Anastrozole as a therapeutic option for gynecomastia in a person receiving antiretroviral treatment: case report

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Abstract

A middle-aged Caucasian man presented with a six-month history of bilateral enlargement of the breasts associated with pain. His hormonal profile was normal and no other underlying cause was identified, we diagnosed him with idiopathic gynecomastia. He is living with HIV, clinically stable (viral load <20copies/mL) and on injectable antiretrovirals cabotegravir/rilpivirine. Tamoxifen is an anti-estrogen recommended for gynecomastia and has been described in persons living with HIV. In this case, tamoxifen could potentially induce the activity of cytochrome P450 3A4 (CYP3A4), reducing rilpivirine concentrations, which consequently may cause virological failure. According to the National Health Service (NHS) guidelines in the UK, an aromatase inhibitor can be used in place of tamoxifen. To date, there have been no reported cases of using anastrozole as a treatment for gynecomastia in people living with HIV, or of its co-administration with antiretrovirals.

INTRODUCTION

Gynecomastia is caused by an imbalance in oestrogen and testosterone levels, which results in a high oestrogen to testosterone ratio. It can occur physiologically during the neonatal period, puberty, and in older men above 50 years (prevalence 36% to 57%), as well as in pathological circumstances(1). In HIV, the prevalence of gynaecomastia ranges from 1.8% to 3% and is associated with androgen deficiency or the use of some antiretroviral drugs, including efavirenz, stavudine and didanosine(2,3).

Tamoxifen is a selective estrogen receptor modulator and has traditionally been the go-to therapeutic option for managing gynecomastia(4,5). In this case, tamoxifen could potentially induce the activity of cytochrome P450 3A4 (CYP3A4), reducing rilpivirine concentrations, which may cause virological failure(6). According to the national health service (NHS) guidelines in the UK, an aromatase inhibitor can be used in place of tamoxifen(7). To our knowledge, this is a first case report highlighting anastrozole as a therapeutic option for gynecomastia in a patient on a non-nucleoside reverse transcriptase inhibitors (NNRTI) accounting for potential drug drug interaction (DDIs).

CASE

A 56 year old man presented at the routine HIV outpatient clinic with complaints of left and right breast discomfort for about six months followed by gradual swelling of the left breast. He did not report any change in body hair, libido or erectile dysfunction. Discomfort was described as pins and needles, no itchiness, no discharge from the nipples or skin changes were reported. He had no previous breast problems, but his mother had a history of breast cancer.

He was known to the HIV service and had been living with HIV since 2001. Previous antiretroviral treatment combinations include: stavudine + lamivudine + efavirenz and zidovudine + lamivudine + efavirenz. Due to progressive multifocal leukoencephalopathy, he was kept on zidovudine + lamivudine + nevirapine +

abacavir. In 2010, he transferred to our care and was prescribed tenofovir + emtricitabine + nevirapine until 2017 when his treatment was changed to include an integrase inhibitor, raltegravir (RAL) alongside tenofovir + emtricitabine. However, due to intolerance to RAL, he was switched back to tenofovir + emtricitabine + nevirapine in 2018. In June 2022, he opted for the injectable combination of cabotegravir/rilpivirine to allieviate the anxiety around daily HIV medication intake. He showed adherence to injection appointments and remained virologically suppressed.

His current co-morbidities included well controlled hypertension, hyperlipidaemia, non-obstructing calculi of the right kidney, benign prostate hyperplasia and a recurring reducible left inguinal hernia. His previous co-morbidities were left hernia repair, progressive multifocal leukoencephalopathy with peripheral neuropathy, hypogonadism and hypothyroidism. His current co-medications were atorvastatin, solifenacin, ramipril, tadafil, multivitamins and probiotics. He is a non-smoker and drinks alcohol occasionally. He works as a personal trainer and is usually very active with no history of anabolic steroid use.

On physical examination, he appeared well. His body mass index was 27.35 kg/m2, blood pressure 144/91mmHg and other vital signs were in normal range. He had bilateral, sub-areolar, concentric breast masses, with palpable nodules that were soft and mobile. There was tenderness on palpation with no nipple discharge or axilla lymphadenopathy. His hormonal blood workup was within normal range, . We suspected him to have idiopathic gynecomastia and we referred him to the breast clinic for further evaluations as well as to rule out pseudo-gynecomastia and breast cancer.

INVESTIGATIONS

At presentation (06/04/2023) his laboratory work up comprised general haematology, biochemistry and endocrinology panels (thyroid stimulating hormone, free testosterone, cortisol, luteinising hormone, estradiol, progesterone, sex hormone binding globulin, testosterone, follicle-stimulating hormone levels and cancer antigen 15-3 level) were all within the normal range with exception of a low estimated GFR CKD EPI (glomerular filtration rate chronic kidney disease epidemiology collaboration) 72ml/min/1.73m^2 with a normal range serum creatinine. One week later (on 13/04/2023), he was booked into the breast clinic for further evaluations. An ultrasound scan was performed by a consultant radiologist and it showed a large amount of glandular looking breast tissue, with no signs of malignancy on the left side. On the right side, there was no convincing glandular breast tissue and no signs of malignancy either. A mammogram was also performed and showed a small amount of glandular looking tissue slightly more on the left side than the right side with no signs of malignancy on both sides. This appearance is consistent with bilateral asymmetrical true gynecomastia. His follow up biochemistry laboratory tests at the great clinic were also within normal range, with exception of a low Estimated GFR CKD EPI 80ml/min/1.73m^2 (normal range serum creatinine). And a month later (05/05/2023), a control of his endocrinology panel was repeated and results were still within normal range. A testicular sonogram was performed and revealed a reducible left inguinal hernia containing peritoneal content. His last (26/06/2023) biochemistry work up remains within normal range.

TREATMENT

Based on clinical history, laboratory and radiological findings, he was diagnosed with true gynecomastia. The patient was discussed at the HIV service's multidisciplinary clinic and anastrozole was proposed as an alternative to tamoxifen to avoid the possible drug-drug interaction with rilpivirine. He was started an oral dose of anastrozole 1 mg once daily. After 10 days from the start of anastrozole, he presented a significant symptom improvement with visible reduction of breast enlargement and decreased discomfort. After six weeks of use of anastrozole, complete resolution of the gynecomastia occurred and the patient stopped anastrozole.

In the meantime (19/05/2023), the patient referred weight gain of 3 kilograms (in a span of 11months) and opted for switching back to oral antiretroviral treatment containing tenofovir + lamivudine + doravirine, while he was still on anastrazole. The latter provided a benefit (versus the most commonly used tamoxifen) with this ARV combination as well, as a drug-drug interaction between tamoxifen and doravirine, although not studied, may occur and again lead to a decrease in doravirine concentrations through CYP3A4 induction[9].

OUTCOME AND FOLLOW UP

After 10 days of treatment, the patient's breast enlargement reduced, but moderate fatigue was experienced. He mentioned taking more frequent naps, having low energy, and lacking motivation for the gym. Examination showed mild tenderness in the peri-areolar area and reduced breast tissue. The patient was advised to continue anastrozole and injectable ARVs. However, due to weight gain concerns, he expressed interest in switching to ARV tablets. After reassurance, he was scheduled to switch next month. At week 4 follow-up, the patient tolerated anastrozole well despite fatigue. He switched to TDF/FTC/doravirine tablets at week 6, reporting complete resolution of breast enlargement and tenderness.

DISCUSSION

Antiretrovirals are essential lifelong medications for managing HIV, and it's crucial to understand the associated drug interactions (DDIs) to improve treatment outcomes and safety. Injectable antiretrovirals can reduce DDI risks by avoiding the gastrointestinal route, but caution is necessary for those metabolized by CYP3A4 in the liver(8). In our case, the patient is on injectable antiretroviral therapy containing rilpivirine and also requires medical treatment for gynecomastia. Combining drugs that induce CYP3A4 activity with antiretrovirals primarily metabolized by CYP3A4 (such as protease inhibitors (PIs) or NNRTIs like rilpivirine) can decrease their levels, potentially leading to viral failure or drug resistance.

Treatment options for gynecomastia include: reassurance or observation, discontinuation of the causative agents and addressing underlying disease. Medical therapies include: estrogen antagonists as first line and alternatively a weak androgen or an aromatase inhibitor(4,5,7). Although tamoxifen is not licensed for treatment of gynecomastia, it is widely used and recommended by several guidelines with reports of good response[1]. It's use in gynecomastia among the general population and people living with HIV has been described previously(9,10). Tamoxifen is an estrogen antagonist and undergoes wide hepatic metabolism involving some isoforms of the cytochromes. It induces the activity of CYP3A4 both in vivo and in vitro(6). According to the HIV liverpool drug-drug interaction checker, when tamoxifen is taken with rilpivirine, this induction may lead to a decrease in the exposure of rilpivirine as well as other antiretrovirals primarily metabolized by CYP3A4.

The European Academy of Andrology (EAA) guidelines discourage the use of selective estrogen receptor modulators, aromatase inhibitors and dihydrotestosterone due to lack of quality data(4). However, the association of breast surgery and Nottinghamshire Area Prescribing Committee (APC) NHS permits the use of aromatase inhibitors (anastrozole) if tamoxifen is not well-tolerated or as a secondary option if anastrozole shows no response(7,11). Anastrozole is a selective non-steroidal aromatase inhibitor that hinders the activity of the enzyme CYP19A1 (aromatase), responsible for converting androgens into estrogens(12). It has been used in chemoprevention and adjuvant therapy for post-menopausal women at risk of breast cancer(13,14), with notable side effects like osteoporosis, nausea, and hot flashes(13–15) and for gynecomastia in adolescents(16,17). Despite the lack of available studies on the co-administration of anastrozole with most antiretroviral agents, the likelihood of a clinically significant interaction is low. This is primarily attributed to anastrozole's inhibitory nature, which reduces the potential for diminishing the concentration of antiretroviral drugs(6).

Our case report offers a contribution on treatment of gynecomastia using anastrozole and explains the possible interactions with antiretrovirals. The increasing use of injectable antiretroviral therapy in the near future leads us to find an alternative to tamoxifen to avoid drug drug interactions with rilpivirine or other antiretroviral therapy as well as other antiretrovirals majorly metabolized by CYP3A4.

CONCLUSION

Tamoxifen potentially interacts with NNRTIs like rilpivirine and doravirine reducing their concentrations. This case report suggests that anastrozole may be used instead of tamoxifen for the treatment of gynecomastia in men living with HIV who are taking NNRTIs or PIs. Aromatase inhibitors may be considered for use for gynecomastia management, to avoid drug-drug interactions but further studies are needed to confirm these

findings.

CONTRIBUTORS

ES, CC and MV contributed to manuscript writing and care of the patient. CA is the nurse responsible for direct care of the patient. MB is the responsible consultant for the care of the patient and was responsible for the revision of the manuscript.

COMPETING INTERESTS

The authors have no competing interests and no financial support to disclose.

INFORMED CONSENT

Written informed consent was obtained from the patient for publication of this case report

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