

The man with bilateral nipple pain

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Case History

Figure 1 is a picture of a 48-year-old male patient who presents with progressive painful enlargement of the areolae of 10 months' duration. There was no bleeding or nipple discharge. He was diagnosed with human immunodeficiency virus (HIV) infection 16 months ago and was initiated on antiretroviral therapy (ARV), which consisted of zidovudine, lamivudine and efavirenz. As his CD4 cell count at diagnosis was less than 200 cells/mm³, he was prescribed trimethoprim-sulphamethoxazole (Bactrim) for prophylaxis against pneumonia due to pneumocystis jirovecii. Physical examination was unremarkable except for bilateral breast enlargement and right-sided old shingles scar in the T4 dermatome distribution.



Figure 1

Answers and discussion

1. Efavirenz. Highly active antiretroviral therapy (HAART) has revolutionised the treatment of HIV-infected individuals by leaps and bounds. However, numerous adverse effects and limitations in tolerability remain a concern.¹ In recent years, gynaecomastia has been reported to occur in HIV-infected patients treated with efavirenz.¹⁻³ It has been estimated that 1.8% to 8.4% of male patients develop gynaecomastia with efavirenz treatment.⁴ Gynaecomastia due to efavirenz usually occurs 4 to 15 months after starting therapy and usually resolves within 5 months after efavirenz withdrawal.¹

The exact mechanism of efavirenz-induced gynaecomastia remains unknown. Two possible mechanisms have been postulated: (a) gynaecomastia due to immune restoration processes and (b) efavirenz-mediated oestradiol-like effects.^{1,3} It may also be caused, at least in part, by drug-induced oestrogen receptor activation in breast tissues.⁴ The indirect evidence came from a reported case of efavirenz-induced gynaecomastia, which was successfully reversed using 20 mg of the anti-oestrogen drug, tamoxifen, daily.^{4,5}

There has been no report of gynaecomastia associated with trimethoprim-sulphamethoxazole (Bactrim), whereas zidovudine and lamivudine seem to have protective effect against gynaecomastia.^{6,7}

Questions

1. Which of the following drugs is most likely responsible for the patient's current complaint?
 - A. Efavirenz
 - B. Lamivudine
 - C. Sulphamethoxazole
 - D. Trimethoprim
 - E. Zidovudine
2. How to clinically differentiate between true gynaecomastia, pseudogynaecomastia and breast carcinoma?
3. How to manage gynaecomastia in this patient?

2. Breast enlargement in HIV-infected patients on HAART may be due to benign or malignant mammary diseases.⁸ Benign changes in these patients comprise true gynaecomastia, lipomastia (pseudogynaecomastia), pseudoangiomatous stromal hyperplasia and infections (tuberculous mastitis or pyogenic abscesses).⁸ Malignant diseases include adenocarcinoma, Kaposi's sarcoma, lymphoma and metastasis.^{7,8}

True gynaecomastia is an enlargement of the male breast due to proliferating glandular tissue.^{7,8} Pseudogynaecomastia consists of adipose tissue deposits in the setting of a lipodystrophy syndrome and is characterised by increased subareolar fat without enlargement of the breast glandular component.^{7,9} In patients with true gynaecomastia, a rubbery, elastic and firm mound of tissue that is concentric with the nipple-areolar complex is felt, which is clinically bilateral in approximately half of the patients. However, in patients with pseudogynaecomastia, no such disk of tissue is found. Tenderness may be observed in gynaecomastia of less than 6 months' duration. Breast carcinoma is usually hard or firm, located outside the nipple-areolar complex, and is mostly unilateral. It may be associated with skin dimpling, nipple retraction, nipple bleeding or discharge.⁹

Once the diagnosis of gynaecomastia is established, conditions to consider in adolescents and young adults with gynaecomastia are physiologic pubertal gynaecomastia, Klinefelter's syndrome, familial or sporadic excessive aromatase activity, incomplete androgen insensitivity, feminising testicular or adrenal tumours, and hyperthyroidism. Medications associated with gynaecomastia include spironolactone, phenytoin, metoclopramide, cimetidine, HAART and antiandrogens used for the treatment of prostate cancer. Drug abuse, especially with anabolic steroids, alcohol, marijuana and opioids are also considered to cause gynaecomastia.⁹

3. Switching from efavirenz to an alternative antiretroviral drug may be one potential strategy to alleviate this adverse effect. However, multiple factors need to be considered before switching to an alternative therapy. Tamoxifen and other anti-oestrogens may be useful in the treatment of efavirenz-induced gynaecomastia. A randomised control trial would be necessary to fully evaluate the utility, and more importantly tolerability, of anti-oestrogens as a treatment for efavirenz-induced gynaecomastia.⁴

If gynaecomastia has been present for more than 1 year, it is unlikely to regress substantially, either spontaneously or with medical therapy, due to the presence of fibrosis.⁹ In such circumstances, surgical intervention with either liposuction, subcutaneous mastectomy or periareolar mastopexy may be considered.¹⁰

In this patient, as he had achieved satisfactory immune restoration (his CD4 cell count improved to >400 cells/mm³ within a year after initiation of zidovudine, lamivudine and efavirenz, with good viral load suppression below 20 copies/uL), the same regimen was continued with close monitoring of the progression of gynaecomastia. Fortunately, gynaecomastia did not progress further and ceased to be a concern for the patient several months after its detection.

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None to declare

How does this paper make a difference to general practice?

- Gynaecomastia is a common clinical condition and can co-exist with a number of different disorders.
- Gynaecomastia should not be underestimated as it can be physically embarrassing and psychologically distressing for patients.
- Broad spectrum of breast disease should be anticipated in HIV patients.
- Clinicians need to be aware of HAART regimens side effects that could possibly lead to non-adherence and eventually therapy failure.
- HAART-induced gynaecomastia should be suspected in HIV patients receiving efavirenz-containing regimens.

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