Breast Enlargement in 13 Men Who Were Seropositive for Human Immunodeficiency Virus

Devon L. Evans, Liron Pantanowitz, Bruce J. Dezube, and David M. Aboulafia

Departments of Medicine and Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; and Division of Hematology/Oncology, Virginia Mason Medical Center, Seattle, Washington

Breast enlargement, a condition that was rarely reported in the era before highly active antiretroviral therapy, is emerging as a problem in the treatment of male human immunodeficiency virus (HIV)-infected patients. Evaluation of this condition must distinguish between gynecomastia (proliferation of ducts and periductal stroma), lipomastia (adipose-tissue deposition), and malignancy. We describe 13 HIV-infected men, all of whom had exposure to antiretroviral therapy, who presented with breast enlargement. Nine of these patients had gynecomastia, only 1 had lipomastia, and 3 had lymphoma (2 had non-Hodgkin lymphoma and 1 had Hodgkin disease). Gynecomastia was unilateral in all but a single case. In addition, all but 1 of our patients with gynecomastia had prolonged exposure to protease inhibitors. Six patients had potential causes of gynecomastia other than antiretroviral therapy, including liver disease (in 2 patients), mild hypogonadism (in 1), long-term marijuana use (in 2), and use of medications that have known associations with gynecomastia (in 3). Although most causes of breast enlargement in HIV-infected men are likely to be benign, malignancies other than carcinoma are of concern.
problems, although patients also cite the fear of having a malignancy as a reason for seeking evaluation. Because breast carcinoma is rare in male patients [15], most cases of breast enlargement in HIV-infected patients have been presumed to be benign. However, there have been recent reports of various malignancies presenting in the breasts of HIV-infected men, including Kaposi sarcoma [16], plasmacytoma [17], and carcinoma [18–22]. In addition, non-Hodgkin lymphoma (NHL) may rarely present as a breast mass [23], although this has not been reported specifically in an HIV-infected individual. These infrequent reports serve as a reminder that breast enlargement in HIV-infected men may have a neoplastic origin. We describe 13 consecutive cases of breast enlargement in HIV-infected men who were seen and evaluated at our institutions, to provide information with regard to the frequency of gynecomastia and lipomastia and the risk of malignancy in this population. Three illustrative cases are presented in detail, 1 case each of gynecomastia, lipomastia, and lymphoma. In addition, the clinicopathologic features of gynecomastia and lipomastia are highlighted to aid in their differentiation.

METHODS

Study population. A presenting complaint of breast enlargement was used to identify male HIV-infected patients who presented to outpatient clinics during an 18-month period. Ten patients were observed at the Virginia Mason Medical Center HIV outpatient clinic (Seattle, Washington). Three patients were observed at Beth Israel Deaconess Medical Center (Boston, Massachusetts). Outpatient medical records were reviewed retrospectively. The guidelines for human experimentation of the US Department of Health and Human Services, Beth Israel Deaconess Medical Center, and Virginia Mason Medical Center were followed.

Study assessments. Parameters assessed included clinical symptomatology, medical history, the findings of a physical examination, CD4+ cell count, HIV-1 load, medications used, recreational drug habits, laboratory analysis findings, results of radiographic evaluation, and pathologic data. Available laboratory studies included liver, renal, and thyroid function tests, as well as determination of cortisol, prolactin, human chorionic gonadotropin, testosterone, estradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels. Most patients were studied with both mammography and breast ultrasonography. Pathologic specimens included breast biopsy specimens, surgical excision specimens, and 1 biopsy specimen of tissue from outside the breast. Diagnosis of gynecomastia was based on either radiographic or histopathologic data.

SELECTED PATIENT REPORTS

Patient 1: case of gynecomastia. A 38-year-old man with stable cutaneous Kaposi sarcoma sought evaluation of a mass on the right breast of 3 weeks’ duration. He had HIV infection diagnosed 3 years earlier, at which time his CD4+ cell count was 156 cells/µL and his virus load was 428,000 copies/mL. He had been treated with multiple antiretroviral regimens, the most recent of which included saquinavir, stavudine, didanosine, and abacavir, but he had been on a “drug holiday” for several months at the time of evaluation. Physical examination revealed a 1-cm, mobile, subareolar, nontender mass in the right breast. Endocrinologic evaluation revealed an elevated LH level, a low free-testosterone level, and normal levels of total testosterone, FSH, and thyroid-stimulating hormone (TSH). Mammography revealed gynecomastia, which was histologically confirmed by excisional biopsy (figure 1).

Patient 2: case of lipomastia. A 41-year-old, mildly obese man receiving a regimen of HAART that consisted of nevirapine, stavudine, and abacavir presented with bilateral breast enlargement of >1 year’s duration, but he had no focal nodules or breast masses. The findings of mammography were unremarkable, and ultrasonography revealed only increased amounts of adipose tissue. After he received counseling about nutrition and exercise, the patient began exercising regularly and lost 10 pounds, and his breast enlargement was no longer so prominent.

Patient 3: case of breast lymphoma. A 27-year-old man, who had a CD4+ cell count of 140 cells/µL and an HIV-1 load of 37,000 copies/mL while receiving zidovudine monotherapy, developed a 2-cm nodule on the left breast, which doubled in size during a 3-month period. Examination of a needle biopsy specimen yielded a diagnosis of diffuse, large B cell NHL. Staging evaluation revealed localized disease, and the patient was treated with multiagent chemotherapy. He achieved complete remission. He is presently receiving a HAART regimen of nelﬁnavir, stavudine, and lamivudine, and he has had no recurrent breast swelling or malignancy.

RESULTS

Thirteen HIV-infected men with breast enlargement were identified (table 1). Breast enlargement in these individuals was due to gynecomastia (in 9 patients), lipomastia (in 1), and lymphoma (in 3). The median age of the patients was 41 years (range, 27–74 years).

HIV infection status. Data regarding CD4+ cell count and/or HIV-1 load were available for 11 patients at the time of presentation. The median CD4+ cell count was 210 cells/µL (range, 19–600 cells/µL). Five patients had undetectable virus loads, and 5 others had virus loads of 1100–89,000 copies/mL.
HIV-1 load and the degree of immunosuppression did not correlate with the etiology of breast enlargement in these patients.

**Medications.** All patients had been treated with antiretroviral therapy after they had HIV infection diagnosed. Nine (69%) of these patients were receiving HAART at the time of presentation for breast enlargement. Protease inhibitor–based regimens included regimens with saquinavir, indinavir, nelfinavir, ritonavir, and lopinavir. The duration of HAART was >10 months for all of these patients. It is interesting to note that 2 of the patients (patients 1 and 11) who were not receiving HAART had other potential causes of gynecomastia, as discussed below. Multiple, sequential combinations of antiretrovirals had been taken by 3 individuals (patients 1, 10, and 11), all of whom were found to have gynecomastia. Two patients (patients 1 and 10) had been receiving regimens that

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Figure 1.  **Top,** Gynecomastia, florid type. There is a proliferation of ducts and stroma with very little adipose tissue. (Hematoxylin-eosin stain; original magnification, ×40.)  **Bottom,** Details of gynecomastia. At this magnification, the loose, cellular periductal stroma is distinguishable from the less-cellular background connective tissue. Also evident is ductal epithelial hyperplasia. (Hematoxylin-eosin stain; original magnification, ×100.)
Table 1. Characteristics of and findings for 13 HIV-1–positive men with breast enlargement.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>CD4⁺ cell count, cells/µL</th>
<th>HIV-1 load, copies/mL</th>
<th>Breast signs and symptoms</th>
<th>Potential causes other than HAART</th>
<th>Antiretroviral regimen at time of presentation</th>
<th>Other medication used</th>
<th>Mammography findings</th>
<th>Pathologic findings</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>NA</td>
<td>NA</td>
<td>Mass</td>
<td>KS, hypogonadism</td>
<td>None</td>
<td>—</td>
<td>Gynecomastia</td>
<td>Gynecomastia</td>
<td>Unilateral</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>NA</td>
<td>NA</td>
<td>Enlargement</td>
<td>—</td>
<td>HAART</td>
<td>—</td>
<td>Lipomastia</td>
<td>—</td>
<td>Bilateral</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>140</td>
<td>37,000</td>
<td>Nodule</td>
<td>—</td>
<td>Unknown</td>
<td>—</td>
<td>—</td>
<td>Lymphoma</td>
<td>Unilateral</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>195</td>
<td>&lt;50</td>
<td>Painful mass</td>
<td>—</td>
<td>HAART</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>600</td>
<td>&lt;50</td>
<td>Nontender mass</td>
<td>HCV infection, KS</td>
<td>HAART</td>
<td>—</td>
<td>Gynecomastia</td>
<td>Gynecomastia</td>
<td>Unilateral</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>390</td>
<td>&lt;50</td>
<td>Painful mass</td>
<td>—</td>
<td>HAART</td>
<td>—</td>
<td>Gynecomastia</td>
<td>Gynecomastia</td>
<td>Unilateral</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>283</td>
<td>&lt;50</td>
<td>Painful mass</td>
<td>Marijuana use</td>
<td>HAART</td>
<td>—</td>
<td>Gynecomastia</td>
<td>Gynecomastia</td>
<td>Unilateral</td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>110</td>
<td>1100</td>
<td>Painful enlargement</td>
<td>—</td>
<td>HAART</td>
<td>—</td>
<td>—</td>
<td>Solid mass</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>292</td>
<td>&lt;50</td>
<td>Enlargement</td>
<td>—</td>
<td>HAART</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>135</td>
<td>89,000</td>
<td>Painful enlargement</td>
<td>Hemophilia, HCV infection</td>
<td>HAART</td>
<td>—</td>
<td>Gynecomastia</td>
<td>—</td>
<td>Unilateral</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>450</td>
<td>6500</td>
<td>Mass</td>
<td>Marijuana use</td>
<td>None</td>
<td>Norandrostenodione</td>
<td>Gynecomastia</td>
<td>Gynecomastia</td>
<td>Bilateral</td>
</tr>
<tr>
<td>12</td>
<td>38</td>
<td>19</td>
<td>16,530</td>
<td>Painful nodules</td>
<td>Lymphoma</td>
<td>HAART</td>
<td>—</td>
<td>—</td>
<td>Lymphoma</td>
<td>Bilateral</td>
</tr>
<tr>
<td>13</td>
<td>41</td>
<td>210</td>
<td>NA</td>
<td>Painful mass</td>
<td>—</td>
<td>Dual nucleoside</td>
<td>—</td>
<td>—</td>
<td>Hodgkin disease</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE. HCV, hepatitis C virus; KS, Kaposi sarcoma.
included dual protease inhibitors; both of these patients had
gynecomastia.

In addition to HAART, 3 patients with gynecomastia (pa-
patients 5, 9, and 11) took prescription medications other than
HAART that have been independently associated with this con-
dition, including spironolactone, norandrostenedione, and ami-
triptiline. A history of long-term marijuana use was noted for
2 patients (patients 7 and 11), both of whom had gynecomastia.

**Comorbidities.** Coinfection with hepatitis C virus (HCV)
was present in 2 patients who had gynecomastia. One patient
(patient 5) had a liver biopsy performed at the time of HCV
diagnosis that revealed minimal inflammation. The other pa-

tient (patient 10) did not have a biopsy performed. Two patients
had a history of Kaposi sarcoma; one had been treated with 9-
cis-retinoic acid (patient 1), and the other had remained un-
treated (patient 5). Both had minimal cutaneous Kaposi sar-
coma at the time of presentation. One of the patients who had
received a diagnosis of NHL (patient 12) had previously been
treated for lymphoma, which was in complete remission before
his presentation with breast enlargement. This patient had no
prior lymphomatous involvement of the breast. His disease had
been limited to the abdomen and pelvis.

**Clinical signs and symptoms.** At clinical presentation, 8
patients (62%) had focal enlargement in a single breast, and 5
(38%) had bilateral findings. Radiographic or pathologic stud-
ies confirmed the diagnosis of gynecomastia in 9 cases; all cases
but 1 were unilateral. The single patient with lipomastia pre-

tended with bilateral disease. Features of lipodystrophy syn-
drome other than breast enlargement were present in 1 patient
(patient 5), who, in fact, had gynecomastia and not lipomastia.
Of the 3 patients with lymphoma (NHL or Hodgkin disease),
2 had unilateral disease. Seven (54%) of the 13 examined pa-

tients had pain associated with breast enlargement. Pain was
not associated with any specific diagnosis.

**Serologic studies.** All patients underwent extensive en-
docrinologic testing, including thyroid function tests and de-
termination of cortisol, LH, FSH, prolactin, testosterone, free
testosterone, and estradiol levels. Evidence of mild hypogo-
nadism was found in a single patient with gynecomastia (patient
1). Of the 2 patients who had HCV infection, only 1 patient
(patient 10) had evidence of cirrhotic liver disease.

**DISCUSSION**

As the life expectancy of HIV-infected patients in the HAART
era is extended, health care providers and patients are paying
more attention to the morphologic changes induced by HIV
infection and its treatment. Our case series provides infor-
mation regarding the various causes of breast enlargement in
13 HIV-seropositive men. Ten of these cases (9 cases of gy-

necomastia and 1 case of lipomastia) were found to have a

benign etiology. Our data suggest that physical examination
alone can be helpful in distinguishing gynecomastia from li-

pomastia, although imaging studies or biopsy studies are nec-
essary for a secure diagnosis. Gynecomastia was more likely to
be present in patients with unilateral, focal findings, whereas
lipomastia typically presented as bilateral, more-generalized en-

largement. Breast pain did not seem to be predictive of any
particular diagnosis. Whether the presence of morphologic
changes of the fat maldistribution syndrome increases the like-
likeliness that breast enlargement is due to lipomastia rather than
gynecomastia is an important issue [24]. Given the retrospective
nature of our series and, in particular, the lack of information
on morphologic changes in our patients, this issue will need
to be the subject of future studies. The preponderance of uni-

lateral breast enlargement in our series may be a reflection of
increased patient concern about unilateral processes (compared
with bilateral findings) and the subsequent desire of patients
to have such findings evaluated.

HAART has been associated with both lipomastia and gy-

necomastia in multiple case reports [3–12]. Lipomastia in

HIV-infected patients is considered to be secondary to the
metabolic derangements of the fat maldistribution syndrome
[13]. Gynecomastia results from alterations in the ratio of ef-
fective estrogen to testosterone, which may have many causes
[14], including increases in the amount of estrogen (due to
estrogen-secreting testicular tumors or ingested androgens), de-
creased testosterone levels (due to ketoconazole use or sec-

ondary hypogonadism), or both (due to liver disease, primary
hypogonadism, or spironolactone use) [25, 26]. The prevalence
of gynecomastia among HIV-infected patients who are treated
with HAART likely reflects both the effects of protease inhib-
itors and a higher frequency of exposure to other agents that
cause gynecomastia. In the HIV-infected population, these
agents may include drugs used for the treatment of liver and
renal disease and such medications as antifungals, antituber-
culous drugs, and tricyclic antidepressants. In our series, all
but 1 of the patients with gynecomastia had been treated with
protease inhibitors, echoing the findings of previous case re-
ports. Although no specific protease inhibitor used by our pa-
ients was associated with an increased risk of gynecomastia,
long-term exposure to protease inhibitors may be implicated
as a cause of this condition. Six of 9 patients also had potential
secondary causes of gynecomastia, including HCV infection (in
2 patients), mild hypogonadism (in 1 patient), long-term ma-

rijuana use (in 2 patients), and use of norandrostenedione,
spironolactone, or amitriptyline (1 patient each). Of note, an
endocrinologic evaluation was undertaken for all 13 patients,
which revealed only a single case of hypogonadism. This sug-
gests that the benefit of such an evaluation in this patient pop-
ulation may be minimal. Exactly how greatly HAART contrib-
utes to gynecomastia requires further study, particularly given
the relatively high prevalence of gynecomastia in the general population and the high prevalence of confounding factors in the HIV-infected population. Although many recent reports of breast enlargement in HIV-positive male patients have centered around a possible association with use of antiretroviral medications, malignancy is a well-known and dreaded complication of HIV infection. Both NHL and Kaposi sarcoma are AIDS-defining malignancies, whereas many other malignancies, such as Hodgkin disease, are associated with HIV infection [27]. Plasmacytoma and Kaposi sarcoma have recently been reported to present as breast masses or breast enlargement in HIV-infected individuals [16, 17]. Multiple cases of breast carcinoma in HIV-infected patients (most of whom were women [18–20]; less often, they were men [21, 22]) have also been described. These cases have spurred some debate about whether a relationship exists between breast cancer and HIV infection, although no definite link has ever been demonstrated. In data presented from a review of diagnostic coding [28], members of our group (L.P. and B.J.D.) reported that breast cancer in HIV-infected patients was rare at our institution. In addition, data from several African tumor registries show no increase in the incidence of breast cancer during the current HIV epidemic, although these data are clouded by the shorter life span of the HIV-infected population in Africa [29, 30].

Three patients in this series had malignant causes of breast enlargement, although no cases of breast carcinoma were identified. Two patients had NHL (one of whom had recurrent disease), and 1 patient had Hodgkin disease, which reflects the increased risk of these lymphomas known to be associated with HIV infection [27]. Although the malignancy was proven by biopsy to involve the breast in 2 cases (1 case each of NHL and Hodgkin disease), in 1 patient with NHL, breast biopsy was not performed. Whether this latter patient’s nodules were lymphomatous or simply prominent reactive intramammary nodes could not be determined.

Given the myriad of causes of gynecomastia, and given the potentially serious diagnoses included in the differential diagnosis, patients with HIV infection and isolated breast enlargement need to undergo careful evaluation, including obtaining of a history and performance of physical examination, breast imaging, and biopsy, as necessary. Our experience and the experiences described in the medical literature suggest that most cases of breast enlargement in HIV-positive men are caused by gynecomastia or lipomastia. However, gynecomastia cannot be assumed to have resulted from receipt of HAART until other potential causes are ruled out. The presence of lymphoma in 3 patients highlights the possibility that breast enlargement in the HIV-infected individual may be due to a malignancy other than breast carcinoma. Although gynecomastia has been implicated as a risk factor for breast carcinoma in men in the general population [15, 31], it is unclear whether HAART-related gynecomastia carries a similar risk. As more patients receive HAART, the prevalence of gynecomastia will likely increase, which emphasizes the need to further examine the relationship between gynecomastia and breast cancer, as well as to thoroughly investigate the causes of breast enlargement in all HIV-positive individuals.

Acknowledgments

We acknowledge the expert medical care that Denise Bundow provided a number of these patients, as well as the secretarial efforts of Ms. Arleen Sierra.

References