Gynaecomastia associated with highly active antiretroviral therapy (HAART)

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ABSTRACT

There is a global Acquired Immune Deficiency Syndrome (AIDS) epidemic. It is estimated that the total number of people living with Human Immune deficiency Virus (HIV) is 33.2 million in the year 2007. An estimated 2.1 million people died from AIDS in 2007. As highly active antiretroviral therapy (HAART) becomes more widely used, the side effects of this regime are becoming more evident in clinical practice. We present 2 cases that demonstrate the association of HAART and gynaecomastia. Imaging features of gynaecomastia and the differential for these changes will be reviewed. Proposed mechanisms for the pathogenesis of gynaecomastia will be discussed. Possible therapeutic options will also be briefly considered.

CASE REPORT

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Case 1

A 29 year old male on antiretroviral therapy for the preceding eight months presented with bilateral, tender breast masses. Clinically bilateral, central, mobile breast masses were noted. The right mass measured 50mm and the left 30 mm, in diameter.

Mammogram demonstrated well defined subareolar densities with a peripheral fan like configuration. No microcalcifications were present mammographically. (Fig. 1 and 2). Ultrasound (Fig. 3) revealed glandular tissue (more prominent on the right) with bilateral reactive axillary lymph nodes corresponding to the known diagnosis of Human Immunodeficiency Virus (HIV) infection.

This patient was reassured that there was no underlying malignancy. His treatment was not altered as he had no other significant side effects and he was responding well to the treatment regime.

Case 2

A 47 year old male on antiretroviral therapy for 2 years, presented with a left breast mass. Examination revealed a palpable, non tender, 30mm mobile left subareolar mass.

Mammography (Fig. 4 and 5) demonstrates the bilateral but asymmetric diffuse glandular pattern of gynaecomastia with the left breast changes more prominent than the right.. Ultrasound confirmed subareolar glandular tissue, with bilateral axillary nodes (Fig 6. and 7).

DISCUSSION

It is estimated that in 2007, 33.2 million people worldwide were living with HIV, and in that year 2.1 million people died of Acquired Immune Deficiency Syndrome (AIDS). As the HIV epidemic continues the radiologist will increasingly assess breast masses in this population group.

Gynaecomastia is enlargement of the male breast secondary to stromal proliferation and ductal hyperplasia [9].Possible mechanisms for gynaecomastia in HIV infected males are hypogonadism (as evidenced by a significantly lower free testosterone level) and drug therapy (e.g. anti-tuberculous drugs) [2,4] .

With the introduction of highly active antiretroviral therapy (HAART), breast enlargement emerged as a side effect. The incidence of gynaecomastia in patients treated with highly active antiretroviral therapy for more than 2 years is estimated at 2.8% [15].The mean delay of appearance of gynaecomastia following initiation of HAART is 9 months[4].Gynaecomastia is initially unilateral but progresses to bilateral, but asymmetric, disease in more than half the patients [4,6].

HAART consists of three or more combination anti-retrovirals initiated when the CD4+ counts decline. Antiretrovirals are classified according to the phase of the retrovirus life cycle they inhibit. Commonly nucleoside and nonnucleoside reverse transcriptase inhibitors and protease inhibitors are used in combination. The principle of HAART is to decrease the incidence of drug resistant strains emerging on therapy [3].

HAART associated gynaecomastia may be related to oestrogen or progesterone mimics at peripheral sites [4]. Another hypothesis is the immune restoration process which is the recovery of the immune system due to viral suppression by HAART. HAART improves helper T cytokine response which improves oestrogen availability producing gynaecomastia [5].

In this setting most breast masses are due to true gynaecomastia or lipomastia. Lipomastia/ pseudogynaecomastia may appear as part of the HAART associated lipodystrophy syndrome (peripheral lipoatrophy and central lipohypertrophy). Lipomastia would appear radiolucent on mammogram [7].

The most important differential diagnosis is that of a breast malignancy. Clinically a firm, eccentric mass is palpable. There may be associated skin changes and a possible history of nipple discharge. Pathological axillary adenopathy is present in 50% of cases at the time of diagnosis [7, 9]. Mammographic findings include a well circumscribed or spiculated mass which may have associated microcalcifications and skin thickening [9].

Opportunistic infection, lymphoma, Kaposi's sarcoma and pseudoangiomatous stromal hyperplasia (PASH) form part of the further differential diagnosis[3,7]. Infection should be considered in a patient with an acute history with appropriate clinical features i.e. a tender, erythematous, swollen breast. An infective process may be complicated by abscess formation which sonographically appears as an inhomogeneous mass with possible areas of breakdown.

Breast lymphoma may be primary or secondary. The masses may be solitary or multiple and may involve one or both breasts. Mammographically the breast masses lack the classical features of malignancy e.g. spiculation and microcalcification[9].

Kaposi's sarcoma may be primary or secondary as part of disseminated disease. It may present as a breast mass or as a purple to red cutaneous lesion. Imaging features vary from mimicking malignancy to hypoechoic masses on ultrasound to features of gynaecomastia on imaging [16].

PASH is a benign myofibroblastic process and may present as a rapidly growing breast mass. It is a well circumscribed round to oval mass on mammogram. On ultrasound it is well circumscribed with a macrolobulated contour with mixed but predominantly hypoechoic internal echoes [9,16].

Routinely imaging clinical gynaecomastia in a non HIV setting is controversial as some authors believe that imaging should be performed only if malignancy is suspected. The role of imaging the breasts in the setting of HIV/AIDS has not been defined but a lower threshold for imaging may be indicated in this group [13].

Three patterns of gynaecomastia are recognised mammographically .The early nodular pattern demonstrates a defined subareolar mass which extends posteriorly in a fan like configuration. The late dendritic phase has a central mass associated with linear projections into the deep breast tissues. The diffuse glandular pattern mimics the appearance of the female breast but lacks Cooper ligaments [9].

Sonographically the early nodular phase demonstrates a small hypoechoic subareolar mass with prominent ducts. The late dendritic phase shows posterior finger like projections in addition to the subareolar mass. The diffuse glandular pattern appears similar to the female breast [9].

Management of gynaecomastia associated with HAART includes several options. There are few studies with small numbers addressing this issue and therefore there are no definitive treatments as yet [6]. Spontaneous resolution may occur [3]. Sometimes discontinuation of an antiretroviral drug may reverse gynaecomastia [6].

Testosterone is safe and effective both transdermally or intramuscularly [4]. Percutaneous dihydrotestosterone gel (5g daily given once daily for 1-3 months) may be used [5].

Limited studies that have demonstrated success with Tamoxifen 10-20mg twice daily for recent onset and tender gynaecomastia [8, 14].

Fibrous tissue develops after one year with minimal chance of regression or response to medical therapy. Surgery may then be considered [6].

TEACHING POINT

The radiologist needs to be aware of HAART associated gynaecomastia and to be able to differentiate this from other breast pathology in the setting of an immuno compromised patient. Within the current context of the HIV/ AIDS epidemic the radiologist needs to understand the relationship between HIV, antiretroviral treatment and gynaecomastia.

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FIGURES

Figure 1. Case 1. A 29 year old male with HIV on HAART with gynaecomastia. Left mediolateral oblique view mammogram demonstrates a left subareolar density, well defined and extending into the posterior tissues. These features are consistent with the early nodular pattern of gynaecomastia of less than one year's duration. Exposure factors: 28kVp and 24 mAs.

Figure 2. Case 1. 29 year old male patient with HAART associated gynaecomastia. Right mediolateral oblique view mammogram. Well defined subareolar mass with peripheral tapering into the posterior tissues in a fan like configuration. The right breast changes are more pronounced than the left and are those of the nodular pattern of gynaecomastia. Exposure factors:28 kVp and 28 mAs.

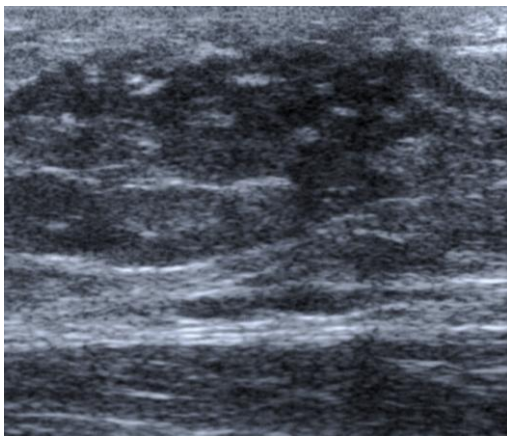

Figure 3. Case1. 29year old male with HAART associated gynaecomastia. High frequency linear ultrasound (12MHz) demonstrates a subareolar mass. No posterior acoustic shadowing is present and the surrounding tissue is not disrupted. Sonographically consistent with gynaecomastia.

Figure 4. Case 2. 47 year old male known to be HIV positive on antiretroviral therapy for 2 years duration with HAART associated gynaecomastia. A left mediolateral oblique view mammogram confirms gynaecomastia with a diffuse glandular pattern. There is dense breast parenchyma which mimics the female breast in appearance but lacks Cooper ligaments. Exposure factors: 28kVp and 32mAs

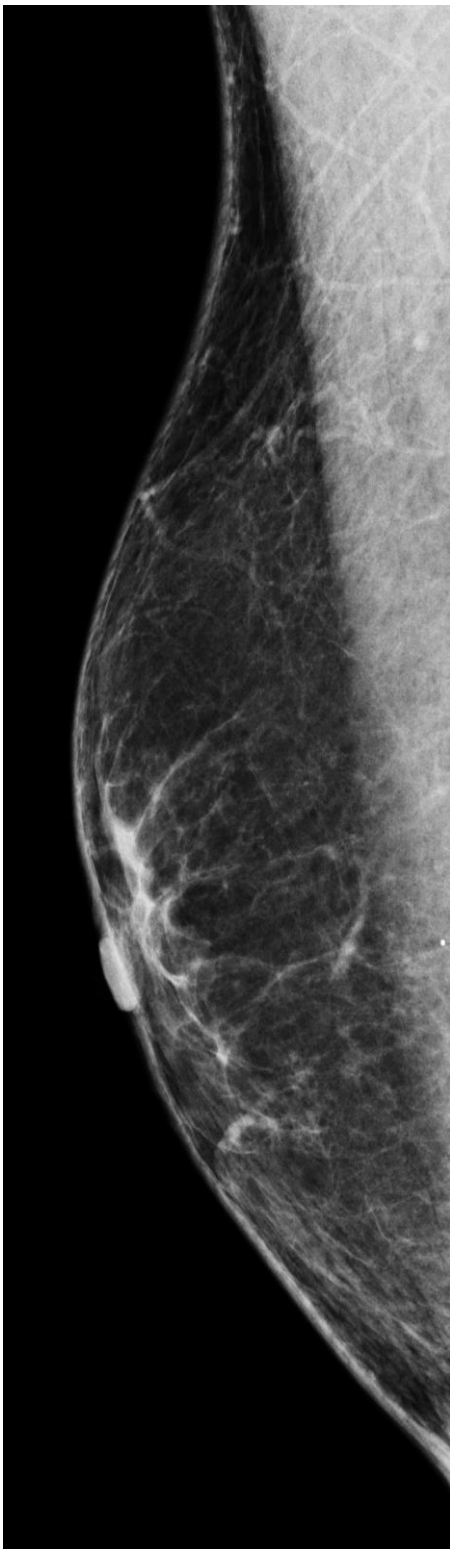

Figure 5. Case 2. 47 year old male on antiretroviral therapy for 2 years with gynaecomastia. Right mediolateral oblique view mammogram demonstrates a diffuse glandular pattern of gynaecomastia.This patient has bilateral but asymmetric changes. Exposure factors: 28kVp and 26 mAs.

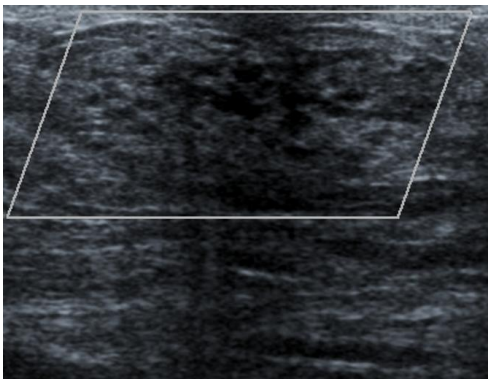

Figure 6. Case 2. 47 year old male with HIV on antiretroviral therapy for 2 years with HAART associated gynaecomastia. High frequency (14MHz) linear ultrasound confirms glandular appearance of the subareolar tissue similar to female breast tissue.

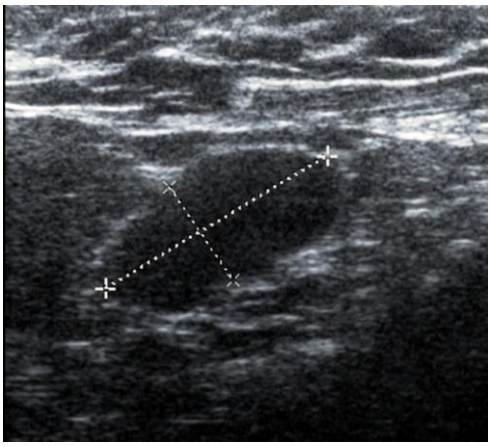

Figure 7. Case 2. High frequency (14MHz) linear ultrasound of left axilla demonstrating an abnormal lymph node in 47 year old male patient. It measures 19.8mm x 8.6mm in size. Although it maintains a normal oval shape there is loss of the normal fatty hilum. Multiple bilateral axillary lymph nodes are present in the setting of HIV.

	Mammogram	**Ultrasound**
True gynaecomastia	Flame shaped subareolar density.	Subareolar hypoechoic mass, prominent subareolar ducts, may have posterior finger like projections, resembles female breast tissue.
Male breast cancer	Mass, often eccentric to nipple. Mass may be spiculated or circumscribed. Skin thickening and nipple retraction may be present. Calcifications less common than in female breast cancer, tend to be coarser and scattered.	Hypoechoic mass which is oval to round in shape. Margins may be indistinct or circumscribed. Posterior acoustic shadowing common. May have echogenic halo. Complex cystic masses are also suspicious for malignancy. Associated pathological lymph nodes may be present in the axilla.
Pseudogynaecomastia/ lipomastia	Fatty infiltration which is radiolucent on mammography.	No ductal or stromal development. Fatty infiltration.
Opportunistic infection	Especially in setting of immune compromise. Clinical features and history will confirm an acute process with appropriate signs of infection.	If an abscess develops ultrasound may show a heterogeneous mass with breakdown and surrounding oedema.
Pseudoangiomatous stromal hyperplasia.	Benign myofibroblastic process. Well circumscribed, round or oval mass. Calcification not common.	Usually circumscribed mass with macrolobulated margins. Mixed but predominantly hypoechoic internal echoes.
Lymphoma	Solitary or multiple masses. May be bilateral. Masses lack spiculation, calcification or architectural distortion.	Usually mixed echogenicity, but may be homogenous and hyper or hypoechoic.
Kaposi's sarcoma	May be primary or secondary. Imaging features vary. May mimic malignancy on mammogram.	Features vary from a hypoechoic area on ultrasound to mimicking malignancy.

Table 1: Differential diagnosis table for gynaecomastia

Aetiology	Multifactorial: • Hypogonadism in HIV infected patients • Oestrogen or progesterone mimics at peripheral sites from HAART • Immune restoration process
Incidence	• 33.2 million people with HIV in 2007 • Estimated 2.8% in patients treated with highly active antiretroviral therapy for greater than 2 years
Gender ratio	Males develop gynaecomastia however females on HAART develop breast hypertrophy.
Risk factors	HIV infection on HAART
Treatment	• Spontaneous resolution • Discontinue some of the antiretroviral drugs • Percutaneous Dihydrotestosterone gel • Tamoxifen • Surgery
Prognosis	Small studies demonstrate good response to Dihydrotestosterone gel and Tamoxifen. No large trials as yet.
Findings on imaging	• Mammogram: Subareolar fan shaped density extending to deeper tissues. • Ultrasound: Subareolar hypoechoic mass with ducts may have posterior finger like projections. Resembles female breast parenchyma.
Age predilection	Sexually active population.

Table 2: Summary table for gynaecomastia in patients undergoing HAART

ABBREVIATIONS

AIDS = Acquired Immune Deficiency Syndrome
HIV = Human Immunodeficiency Virus
HAART = Highly Active Antiretroviral Therapy

KEYWORDS

Gynaecomastia imaging, HIV, AIDS, highly active antiretroviral therapy, HAART

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