CASE REPORT

Fluoxymesterone-induced gynaecomastia in a patient with childhood aplastic anaemia

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SUMMARY

Gynaecomastia is a benign condition characterised by enlargement of the male breast. Drug-induced gynaecomastia merits deep consideration as it may account for as many as 25% of all cases of gynaecomastia in adults. Although the mechanism is not fully clear, some mechanisms include oestrogen-like activities, stimulation of testicular production of oestrogens, inhibition of testosterone synthesis or blockade of androgen action. Anabolic steroids, in particular when used during the pubertal stage, may cause significant irreversible gynaecomastia. We report a case of 28-year-old Filipino man with persistent gynaecomastia from fluoxymesterone used for aplastic anaemia during his prepubertal stage. Hormonal work ups for gynaecomastia all turned out normal, thus isolating the drug as the cause. The patient was unable to undergo breast reconstruction surgery due to haematological contraindications, but eventually referred to psychiatry for counselling. This case will highlight the paradoxical effect of androgenic steroid used during childhood on male breast proliferation during puberty.

BACKGROUND

Gynaecomastia is a benign condition characterised by enlargement of the glandular tissue and local fat deposition. It can be physically uncomfortable, psychologically distressing and may have a negative impact on self-confidence and body image. Pseudogynaecomastia, however, is common in obese men, and consists of lipomastia alone, without glandular proliferation.¹

Asymptomatic and physiological gynaecomastia is very common and has a trimodal age distribution, occurring in neonatal, pubertal and elderly men. Its prevalence is 60–90% in neonates, 50–60% in adolescents and up to 70% in men aged 50–69 years.² However, non-physiological gynaecomastia is less common and may be caused by chronic conditions (eg, cirrhosis, hypogonadism, renal insufficiency); use of medications, supplements, or illicit drugs; and, rarely, tumours.³ Variation in reported prevalence across studies is attributed to variations in the size of the palpable breast tissue used to define gynaecomastia and to population characteristics.²

Gynaecomastia is relatively common and clinically important. Nevertheless, major gaps in knowledge regarding its modern epidemiology exist, and it has not been proven whether the apparent rise in its incidence is true. Nonetheless, over recent decades, there have been substantial increase in the

use of anabolic steroids and in environmental contamination with xenoestrogens or oestrogen-like substances that, at least theoretically, can stimulate glandular proliferation of the male breast.⁴ Although the adult male breast contains minimal amounts of adipose and glandular tissue, there is potential for proliferation if oestrogen or progesterone levels increase. Gynaecomastia, which can be physiological or non-physiological, occurs when the oestrogen-to-testosterone ratio in men is disrupted, leading to proliferation of glandular breast tissue.⁵

Drug-induced gynaecomastia merits deep consideration as it may account for as many as 25% of all cases of gynaecomastia in adults. Although the mechanism is not fully clear, some mechanisms include oestrogen-like activities, stimulation of testicular production of oestrogens, inhibition of testosterone synthesis or blockade of androgen action.⁶ Anabolic steroids, in particular when used during the pubertal stage, may cause significant irreversible gynaecomastia.³

We report a case of persistent pubertal gynaecomastia from fluoxymesterone (anabolic steroid) use in the treatment of childhood aplastic anaemia.

CASE PRESENTATION

This is a case of a 28-year-old Filipino man who presented with persistent pubertal gynaecomastia. At the age of 9 during his prepubertal age, he was diagnosed to have aplastic anaemia based on bone marrow biopsy and aspirate result after presenting with several months of recurrent gum bleeding, purpura and febrile episodes. He was then seen by a haematologist-oncologist who started him on prednisone (20 mg/day), human antithymocyte globulin and fluoxymesterone (25 mg/day). At the age of 10, secondary sexual characteristics appeared. He had gradual breast budding and enlargement initially tender then becoming more glandular similar to his female friends.

The patient was on continued follow-up and treatment for aplastic anaemia for 2 years until remission was achieved. At this time, prednisone was tapered and discontinued but fluoxymesterone was continued for another 6 years, tapered and finally stopped at the age of 16 years, when the patient was considered cured of the disease. His breasts continued to enlarge and reached female-like maturity without galactorrhoea. This caused him social embarrassment especially when with his male peers.

The patient lived a normal life as a fisherman and got married at the age of 20, after which he fathered his first child at the age of 21. He denied

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Figure 1 Grade 3 gynecomastia characterised as major breast hypertrophy with glandular ptosis and nipple-areolar complex situated same height as the inframammary fold.⁷ (A) Anterior view and (B) lateral view.

intake of other medications or herbal products. He had no relatives with gynecomastia. His sexual libido was unchanged. Since of the cosmetic and social effect of his persistent gynecomastia, he consulted at the outpatient clinic of the Philippine general hospital.

On physical examination, the patient had a normal body mass index and a normal male body habitus. He was examined to have Tanner stage 5 for pubic hair, testicular size and penile length. What was striking was the presence of a grade 3 gynecomastia and the absence of discharge on breast nipple expression⁷ (figure 1).

INVESTIGATIONS

Biochemical and hormonal tests to rule out pathological causes of gynecomastia were normal (table 1). Breast mammography

showed normal glandular breast and normal breast tissue on biopsy. Abdominal ultrasound revealed normal liver, pancreas, kidneys and prostate. Based on the clinical history, temporal relationship between drug initiation and appearance of gynecomastia and the absence of pathological causes, the patient was diagnosed to have drug-induced (fluoxymesterone) gynecomastia.

DIFFERENTIAL DIAGNOSIS

True gynecomastia is defined as male breast enlargement of >4 cm and presence of glandular tissue. With true gynecomastia, intake of previous or current drugs and its temporal relationship with the onset of gynecomastia must be established. Renal, hepatic and thyroid diseases must be ruled out as aetiological causes of gynecomastia. Endocrine causes of gynecomastia require certain hormonal tests to rule them out. A simple diagnostic algorithm has been proposed by the Mayo Clinic (figure 2).²

TREATMENT

A planned breast reconstruction surgery was temporarily postponed because of thrombocytopenia on repeated examinations. A repeat bone marrow aspiration was compatible with a reactive bone marrow indicating continuous remission with residual thrombocytopenia from the aplastic anaemia (figure 3).

OUTCOME AND FOLLOW-UP

The patient is on follow-up with the haematology service for constant monitoring of haematological parameters. Although he was unable to undergo breast reconstructive surgery, he was referred to a psychiatrist for psychological counselling. As of the last visit, he lives a happy life as a fisherman and father of two children.

DISCUSSION

Fluoxymesterone is a drug belonging to a group of fluorine-substituted derivatives of methyltestosterone and has been shown to have more potent anabolic and androgenic properties than testosterone and methyltestosterone. This potent anabolic androgenic steroid has been clinically used to treat male hypogonadism.⁸ In combination with the antithymocyte globulin, it was a promising treatment for cases of aplastic anaemia during the 1980s. Certain studies showed beneficial additive effect^{9 10} while others did not,^{11 12} hence its usage was controversial.

Certain adverse effects have been associated with this drug. Among them are included hepatotoxicity, psychological

Table 1 Clinical and hormonal tests

Test performed	Normal values	Result	Ruled out causes of gynecomastia
Hormonal tests			
β-hCG	0–5 IU/L	4.8 IU/L	Germ cell tumour, hCG-secreting tumours
Oestradiol	7.63–42.6 pg/mL	42.1 pg/mL	Leydig or sertoli cell tumours
Follicle-stimulating hormone	1–10.5 mIU/mL	3.8 mIU/mL	Hypogonadism
Luteinising hormone	1.9–9.4 mIU/mL	4.4 mIU/mL	Hypogonadism
Prolactin	80–430 mIU/L	419.6 mIU/L	Prolactinoma
Serum testosterone	9–38 nmol/L	18.06 nmol/L	Hypogonadism
Thyroid-stimulating hormone	0.3–3.8 μIU/mL	1.5 μIU/mL	Hyperthyroidism
Biochemical tests			
Creatinine	53–115 μmol/L	63 μmol/L	Chronic renal disease
ALT	15–41 IU/L	22 IU/L	Liver cirrhosis

ALT, alanine transferase; β-hCG, human chorionic gonadotropin.

Figure 2 Diagnostic algorithm for gynecomastia, proposed by the Mayo Clinic (hCG, human chorionic gonadotropin; LH, luteinising hormone; LFTs, liver function tests; Prl, prolactin; TSH, thyroid-stimulating hormone; US, ultrasound).²

disturbances, virilisation, reduced spermatogenesis, gynecomastia and cardiovascular complications. The underlying molecular mechanisms of the side effects remain unknown. Therapeutic doses of testosterone can be aromatised to oestrogen peripherally and cause gynecomastia. Non-aromatisable androgens such as methyltestosterone and dihydrotestosterone can also cause gynecomastia via other unknown mechanisms.¹³

The aromatisation of testosterone to oestradiol and related compounds can stimulate and facilitate the growth of a tender, oestrogen-sensitive tissue under the male nipple leading to gynecomastia. This effect is more prominent during the pubertal age as male breast tissue is more susceptible to oestrogen stimulation. Hence, introduction of androgenic drugs during puberty can have a significant and irreversible effect on the breast tissue.¹⁴ Most adverse effects of anabolic-androgenic steroid use are dose dependent and

are reversible with cessation of the offending agent or agents. However, with prolonged use, increased stromal hyalinisation and proliferation lead to fibrosis resulting in permanent gynecomastia.¹⁵

In a patient with a high probability of irreversible persistent gynecomastia, treatment or intervention should be discussed and offered. Medical treatment with the use of androgens, anti-oestrogens and aromatase inhibitors can be initiated during the early proliferative phase, before stromal hyalinisation and fibrosis of the glandular structure occur.¹ However, for long-standing gynecomastia, as in our case, surgery appears to be the better treatment to restore chest contours, eliminate inframammary fold, correct nipple-areolar complex position, remove redundant skin, create male breast symmetry and minimise scarring.¹⁶ Comorbidities may delay the surgical procedure, as in our case. Psychological counselling may provide emotional acceptance and support for future cosmetic issues.

Figure 3 Bone marrow aspirate and biopsy showing trilineage haematopoiesis with scanty megakaryocytes indicative of a reactive marrow.

Learning points

- ▶ Use of fluoxymesterone, especially during puberty, can lead to irreversible and persistent gynaecomastia.
- ▶ Its use should always outweigh probable harm, as certain associated adverse effects can lead to permanent physical abnormalities brought about by hormonal disruptions.
- ▶ Although breast reconstruction surgery is the treatment of choice for this case, psychological counselling appears to be supportive, especially for cases unfit for surgery.

Contributors TENL was the primary author and doctor in charge and saw the patient. ZCA was the haematologist, carried out the biopsy and managed the aplastic anaemia of the patient. FLL-A was the senior attending consultant, gave inputs and edited the final manuscript.

Competing interests None declared.

Patient consent Obtained.

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