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Gynecomastia treatment with tamoxifen or tamoxifen followed by letrozole: prototype clinical study

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Abstract

Gynecomastia is very common cause of a patient's visit to a mastology office. Gynecomastia is experienced in up to 70% of mid-puberty males and in up to 65% of middle-aged men. The treatment starts with the identification of the cause, but in most cases the patient is treated with tamoxifen, aromatase inhibitors, liposuction or surgery. Treatment of gynecomastia is not well standardized. In our prospective study, we examined the use of tamoxifen followed by letrozole and a clinically important reduction was achieved, when compared with those who were treated only with tamoxifen. Further research needs to be conducted in order to confirm this promising protocol.

KEYWORDS

gynecomastia, tamoxifen, aromatase inhibitors, letrozole

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1. INTRODUCTION

Gynecomastia is a term used, when the breast tissue of a male is enlarged. It is a condition caused by an imbalance in estrogen and testosterone levels leading to high estrogen to testosterone ratio. This imbalance results in hyperplasia of ductal epithelial, elevated stromal and periductal tissue growth. This is the definition of true gynecomastia. Accumulation of only fatty tissue leading in male breast enlargement is defined as pseudo-gynecomastia or adipomastia [1,2,3]. Gynecomastia can be physiologic or pathologic.

Physiologic is when male breast development can occur normally and this situation can be faced during three stages of life. These stages are after birth, puberty and in older ages (usually after 60). Pathologic gynecomastia happens when the ratio of estrogen to androgen is increased locally or in the circulation [4]. The breast experts tend to wait 6 months before treatment, because gynecomas-

tia can resolve without intervention. If it does not resolve, the treatment can be with medical such as anti-estrogens, aromatase inhibitors and rarely androgens. When there is no outcome and the condition is very annoying, liposuction or mastectomy can be considered. In our study, we examine the treatment with tamoxifen followed by letrozole [5].

2. MATERIALS AND METHODS

We designed a prospective study regarding the efficiency of iterative treatment with tamoxifen and letrozole in male patients with gynecomastia. We enrolled ten patients with gynecomastia totally explored with medical history, hormonal levels and tumor markers. The median age of the patients was 33 years old (19 to 72). In all the patients the cause of gynecomastia, when it was established, was treated specifically. Despite the specific management, the gynecomastia remained in 7 patients.

In all patients we studied the volume of the breasts before the treatment, after 3 months of tamoxifen 20 mg per day and after 3 months of tamoxifen followed by 3 months of letrozole 2.5 mg per day. Patients with medical history of thrombosis, cataract, high hypercholesterolemia and osteoporosis were excluded. One of the seven patients was excluded, because of a medical history of thromboembolism. Finally, our study was done on 6 patients. The six patients of our series were assessed clinically and with breast ultrasound. Clinically, we noted the discomfort (tenderness itching) created by the gynecomastia before the treatment, after 3 months of treatment with tamoxifen and after 6 months of treatment with tamoxifen followed by letrozole. The score used was: 0: no discomfort, 1: mild, 2: medium and 3: severe.

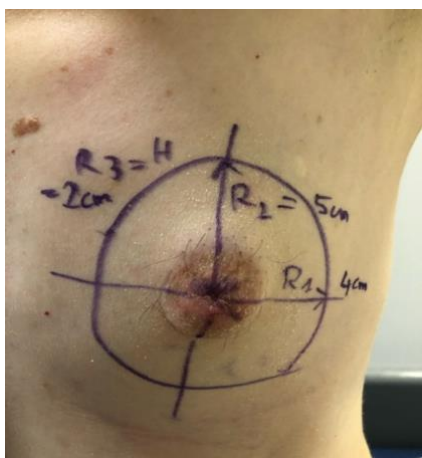


Figure 1

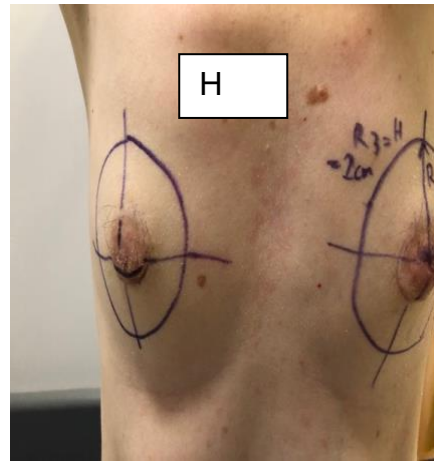


Figure 2

Figures 1 and 2. Geometric calculation of the breast volume. R1: Horizontal radial, R2: Vertical radial, R3=H= Height by ultrasound.

The appreciation of the breast aspect was quoted in 3 categories by the physician: 1: poor, 2: medium and 3: good. The volume of the breast was calculated with the formula $v=2/3*\pi*R1*R2*H$, which is approximately the volume of a half sphere. R1 was the half horizontal diameter of the breast (radial), R2 was the half vertical diameter of the breast (radial) measured on the patient skin. H was the depth of the breast measured with ultrasound: from the skin to the major pectoralis muscle. We assessed the decrease of the breast size after one and two steps therapy and the possible significance.



Figure 3. Breast ultrasound. H=height= R3

3. RESULTS

The patient discomfort: from the 6 patients, 5 had breast discomfort. In 3 of them it decreased: score 3 to 1 in 2 cases, 2 to 1 in 1 case. In 2 cases the discomfort was 0 and remained 0. This result shows a good clinical improvement.

Regarding the appreciation of the physician, there was an improvement in all the 6 cases. More precisely it was good in 5 cases and medium in 1 case. The volume of the breasts was assessed during the first consultation with the symptom of gynecomastia: V_g , then after the treatment with tamoxifen: V_t and after the treatment with tamoxifen followed by letrozole: V_{tl} . Because of the variability of the volumes depending of the body size and the BMI of each patient we expressed our measurements in percentage of change between V_g , V_t and V_{tl} , for each patient. The percentage of reduction of the volume was calculated with the formula: $V_g - V_t / V_g$ and $V_g - V_{tl} / V_g$. For example, in case of there was no change $V_g = V_t$ the percentage of reduction would be $V_g - V_t / V_g = 0\%$.

The breast volume was decreased in 4 cases of 6, after tamoxifen: 32%, 28% 52%, 73% and not reduced in 2 cases 2%, 3%. Because of the possibility of technical bias of the mensuration technique, we considered a reduction less than 10% as no reduction. The decrease of the gynecomastia was obtained in 4/6 cases :66.6% and the mean reduction was 31,6%.

The patients after the treatment with tamoxifen followed by letrozole had a reduction of: 41%,29%,65%,82%,11%,3%, showing a greater decrease after the two treatments in 5 of the 6 cases:83.3% and a mean reduction of 38,5%. For individual cases, the volume difference before and after treatment with letrozole was 25%, 3.5%, 22%, 12%, 138%, and 0% respectively. Since a reduction less than 10% was considered as no reduction, a clinically important reduction was achieved in four cases with tamoxifen followed by letrozole. Moreover we noted that the 2 cases which the treatment was not or very little efficient were patients older than 50 years versus patients older less than 30 years. This result could be explained by the difference of sensibility to the hormonal receptors depending on the age.

4. CAUSES OF GYNECOMASTIA

Firstly, it reasonable to analyze the causes of physiologic gynecomastia. These causes are different in each of three categories stated before. In after birth gynecomastia the breast tissue is stim-

ulated by the estrogens and progesterone produced by the mother. Also, another one cause that increases estrogens in circulation in this phase, is the neonatal surge of luteinising hormone (LH). This type of gynecomastia usually persists for 2 months. A milky discharge may be noted [1]. Gynecomastia during puberty is a very common incident and is located in up to 70% of boys between 13-14 years old. It is caused, because of decreased androgen or increased aromatase activity leading to increased estrogen to androgen ratio. It resolves within 3-4 years [2]. Gynecomastia of the older men affects 36-57% of men older than 60 years old. It has been attributed to a combination of factors. The factors are increased aromatase activity due to increased fatty tissue in this age, elevated LH, lower testosterone and increased Serum sex hormone binding globulin (SHBG). SHBG binds more testosterone than estrogen, so the ratio estrogen to testosterone is increased [3,4]. Pathologic gynecomastia happens when the ratio of estrogen to androgen is increased locally or in the circulation. This can be caused by increased aromatase activity, increased SHBG, decreased testosterone, androgen resistance, tumors, drugs and other diseases. Increased aromatase activity is related with obesity and increased adipose tissue. SHBG mechanism that causes gynecomastia is stated before. This condition is commonly caused by drugs, such as spironolactone.

Decreased testosterone increases the estrogen to androgen ration leading to gynecomastia. Low testosterone levels are noted in situations such as primary hypogonadism (Klinefelter syndrome), primary testicular failure, testicular diseases (orchitis, trauma, radiation), enzyme deficiencies (deficiency of 17-oxosteroid reductive, an enzyme which converts androstenedione to testosterone) and secondary hypogonadism (Kallman syndrome). Androgen resistance syndromes obviously can lead to gynecomastia. The decreased sensitivity of the androgen receptor leads to low impact of the existing testosterone and gynecomastia. One of these syndromes is Kennedy disease. Drug induced gynecomastia is about 20% of all cases. The mechanisms of action are different and not fully understood. A drug can cause gynecomastia by increasing estrogen (contact with vaginal estrogen creams, sprays, phytoestrogen herbs), having action of estrogen on estrogen receptor, supplying aromatizable estrogen precursors, blocking testosterone or androgens and by displacing estrogens from SHBG affection. Common types of drugs that cause gynecomastia are cardiac and antihypertensive drugs (calcium channel blockers, ACEI, alpha-blockers, nitrates, amio-darone, methyl-dopa), psychoactive drugs (neuroleptics, anxiolytic

agents, tricyclic agents), drugs of abuse (amphetamines, heroin), flutamide (anti-androgen used for prostate cancer), omeprazole, statins, heparin and other. Also, ethanol induces gynecomastia by

increasing SHBG, increasing the hepatic clearance of testosterone and by its toxic effect on testes. Finally, marijuana has been associated with gynecomastia.

Table 1. Drugs that cause gynecomastia

Cardiovascular Drugs	Psychoactive Drugs	Drugs of Abuse	Antibiotics and Antiviral Agents	Others
Calcium channel blockers (nifedipine, diltiazem)	Neuroleptics (haloperidol)	Amphetamines	Ketoconazole	Flutamide
A-CEI inhibitors (captopril, enalapril)	Anxiolytic agents (sertraline, duloxetine)	Heroin	Metronidazole	Omeprazole
Alpha-blockers (dutasteride, finasteride)	Tricyclic agents (amitriptyline, imipramine)	Methadone	Isoniazid	Statins
Nitrates			Efavirenz (AIDS)	Heparin
Amiodarone			Ethionamide	Domperidone
			Minocycline	Methotrexate
				Penicillamine

Additionally, tumors can cause gynecomastia. These tumors are more often testicular but they can also be adrenal, extragonadal germ cell tumors, tumors of lung, hepatocellular carcinoma, gastric or renal tumors. Tumors of testis that can cause gynecomastia are Leydig, Sertoli, Granulosa or Gonadal germ cell tumors. These tumors can lead to gynecomastia by increased production of estrogen, increased production of androgens, aromatisation of androgens to estrogens and increased secretion of hCG that stimulates Leydig cells through LH receptor. Leydig cell tumors are 1-3% of testicular tumors and can cause gynecomastia by production of testosterone or estrogen. They can be palpable or only seen by ultrasound. Sertoli cell tumors are 1% of testicular tumors, 10% of them are malignant and can cause gynecomastia by production of estrogen or by increased aromatase activity in Peutz-Jegher syndrome. This syndrome is also characterised by pigmented macule on the lips and gastrointestinal polyposis. Granulosa cell tumors are rare and they can cause gynecomastia by production of estrogen. Germ cell tumors, which is the most common type of testicular cancer in the age between 15-35 years old, can cause gynecomastia by overproducing hCG or hCG subunits that stimulate Leydig cells through LH receptor. The same mechanism with increased hCG or hCG subunits causes gynecomastia in large cell carcinomas of lung. Adrenal tumors can cause gynecomastia by overproduction of DHEA, DHEAS or androstenedione that are converted in the periphery to estrogens or in some rare cases they can produce estrogen di-

rectly. Fibrolamellar hepatocellular carcinoma can cause gynecomastia by increasing the aromatase activity. Finally, other diseases can cause gynecomastia. End-stage renal disease is one of them and leads to that outcome, because of reduced testosterone. Liver diseases also can cause gynecomastia perhaps due to increased SHBG or decreased hepatic clearance of estrogens. Thyrotoxicosis can cause gynecomastia by increasing peripheral aromatization, increased LH or increased SHBG. Also, primary and secondary hypogonadism can lead to gynecomastia due to androgen deficiency. HIV patients can develop gynecomastia. This is caused by drugs used in HIV treatment and androgen deficiency, which is common in these patients [4,5,6,7,8].

5. DIAGNOSIS

Gynecomastia is diagnosed clinically when there is subareolar breast tissue with diameter 2 cm or greater. However, when we have the diagnosis of gynecomastia, there are certain things to be investigated in order to find the cause and exclude the possibility of neoplasm. First, the complete history of the patient must be asked. Medications, drugs, alcohol or illnesses that affect the thyroid gland, liver or kidneys can cause gynecomastia. Physical examination of the breast and axilla is essential. Tumor in axilla, immobility of the breast tumor, skin dimpling, nipple retraction, discharge are things to be aware in order to exclude breast cancer. Gynecomastia is mostly bilateral, concentric and sometimes painful, when the enlargement is rapid and

recent. Breast cancer is rare in males, unilateral, more peripheral, and painless. Ultrasound is a very helpful tool in the evaluation of the breast tissue when gynecomastia is suspected. Sometimes MRI may be offered. If there is uncertainty biopsy should be taken. Testicular examination is necessary. The physician must search for mass in both testicles, check for asymmetry and size. If no finding exists, an ultrasound is a good method to exclude palpable masses of the testicles. Laboratory exams should be performed. The levels of testosterone, estradiol, FSH, LH, prolactin and hCG should be evaluated. Increased levels of hCG should lead to the investigation of testicular tumor

and if there is no finding CT of thorax or abdomen should be performed in order to search for other extragonadal tumors. LH and testosterone are important to differentiate primary hypogonadism, secondary hypogonadism and androgen resistance. Increased LH and low testosterone characterises primary hypogonadism. One example is Klinefelter syndrome. Both decreased testosterone and LH lead to secondary hypogonadism and central causes. Both increased testosterone and LH can be seen in androgen resistance situations. Finally, liver, kidney and thyroid function can be tested if any problem is suspected in these systems or if there exists pathology in the medical history [1,9,10].

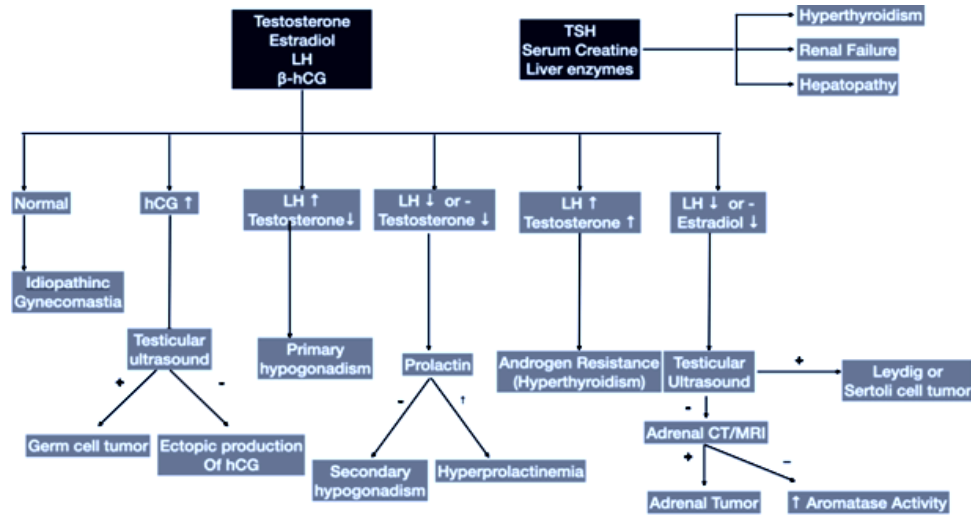


Figure 4. Flowchart of Hormonal impact in gynecomastia.

6. TREATMENT

The first step in treatment of gynecomastia is the identification of a possible pathologic cause. If there can be found no cause and the situation is severe, annoying, less than 6 months and does not settle itself, medical treatment is indicated. If medical treatment has no outcome, gynecomastia persists for more than 6 months, affects the patient daily life and psychology and malignancy has not been ruled out, then surgical treatment must be considered. Finally, if there is found a certain cause, then there is followed a treatment that targets this cause.

As stated before, in the occasion when there can be found no cause and the situation is severe, annoying, less than 6 months and does not settle itself, medical treatment is indicated. There are 3 types of medicine that are administered in this occasion. Anti-estrogens, aromatase inhibitors and androgens.

The commonly used anti-estrogens are tamoxifen, raloxifene and clomiphene citrate. Tamoxifen achieves statistically significant regression of breast tissue size, has relatively lesser and milder side effects and high efficacy, when compared with other types of therapies. Raloxifene has been purely used and there are needed further randomized prospective studies for evaluation of its efficacy. Clomiphene citrate in a cohort study had response in 64% of pubertal patients. Tamoxifen and SERMS has been used widely for pubertal gynecomastia and tamoxifen is the chosen drug of treatment but in general the data is partial and research is insufficient. However, in pubertal gynecomastia the indication for using tamoxifen is disc size ≥ 4 cm and the duration of treatment must be 4-6 months. In order to start tamoxifen the disc size should be ≥ 3 cm and for optimal effect studies show that the therapy should be continued for at least 6 months [11,12,13,14,15].

Aromatase inhibitors, such as anastrozole and letrozole, are used in gynecomastia treatment but their efficacy has not been proven. Some studies have found no difference between placebo groups and patients taking aromatase inhibitors. Large-scale high-quality studies are warranted [16]. However, in a case where in 5 boys with pubertal gynecomastia anastrozole was administered for 6 months, in 4 of 5 patients the breast size decreased and in 1 of 4 the breast tissue disappeared. It seems that anastrozole can be treatment for tenderness, because in 4 weeks tenderness resolved in all boys and it can be also helpful in patients with risky surgery. It might not help in treatment of gynecomastia, because it does not seem to fully resolve breast tissue [17]. Further double-blind trials are needed to become in this field for safer outcomes. Additionally, in some studies it seems that in cases of Large cell calcifying Sertoli cell tumors the use of anastrozole might be helpful [18]. Also, in patients with Peutz-Jeghers Syndrome, prepubertal gynecomastia and testicular tumors can be present. In this case, it seems that anastrozole can replace orchidectomy by controlling the circulating estrogen levels and with subcutaneous mastectomy the outcome and patient satisfaction is beyond good [19]. Additionally, aromatase inhibitors use has been described in a case report in with HIV and gynecomastia. No certain outcomes exist, because there are no other recorded cases but this medicine has been used, because tamoxifen can induce the activity of CYP3A4 and cause virological failure and resistance [20]. Finally, it is important to be stated the outcome of a case report in men with gynecomastia, which was induced by testosterone replacement treatment (TRT). Both were treated successfully with anastrozole [21]. The androgens that had been used for gynecomastia are testosterone, dihydrotestosterone and danazol.

Testosterone has been used in hypogonadism but there is limited data in this case and there is danger, because the aromatisation of testosterone to estradiol, raises the estrogen to androgen ration and can cause gynecomastia. Dihydrotestosterone is not aromatised to estrogens and can possibly have good effect in gynecomastia. Danazol seems to have a positive outcome in gynecomastia but its side effects such as acne, cramps and edema are not balancing its benefits. Also, the percutaneous use of dihydrotestosterone gel (andractim) has been used in the therapy of gynecomastia. In a clinical trial, after the percutaneous use of 125mg twice daily for 4 to 20 weeks in 40 men with idiopathic gynecomastia, the breast tissue completely disappeared in 10 men, regressed partially in 19 men and in 10 the was no change. However, further trials are needed to be done in the use of androgens for the treatment of gynecomastia [22].

If medical treatment has no outcome, gynecomastia annoys the patient in daily activities or affects his psychology or the risk of malignancy has not been excluded, then surgical treatment should be considered. This treatment can be the removal of the breast tissue or liposuction. Also, if gynecomastia exists for more than 6 months, then the patient has chronic gynecomastia and the breast tissue has developed fibrotic tissue. In this case, medical treatment has not outcomes and there is need for surgery. Surgery in most cases must be performed after puberty, because 80% of pubertal gynecomastia resolves until the age of 20 and there can be avoided recurrences. In no pathologic pubertal gynecomastia a breast examination should be performed every 3-6 months in order to track stabilization or changes of breast tissue.

In cases where there is an identified cause of gynecomastia the therapy targets this cause. If a medication is the cause, in most cases after 1 month of discontinuation the breast tissue starts regressing. In cases of testicular tumors, surgery is indicated and if the tumor is germ cell tumor, then chemotherapy is needed. In dysfunction of thyroid gland, kidneys, hepatic failure, hypogonadism, androgen resistance syndromes or other endocrinological issues the patient should be referred to the expert of each occasion.

Finally, it is important to be stated that there exists the option of combined surgical and medical treatment in gynecomastia. Surgery is usually planned in late adolescence, because symptoms may recur in adolescents. Additionally, in one case of a boy with excessive breast enlargement and estradiol secretion from the age of 9, tamoxifen treatment did not manage to stop this situation. So at the age of 13,5 years old total mastectomy was performed and tamoxifen was changed to anastrozole do the assessment of elevated aromatase activity. This combined treatment had positive outcome and stated the fact that medical treatment should be tested and changed, if the pathophysiological background of certain occasion fits better to other medicine [23].

However, when searching in bibliography there exists no other case, where there is a scheduled switch from tamoxifen to anastrozole or other medical treatment. In most cases tamoxifen alone is given. Consequently, this type of combined treatment, that is described seems to be very interesting and promising.

7. DISCUSSION

Gynecomastia treatment is not well standardized. The adjunction of letrozole to tamoxifen in gynecomastia decreases significantly the size of the breast

in our small cohort. This new protocol not yet published should be proposed to improve the treatment with tamoxifen alone. More studies with higher number of cases should confirm our findings.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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