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HIV-infected hemophilia A patient presenting with gynecomastia

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ABSTRACT
We describe the case of a 24-year-old hemophilic man who had been a human immunodeficiency virus (HIV)-positive for the past 22 years and presented to our hospital with bilateral breast enlargement with the presence of microcalcifications. Etiology of breast enlargement in male HIV population and differential diagnosis between true gynecomastia and lipomastia are also discussed.

Key words: • *HIV* • *gynaecomastia* • *antiretroviral therapy*

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Highly active antiretroviral therapy (HAART) has dramatically extended survival in human immunodeficiency virus (HIV) seropositive patients. However, HAART treatment is associated with various side effects (1). Recent reports have described cases of breast enlargement in adult HIV patients who were being treated with various combinations of antiretroviral drugs (2–6).

Gynecomastia appears as a physiologic phenomenon in newborns, at puberty, and in the elderly. In adults treated with HAART, gynecomastia is generally of benign origin; nevertheless, should be considered.

Case report

A 24-year-old patient with hemophilia A presented to our hospital with bilateral breast enlargement that had developed gradually over the past six months. The patient had no pain or nipple discharge. There was no family history of breast cancer. The patient had been HIV seropositive since 1982, and he exhibited HIV-related thrombocytopenia with frequent subcutaneous hematomas in 1988 that responded to antiretroviral therapy, started in 1990. His current HIV stage (CDC) is B2, and his HAART regimen includes stavudine, lamivudine, and efavirenz for three years. He was coinfected with hepatitis C virus and has not responded to combined therapy with interferon plus ribavirin. He has not used alcohol, recreational drugs, methadone, or medications other than antiretroviral therapy.

A physical examination was done, which revealed a slightly tender bilateral breast enlargement. Laboratory examination showed a CD4+ cell count of 432 cells/μL and an HIV-RNA of 42000 copies/mL. Endocrinologic investigations including prolactin, thyroid-stimulating hormone (TSH), follicular-stimulating hormone (FSH), luteal hormone (LH), free testosterone (FT), estradiol, FT3, and FT4 revealed values within the normal ranges. The results of chest radiographs and blood and urine cultures for *Mycobacterium tuberculosis* and *Mycobacterium avium* were negative.

Mammography revealed enlargement of both breasts. The presence of a glandular tissue was demonstrated in a pattern similar to that seen in the heterogeneously dense female breast (Fig. 1). At the upper outer quadrant of both breasts; round and punctuate, well-circumscribed, high density, round microcalcifications were also seen (Fig. 2). No other abnormal lesion was present. Breast ultrasonography revealed the presence of a normal-appearing glandular tissue without other abnormalities. Well-circumscribed enlarged lymph nodes were demonstrated in both axillae. Abdominal computed tomography (CT) revealed diffuse fatty liver infiltration and spleen enlargement. Ultrasonography of the testis showed the presence of a small calcified lesion with characteristic acoustic shadow in the lower part of the scrotal sac.

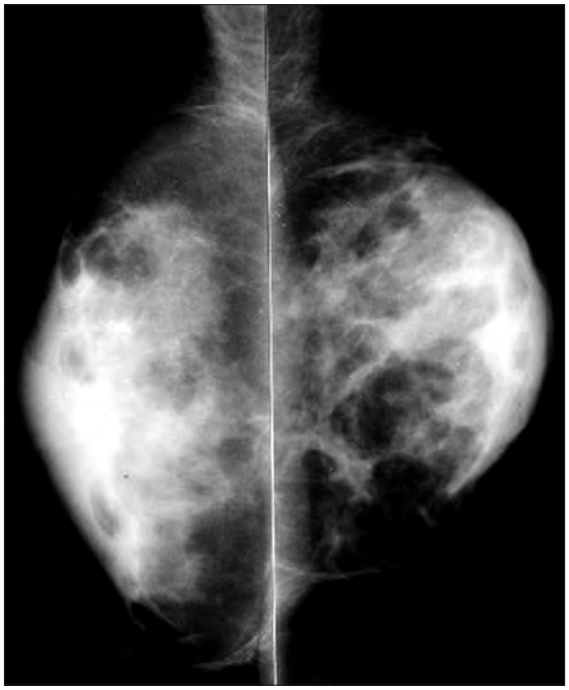

Figure 1. Mammograms showing the enlargement of both breasts. The glandular tissue is demonstrated in a pattern similar to that seen in heterogeneously dense female breast.

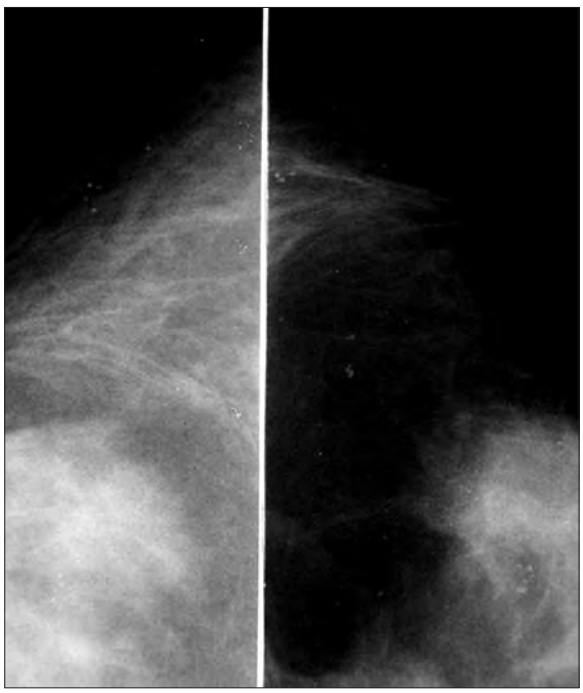

Figure 2. On the mammograms, round and punctuate, well-circumscribed, high density, round calcifications are seen at the upper outer quadrant of both breasts.

Magnetic resonance (MR) mammography was performed to investigate the cause and possible management choices for breast enlargement in our patient. The patient refused intravenous administration of contrast agent. Both T1-weighted and T2-weighted images showed the breast glandular tissue producing low signal intensity, whereas MR mammography with fat saturation sequence showed the presence of the enlarged glandular tissue, which could be easily differentiated from an adipose tissue (Figs. 3–5). Biopsy was postponed, and it was decided to follow the patient with close observation. On follow-up three and six months after diagnosis, mammographic findings remained stable.

Discussion

Breast enlargement in the HIV infected population was first described in 1987 (7). Since then there has been an increasing number of reports in the medical literature, suggesting that breast enlargement could present as a late side effect of HAART (2–6).

Patients on HAART who develop breast enlargement frequently find cosmetic issues distressing. Some patients also fear development of breast malignancy. The evaluation of breast enlargement helps to distinguish between benign cases of breast enlargement, which include true gynecomastia, pseudoangiomatous stromal hyperplasia, lipomastia, and opportunistic infections (8), and malignancy.

According to Piroth et al., the incidence of gynecomastia in male HIV patients treated with HAART was 0.8/100 patients/year, with a prevalence of 2.8% in those treated longer than two years (9). In another study, the incidence was 2.4 cases/100 patients receiving HAART per year. It developed mainly in subjects with good immunologic and virologic status, after an average of three years of HAART (10). The cases described in the medical literature suggest that most cases of breast enlargement in HIV-positive men are caused by gynecomastia or lipomastia. The pathogenesis of true gynecomastia (proliferation of ducts and peripheral stroma) (11) is unclear; in more than 50% of cases of gynecomastia, no cause can be found despite extensive investigation (12).

Breast enlargement may be secondary to the use of HAART medication including three to four antiretroviral drugs belonging to the nucleoside and nonnucleoside reverse transcriptase inhibitor categories and protease inhibitors (13). However, in a study, it was reported that gynecomastia was related to hypogonadism, rather than to the side effect of antiretroviral drugs (14).

Gynecomastia may also be related to a higher frequency of exposure of the HIV population to other agents that may cause gynecomastia, including antifungals, antituberculous drugs, and tricyclic antidepressants (15) in addition to drugs used for treatment of liver and renal diseases. Drugs used

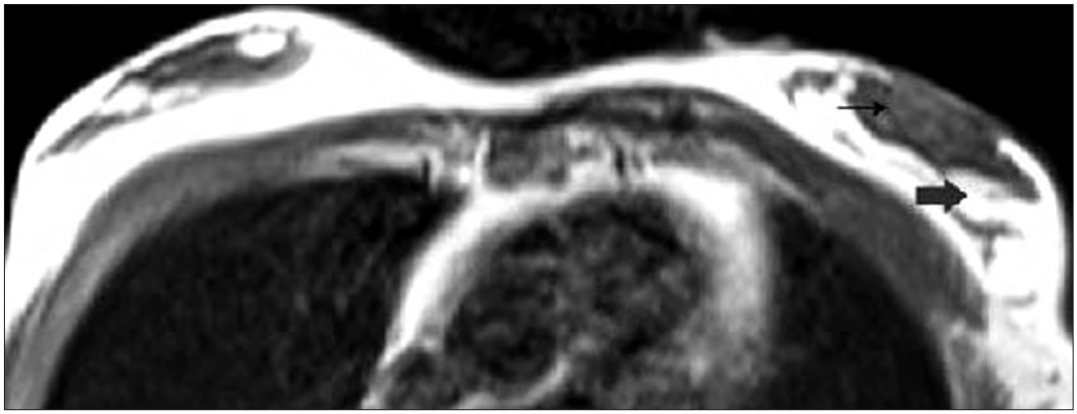

Figure 3. An axial T1-weighted MR image showing breast parenchyma with a low signal intensity due to the presence of glandular tissue *(narrow arrow)*, outlined by a high signal intensity of the surrounding fat *(wide arrow)*.

Figure 4. An axial T2-weighted MR image showing glandular breast tissue that produces low signal intensity *(arrow)*.

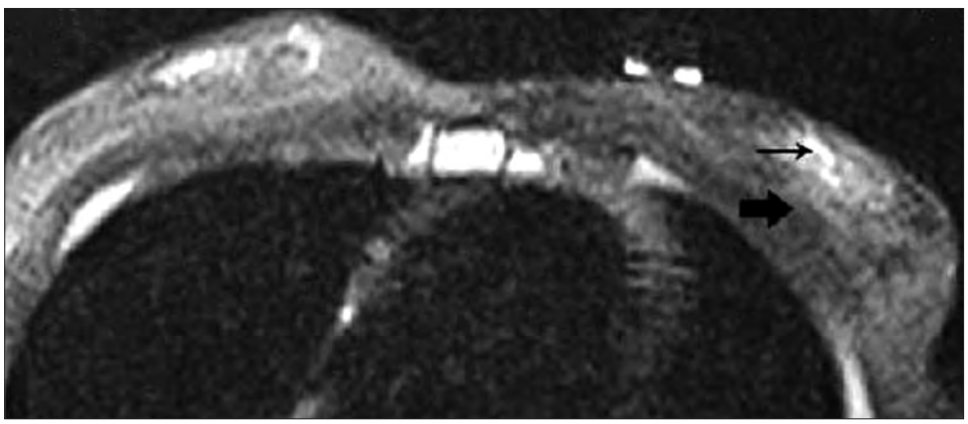

Figure 5. An axial SPIR MR image showing fat tissue with low signal intensity *(wide arrow)* and glandular breast tissue with intermediate signal *(narrow arrow)*.

for treatment of cardiovascular conditions, antiulcer drugs, recreational use of marijuana (11), and underlying medical conditions (e.g., liver disease, renal failure, certain neoplasms) (16) may evoke gynecomastia, as they do in adult males without HIV.

True gynecomastia in HIV patients is nearly always unilateral with focal findings. When bilateral, it is usually asymmetric (12). It can develop rapidly, and the breasts may be tender. However, gynecomastia may initially present unilaterally and progress to both breasts (10). In most cases spontaneous resolution will occur within six to twelve months without modifying therapy (10, 13).

There are three mammographic patterns of gynecomastia. First one, nodular gynecomastia, appears as fan-shaped density radiating from the nipple; there is a gradual tapering of the soft tissue into the surrounding fat. Nodular gynecomastia represents the early phase of gynecomastia and, when unilateral, may be confused with cancer. Second pattern which is dendritic type appears as a retroareolar soft tissue with prominent extensions radiating into the adipose tissue. Finally diffuse gynecomastia has a mammographic appearance similar to the heterogeneously dense female breast (17).

Lipomastia is characterized by increased amounts of adipose tissue in the breast and is one of the body-shape changes that occur in the fat maldistribution (lipodystrophy) syndrome, associated to some extent with HAART (18). In this syndrome, there is a wasting (lipoatrophy) of the peripheral body fat in the face, limbs, and buttocks, and a deposition of fat (lipohypertrophy) centrally in the abdomen, the breasts, and the cervicodorsal fat pad (19).

While the actual mechanisms underlying this abnormality are unknown, HIV-1 protease inhibitors and nucleoside reverse transcriptase inhibitors have been demonstrated to be associated with the development of HIV-associated lipodystrophy, by inducing either mitochondrial toxicity or adipocyte apoptosis (20–23). There are no studies reporting a specific HAART regimen associated with the development of the HIV-associated lipodystrophy.

Typically, lipomastia has a bilateral presentation, with more generalized enlargement than gynecomastia (15). However, there is a report of unilateral lipomastia mimicking breast cancer on US (24).

According to the reports, breast ultrasonography differentiates true gynecomastia from pseudogynecomastia, which is the result of fat tissue accumulation in patients with HIV-associated lipodystrophy (12, 25); it is advised for HIV-infected patients with breast enlargement. On sonograms, the fat in normal breast parenchyma is hypoechoic, and glandular tissue is intermediate in echogenicity (26). However mammography differentiates gynecomastia from lipomastia much more easily. Moreover, microcalcifications can be depicted on mammography, which in case of male breast cancer are fewer and coarser and may not appear rod-shaped as they do in women. Male cancer may appear as a nodular density, which may be well defined or ill defined; positioned eccentric, central, or distal relative to the nipple; rounded, lobulated, or oval shaped (17). MRI with fat saturation sequences is an excellent technique that clarifies the tissue distribution in the mammary gland and helps to assess the amount of fat accumulated in the breast; thus, it is advised in HIV-infected patients with breast enlargement (25).

Opportunistic infections that occur in the breasts may also present as breast enlargement and depend largely on the geography and degree of immune depression. The most common infections include tuberculosis and pyogenic abscesses that may lead to fatal septicemia (8).

Although most cases of breast enlargement in HIV-infected male patients have been benign, there have been reports of cases with breast cancer (27, 28). However, a relationship between breast cancer and HIV infection has not been demonstrated (15).

Kaposi sarcoma (KS) and non-Hodgkin lymphoma, two malignancies seen frequently in HIV-infected patients, can be localized in the breast (15, 29). Hodgkin lymphoma and the rare case of plasmacytoma have also been described to arise in breast tissue in HIV-infected individuals (15, 30).

In our case, the long-lasting use of antiretroviral drugs is implicated as the precipitating cause for the development of gynecomastia. In our patient, the presence of scattered, round, and typically benign microcalcifications led us to attribute these findings to previous subcutaneous hematomas, since extensive necrosis of adipose tissue often follows injury and may furnish a starting point for calcium deposits (31). These hematomas mainly occurred during the period with the HIV-related thrombocytopenia. Breast MR was performed in order to exclude KS or lymphoma. Finally MR examination revealed enlarged normal glandular tissue.

In conclusion, the use of HAART is associated with breast enlargement in HIV-seropositive men. Thorough investigation is required to exclude the rare case of breast cancer and other hormonal disorders and to differentiate true gynecomastia from lipomastia.

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