reported concerns regarding symptoms of progressive weight gain, abnormal body fat distribution in the form of central obesity, and prominent fat deposit at the back of the neck. He denied noticing any purple striae, easy bruising, proximal weakness, or hyperpigmentation. There was an associated history of gradually progressive nonpainful breast enlargement bilaterally for last 4-5 years. He denied the history of erectile dysfunction or decreased facial hair shaving frequency. The patient did not have any addictions in the form of smoking/alcohol/recreational drug use. There was no history to suggest exogenous steroid exposure. However, he had a sedentary lifestyle with irregular and malicious dietary habits. He was also detected to have hypertension and diabetes mellitus 4 years back for which treatment was ongoing with oral antihyperglycemic drugs (OADs) and antihypertensives.

Clinical examination revealed a middle-aged male patient with the following anthropometric parameters: weight: 100.5 kg, height: 172 cm, body mass index: 33.9 kg/m^2, waist circumference: 104 cm, hip circumference: 116 cm, waist-to-hip ratio: 0.896, blood pressure: 142/90 mmHg (right arm, supine position). Grade 4 acanthosis nigricans was noted over the neck. Lipohypertrophy in the form of supraclavicular fat accumulation and a dorsocervical fat pad (buffalo hump) were also seen. Goiter, skin tags, abdominal striae, ecchymosis, and proximal weakness were absent and hyperpigmentation was present in the areas of acanthosis. Bilateral nontender gynecomastia (with glandular diameter >4 cm on both sides) was also noted. Bilateral testes were normally palpable in the scrotum (volume: 20 mL bilaterally by Prader orchidometer). Systemic examination was essentially normal (Figure 1).

Investigative work-up including blood counts, electrolytes, and liver and renal function tests was unremarkable. Fasting venous plasma glucose was 160 mg% with glycated hemoglobin of 7.8%. Fasting lipid profile (after 8 hours of overnight fasting) was deranged with total cholesterol (211 mg%), triglycerides (281 mg%), low-density lipoprotein (LDL) cholesterol (140 mg%) and high-density lipoprotein (HDL) cholesterol (29 mg%). Hormonal investigations including serum T4 (8.4 µg/dL; range: 5.1–14.1 µg/dL), serum thyroid-stimulating hor-

Table 1. Details of antiretroviral treatment received by the patient.

Month/Year	ART Drugs	CD4 Cell Count (/µL)	Comments
Jan 2004-August 2006	Stavudine, Lamivudine, Nevirapine	326-March 2005 262-February 2006	Poor compliance with treatment reported.
August 2006-January 2007	Stavudine, Lamivudine, Efavirenz	180-August 2006 57-December 2006	Patient started on antitubercular therapy for tubercular lymphadenitis. Nevirapine substituted for Efavirenz.
January2007-March 2007	Stavudine, Lamivudine, Nevirapine	20-January 2007 35-March 2007	Nevirapine substituted for Efavirenz after completion of ATT. Drug failure suspected due to persistent CD4 decline. HIV viral load at this time was high (1.8×105 copies/mL) Decision to switch over to PI (Protease Inhibitor) based regimen made.
March 2007 till date	Tenofovir, Emtricitabine, Lopinavir/Ritonavir	414-October 2007 685-July 2013	Immunological and clinical recovery occurred with second line regimen. Patient developed lipodystrophy, dyslipidemia, diabetes, hypertension.

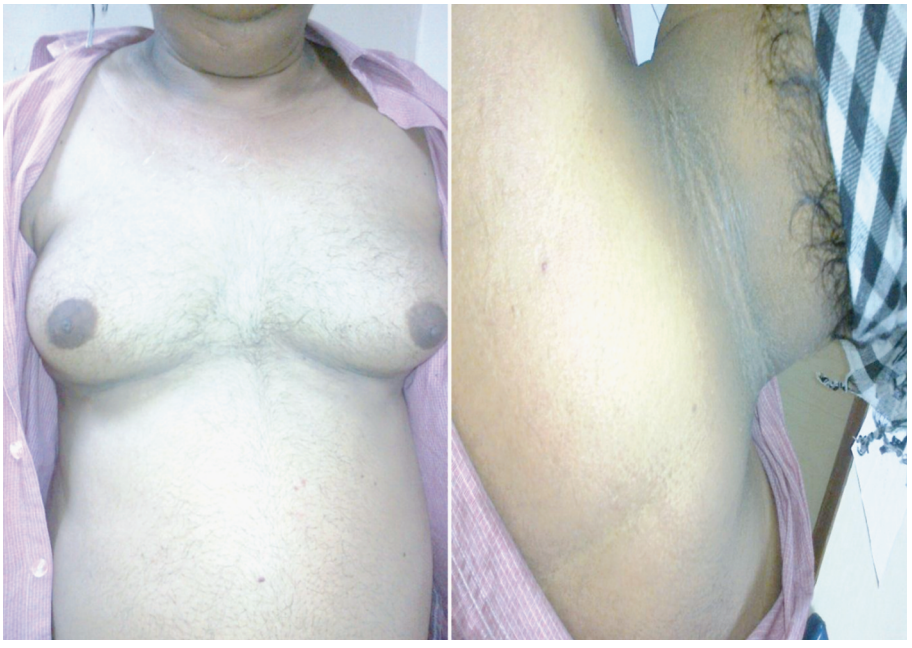

Figure 1: Image showing severe acanthosis nigricans and prominent dorsocervical fat pad and bilateral gynecomastia in the patient.

mone (2.47 mIU/mL; range: 0.27-4.2 mIU/mL), serum luteinizing hormone (LH) (3.5 mIU/mL; range: 1.7-8.6 mIU/mL), serum follicle-stimulating hormone (FSH) (7.4 mIU/mL; range: 1.5-12.4 mIU/mL), serum testosterone (3.7 ng/mL; range: 2.4-8.3 ng/mL), and serum morning cortisol (15.6 µg/dL; range 6.2-19.4 µg/dL) were within normal limits.

He was prescribed dietary and lifestyle modifications in form of 1400-kcal diet and was advised regular aerobic exercise. For dyslipidemia, lipid-lowering therapy with rosuvastatin 10 mg was added. The patient was advised to continue similar OADs and ART regimen.

Discussion

Lipodystrophy, or fat redistribution syndrome, is a term used to characterize the various changes in body fat composition. It may be classified as lipohypertrophy, lipoatrophy, or mixed form. Various mechanisms for lipodystrophy in HIV have been suggested, including chronic HIV infection itself, hypercortisolism and steroid perturbations, mitochondrial dysfunction, cytokine alterations, direct toxicity of PIs, and other antiretroviral use (1-4). Clinically, fat wasting has been described as sunken eyes, sunken cheek, temple hollowness, prominent zygomatic arch, prominent veins, loss of skin folds, and loss of shape and contour of buttocks. Fat hypertrophy is described as facial fat accumulation, dorsocervical fat pad (buffalo hump), breast enlargement, increase in abdominal girth, and presence of lipomas. In order to overcome these body changes, each case must be treated on an individual basis as data for the normality of body fat distribution do not exist.

Male breast tissue development and maintenance is mainly regulated by the local androgen:estrogen ratio. Gynecomastia, defined as a benign proliferation of male breast glandular tissue, is caused principally by an imbalance in the breast androgen:estrogen ratio. Prolactin, growth hormone, insulin, insulin-like growth factor 1, and cortisol are permissive trophic factors that require an imbalance in estrogen and androgens to cause gynecomastia.

Gynecomastia occurs physiologically in neonates, pubertal boys, and adult men. However, males with new onset of gynecomastia that is tender, >4 cm, or with a progressive increase in size should be evaluated. The etiological causes of pathological gynecomastia can be divided into the following categories:

a) Androgen deficiency states as primary and secondary hypogonadism.

b) Conditions with resistance to testosterone action as androgen insensitivity syndrome.

c) Estrogen excess states as estrogen-secreting testicular or adrenal neoplasms, familial aromatase excess syndrome.
d) Systemic diseases such as chronic liver disease, chronic kidney disease, HIV infection
e) Drug-induced gynecomastia due to the use of estrogen, testosterone, human chorionic gonadotropin (HCG) preparations, spironolactone, cimetidine, flutamide, bicalutamide, opioids, marijuana, alcohol, and HAART
Many pathological states, such as thyrotoxicosis, have multiple contributory factors to the causation and cannot be strictly categorized into one broad mechanism. A detailed history and examination, including the examination of genitalia for any ambiguity, testicular asymmetry, or mass lesion, is therefore needed in each patient with pathological gynecomastia.
The minimum laboratory evaluation needed in a patient includes liver and renal function tests, thyroid function tests and serum testosterone, FSH, and LH evaluation. Additional evaluation is based on the history, examination, and the results of initial tests. Prolactin is a permissive lactotrophic hormone that stimulates breast growth when estrogen effects are relatively high compared with testosterone effects, but prolactin alone is unlikely to cause gynecomastia as men with hyperprolactinemia lack this finding. By contrast, tumors secreting estradiol, dehydroepiandrosterone sulfate, and HCG suppress gonadotropin (LH/FSH) levels; therefore, these tests are only needed in selected cases with suppressed gonadotropin levels. In most cases with gynecomastia, a definitive cause is not found; therefore, these cases are labeled as idiopathic gynecomastia.
In our patient, we suspected the possibility of HIV- and HAART-induced gynecomastia; however, a basic evaluation to rule out alternative causes was performed, which was negative. Serum sex hormone-binding globulin levels are increased in 30-55% patients with HIV infection; hence, free testosterone is a better marker to diagnose hypogonadism in these patients. Free testosterone testing could not be performed in our patient as the test is unavailable at our center.
Per se, HIV infection is associated with an increased prevalence of gynecomastia. Possible contributing factors include hypogonadism, increased use of illicit and prescription drugs known to cause gynecomastia, and severe chronic kidney or liver disease. Moreover, any form of HAART regimen may be associated with an increased risk of gynecomastia, but regimens including efavirenz have reportedly been the most likely reasons to cause gynecomastia.
Several studies have described breast enlargement in female patients taking protease inhibitors, suggesting a similar possibility in males (5,6). However, there are only very few reports describing male breast enlargement with PI-based therapy. Donovan et al. (7) described four cases of gynecomastia in a total of 500 men on PI-based therapy (mostly saquinavir), of which gynecomastia was reversed in three cases after discontinuation of the drug. However, it may not be appropriate to attribute gynecomastia entirely to PI-based therapy as several other factors including the use of nucleoside analogs, drug interactions, and HIV infection itself may also contribute. The etiopathogenesis of HAART-induced gynecomastia is not clear, but a proposed hypothesis is that HAART increases the local production of interleukins that increase breast aromatase activity and/or directly stimulate breast growth (13).
Lipodystrophy can be assessed and monitored using patient self-assessment, clinical examinations, skinfold thickness measurement, and imaging techniques (dual-energy X-ray absorptiometry, magnetic resonance imaging, computed tomography). The treatment options for lipodystrophy include switching over non-PI-based therapy, which may not be feasible in all cases; use of recombinant growth hormone, which may place patients at increased risk for developing diabetes; use of lipid-lowering agents; use of antidiabetic agents such as metformin (10) and pioglitazone; and surgical treatments such as liposuction (11) and subcutaneous mastectomy.
Dyslipidemia has been described at a prevalence of 20-80% in HIV-infected patients in various studies. Several factors contributing to lipid abnormality in this population include HIV infection itself; antiretroviral drugs, particularly PIs; genetic factors; and conventional dietary and lifestyle factors. HIV infection is associated with an increase in triglycerides and decrease in HDL cholesterol, LDL cholesterol, and total cholesterol levels, while PI-based therapy leads to increase in total cholesterol, triglycerides and LDL cholesterol and a decrease in HDL cholesterol (1). These abnormalities along with an increase in the incidence of insulin resistance and glucose intolerance (8,9) in patients on PIs place them at risk for the accelerated atherosclerotic disease. Therefore, abnormalities must be sought for and managed aggressively. Along with appropriate dietary and lifestyle management, lipid-lowering

therapy goes a long way in managing this complication.

Most of the hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) are metabolized by the cytochrome (CYP) P450 3A4 pathway, with the exception of rosuvastatin, fluvastatin (CYP2A9), and pravastatin (sulfation). Therefore, caution must be taken while prescribing these drugs with PIs, which are CYP3A4 inhibitors (12), as the accumulation of these drugs can lead to various adverse effects such as hepatotoxicity, myalgia, rhabdomyolysis, and myositis.

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Author Contributions

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