

Approach to the Patient with Gynecomastia

Harold E. Carlson

Department of Medicine, Endocrinology Division, Stony Brook University, Stony Brook, New York 11794-8154

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Learning Objectives

Upon completion of this educational activity, participants should be able to

- Discuss the hormonal pathogenesis of gynecomastia.
- Appropriately evaluate and recommend therapy for patients with gynecomastia.

Target Audience

This continuing medical education activity should be of substantial interest to endocrinologists.

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Gynecomastia is a common and sometimes distressing condition that may occur in males of all ages. Although most cases have benign causes and many are self-limited, male breast enlargement may also be a sign of underlying systemic disease or drug toxicity. Although rare, male breast cancer must also be considered in the differential diagnosis. A careful diagnostic evaluation should be pursued, tailored to the individual patient's circumstances. Treatment may include reassurance, medication, or surgery. (*J Clin Endocrinol Metab* 96: 15–21, 2011)

A 39-yr-old man was referred because of bilateral tender breast enlargement noted 2 months ago, without bleeding or nipple discharge. He was in generally good health until 7 months ago, when he was diagnosed with Hodgkin's lymphoma. He completed chemotherapy with a combination of cytotoxic agents 3 months ago. He is a nonsmoker and drinks 12 ounces of beer two to three times per week. He has two children, ages 7 and 10 yr. His libido and erectile function are normal. There is no family history of breast or testicular cancer.

On physical examination, he was not obese, with a body mass index of 26.0 kg/m². Vital signs were normal, as was the examination of the eyes, thyroid, heart, lungs, abdomen, and extremities. Both breasts were enlarged, with palpable, rubbery glandular tissue centered beneath the areolae measuring approximately 3 cm in diameter bilaterally; the breast tissue was moderately tender. There was no skin or nipple retraction and no ulceration. Both testes were descended and were low-normal in size and consistency; the penis was normal. His beard and body hair were normal.

Laboratory studies showed normal renal, hepatic, and thyroid function. Serum β -human chorionic gonadotropin (hCG) was less than 5 mIU/ml (normal). Total serum testosterone, drawn at 0800 h, was 340 ng/dl (normal, 241–827 ng/dl), estradiol was 54 pg/ml (normal, <29 pg/ml), LH was 38 mIU/ml (normal, 1.5–9.3 mIU/ml), FSH

Abbreviation: hCG, Human chorionic gonadotropin.

was 56 mIU/ml (normal, 1.6–8.0 mIU/ml), and prolactin was 9 ng/ml (normal, 2–18 ng/ml).

Background

Gynecomastia is defined as the presence of palpable breast tissue in males and is common in normal individuals, particularly in the newborn period, at puberty, and in the elderly. Around 60% of all boys develop transient pubertal breast enlargement (1), and 30–70% of adult men have palpable breast tissue, with the higher prevalence being seen in older men and those with concurrent medical illnesses (2–4).

Histologically, the primary feature of gynecomastia is ductular proliferation in a background stroma of fibrous connective tissue (2, 5); about half of all men demonstrate histological evidence of gynecomastia at autopsy (6). Most often, gynecomastia is bilateral, but it may sometimes be unilateral or asymmetric. With the passage of time, the connective tissue component of gynecomastia tends to become denser and more fibrotic (5).

Receptors for androgens, estrogens, progesterone, and prolactin are found in the male breast (7, 8). It has been shown that estrogens stimulate breast tissue proliferation, whereas androgens inhibit this process (9–11). It is believed that most cases of gynecomastia are caused by an imbalance of these two influences, with estrogen-induced stimulation predominating (12, 13). Such an imbalance may occur with increased estrogen action on the breast, decreased androgen action, or a combination of the two. This may be due to an increase in circulating or tissue levels of estrogen, a decrease in circulating or tissue levels of androgen, increased responsiveness of the breast to estrogen (*e.g.* increased numbers of estrogen receptors), or decreased breast responsiveness to androgens (*e.g.* androgen insensitivity due to receptor mutations or drugs). More than one of these derangements may be present in a single patient; for example, the increased prevalence of gynecomastia in older men may be related to increased adiposity with age (14) [adipose tissue is a major site of aromatization of androgens to estrogens (15)], decreased serum free testosterone due to aging [with decreased testosterone production as well as increased binding of testosterone to SHBG (16)], and greater use of medications that may alter androgen or estrogen concentrations or action.

Although prolactin receptors are present in the male breast (8), hyperprolactinemia may lead to gynecomastia through its effects on the hypothalamus to cause central hypogonadism. Prolactin has also been reported to decrease androgen receptors and increase estrogen and progesterone receptors in breast cancer cells (17, 18); if a similar effect were to occur in the male breast, gynecom-

TABLE 1. Causes of gynecomastia

I. Estrogen excess
A. Exogenous estrogens: therapeutic or unintentional exposure, including exposure to aromatizable androgens (<i>e.g.</i> athletes)
B. Endogenous estrogens
1. Increased secretion from testis (Leydig cell or Sertoli cell tumors, stimulation of normal Leydig cells by LH or hCG)
2. Increased secretion from adrenals (feminizing adrenocortical tumors)
3. Increased aromatization of androgens to estrogens (aging, obesity, alcoholic cirrhosis, hyperthyroidism, drugs, hCG-secreting tumors, aromatase excess syndrome)
II. Androgen deficiency: primary or secondary hypogonadism due to disease, trauma, radiation, or drugs
III. Altered serum androgen/estrogen ratio (puberty, aging, refeeding gynecomastia, hepatic cirrhosis, renal failure and dialysis, hyperthyroidism, drugs)
IV. Decreased androgen action
A. Androgen receptor antagonists (spironolactone, cimetidine, bicalutamide, flutamide)
B. Absent or defective androgen receptors
C. Expansion of CAG repeats in the androgen receptor gene (Kennedy disease)

astia might result. The role of prolactin, progesterone, and circulating or locally produced growth factors [*e.g.* IGF-I, epidermal growth factor (EGF), *etc.*] is unclear at present.

Table 1 summarizes the major known causes of gynecomastia. It is important to keep these factors in mind because they will help guide the choice of therapy and may, in some instances, require treatment independent of their role in causing breast enlargement. A more detailed discussion of these individual causes can be found in recent reviews of the topic (13, 19).

Evaluation

Several questions need to be answered in evaluating every male patient with breast enlargement:

1. Is the breast enlargement of recent onset or associated with pain or tenderness?
2. Is the breast enlargement due to increased glandular tissue or is it only adipose tissue (pseudogynecomastia)?
3. Are there findings suggestive of breast cancer?
4. Is there evidence of a testicular tumor, which might lead to gynecomastia by producing estrogen or stimulating its production?
5. Can a cause for the breast enlargement be identified?
6. Is the patient troubled by the breast enlargement?

Gynecomastia is common in normal men and may frequently be noted on routine physical examination. A healthy

man with long-standing stable gynecomastia and a negative history and physical examination generally does not need further evaluation. The presence of new-onset breast pain, tenderness, or enlargement suggests a more recent, ongoing process and should prompt further testing to detect underlying systemic or endocrine problems.

A detailed history should be obtained, including the duration of the gynecomastia, the presence of breast pain or tenderness, systemic disease (*e.g.* chronic liver or renal disease; hyperthyroidism; hypogonadism; prostate, testicular, or other cancer), recent weight gain or loss, use of medication or recreational drugs, exposure to other chemicals, fertility and sexual function. A thorough medication history is particularly important and should include the use of nonprescription medications, anabolic steroids, and dietary supplements (Table 2). A family history of gynecomastia would suggest the possibility of an androgen resistance syndrome, familial aromatase excess, or estrogen-producing Sertoli cell tumors [as may occur in Peutz-Jeghers syndrome or in the Carney complex (20, 21)]. A family history of BRCA2-positive breast cancer significantly increases the lifetime risk of male breast cancer to 8–10% in carriers of the mutation (22).

The physical examination should note features of virilization (voice, facial and body hair, skeletal muscle bulk), testicular size and/or masses, penile size and development, signs of chronic liver or kidney disease, and evidence of hyperthyroidism. The breasts should be carefully examined to differentiate true gynecomastia with palpable glandular

tissue from pseudogynecomastia, in which only adipose tissue can be felt; I have found it useful to examine the patient's breasts in both the supine and seated position, using a pincer movement with the thumb and forefinger to delineate the presence and size of glandular elements, comparing the subareolar area to a nearby fold of adipose tissue. Attention should be paid to the symmetry and smoothness of the glandular tissue; unusual firmness, asymmetry, or an eccentric location (not centered beneath the areola), fixation to the skin or chest wall, nipple retraction, bleeding or nipple discharge, ulceration, or associated lymphadenopathy should all suggest the possibility of breast carcinoma (23) and should lead to biopsy or excision.

Routine biochemical testing should evaluate thyroid, liver, and kidney function, along with measurements of serum testosterone (total and/or bioavailable), estradiol, LH, FSH, prolactin, and β -hCG.

In two reported series of men with gynecomastia, the cause was determined to be physiological (*i.e.* puberty or associated with aging) or idiopathic in more than 50% of the patients (24, 25).

Therapy

Asymptomatic men with long-standing breast enlargement do not require treatment; reassurance is often all that is required. In those with symptoms (pain, tenderness, embarrassment, or excessive worry), treatment is guided by the cause and by the patient's goals (relief of discomfort, restoration of normal appearance, reassurance regarding cancer or treatment of an underlying illness).

In men with an identifiable underlying disorder (*e.g.* hyperthyroidism, testicular tumor), treatment of that disorder will often ameliorate the breast enlargement and symptoms, at least partially. Similarly, if the gynecomastia is believed to be due to a medication or recreational drug, withdrawal of that agent should lead to at least some improvement over a period of a few months. If the breast enlargement has been present for more than 1 yr, complete regression is less likely, due to the predominance of dense fibrous tissue (13, 19). Teenage boys with pubertal gynecomastia can usually be observed, with the expectation that the gynecomastia will spontaneously resolve over 1–2 yr in most cases (26). Gynecomastia related to dialysis or refeeding is also generally self-limited, and reassurance may be sufficient treatment (27, 28).

In some men with hypogonadism of short duration, testosterone replacement may lead to the resolution or improvement of associated gynecomastia (29, 30). However, because testosterone can be aromatized to estradiol, it may worsen the breast enlargement in some cases, and the patient should be warned of this possibility.

TABLE 2. Drugs commonly implicated in gynecomastia

Drugs that increase serum estrogens
Estrogens, including topical preparations
Aromatizable androgens
hCG
Drugs with estrogen-like activity
Digitoxin
Drugs that decrease serum testosterone or dihydrotestosterone
GnRH agonists/antagonists
Leydig cell damage or inhibition
Ketoconazole, metronidazole
High-dose spironolactone
Cancer chemotherapy
Finasteride or dutasteride
Androgen receptor blockers
Flutamide, bicalutamide
Spironolactone
Cimetidine
Marijuana
Increased serum prolactin
Antipsychotic agents
Metoclopramide
Verapamil
Other—mechanism uncertain
Isoniazid
Amiodarone
Antidepressants
Human GH
Highly active antiretroviral therapy (HAART)
Proton pump inhibitors

Antiestrogens have been increasingly used in recent years to decrease the stimulatory effect of estrogens on the male breast. Tamoxifen and raloxifene, which block the estrogen receptor, and aromatase inhibitors such as anastrozole have all been used with varying degrees of success in the treatment of gynecomastia. Although studies of their effects have been limited, there appears to be reasonable evidence supporting the utility of tamoxifen (31–35) and some evidence that raloxifene is approximately as useful as tamoxifen (35). Neither tamoxifen nor raloxifene has been associated with significant side effects in the majority of patients (31–35). Tamoxifen has been used in doses of 10–20 mg/d and raloxifene at a dose of 60 mg/d for 3–9 months. In contrast, anastrozole was no better than placebo in a randomized, double-blind trial in patients with pubertal gynecomastia (36). Anastrozole was successfully used to reduce the estrogen excess and breast enlargement in a patient with familial aromatase excess (37), a patient with a feminizing Sertoli cell tumor (38), and two hypogonadal men with gynecomastia induced by testosterone therapy (39). It should be noted that none of these drugs have been approved for the treatment of gynecomastia.

For men with gynecomastia due to androgen deprivation therapy for prostate cancer, prophylactic radiation therapy directed at the breast has been somewhat successful in preventing new-onset gynecomastia (40–42). Tamoxifen has also been used successfully in this situation (43) and appears to be superior to both radiotherapy (44) and anastrozole (45, 46). Daily administration of tamoxifen was shown to be more efficacious than weekly dosing (47).

Surgery to remove the breast tissue has been widely used in the treatment of gynecomastia. It should probably be performed by highly experienced surgeons to achieve the best cosmetic result. Excision with or without liposuction has been successfully used (48, 49). Surgical treatment of pubertal gynecomastia should generally be postponed until the completion of puberty to minimize the possibility of postoperative regrowth of breast tissue.

Figure 1 illustrates a suggested scheme for the evaluation and treatment of gynecomastia.

Controversies and Areas of Uncertainty

Several parts of the evaluation process remain controversial. Some authors have recommended performing mammography and/or breast ultrasound in all cases (50–52); in agreement with others (24, 53–58), my own practice has been to use these imaging tools only when there are physical findings that raise a suspicion of breast cancer or a BRCA-2 mutation is suspected or known to be present. Although the sensitivity and specificity of mammography are both greater than 90% in the diagnosis of male breast cancer,

the much higher prevalence of gynecomastia compared with breast cancer leads to a positive predictive value of only 55% (59). For breast sonography, the positive predictive value was reported as only 17% (60). Therefore, universal application of imaging seems unlikely to be cost-effective. In one study of male breast mammography, all of the men diagnosed with breast cancer also had physical findings that were suspicious for malignancy (55).

Some authors have felt that the routine laboratory evaluation of all men with gynecomastia to detect underlying disease is also not cost-effective, citing reports that only a small number of patients have unsuspected relevant laboratory findings and suggesting more selective laboratory testing, guided by the individual patient's medical history and examination (53, 57). It is certainly true that asymptomatic men with incidentally discovered palpable breast tissue generally need only a careful history and physical examination and do not usually benefit from laboratory testing. Factors that bear on this question include the potential seriousness of a positive laboratory finding (*e.g.* detection of a malignant tumor secreting hCG), the cost of the laboratory test, and the likelihood of the underlying disease being present in a man with no symptoms or signs other than gynecomastia (*e.g.* hypogonadism, chronic hepatic disease or renal insufficiency, hyperthyroidism, Leydig cell tumor). The perceived need to practice defensive medicine undoubtedly contributes, as well. Unfortunately, there is no consensus on this matter. The issue may particularly arise in older men, in whom palpable breast tissue is a common incidental finding. Although hypogonadism is also common in this age group, it is not clear whether serum testosterone should be measured in all such individuals if they are truly asymptomatic (*i.e.* no local breast symptoms and no symptoms of hypogonadism). There would appear to be little clear benefit from testosterone treatment in the absence of symptoms, so I do not routinely obtain screening laboratory tests in such patients.

In the realm of therapy, medical treatment has its own controversies. The overall response rate to tamoxifen has varied from 50–80%, although reported side effects have been few (31–35). It has not yet been clearly established whether tamoxifen and raloxifene are of equal benefit, although it seems reasonably clear that both are more effective than aromatase inhibitors (36, 45, 46). Surgical therapy is generally agreed to be the most effective means of restoring the normal contour of the breast, but many different techniques and approaches are in current use and are likely to be influenced by the degree of breast enlargement as well as the proportion of glandular and fibrous tissue *vs.* adipose tissue present (61, 62). In addition, not all patients treated surgically are pleased with the results (63).

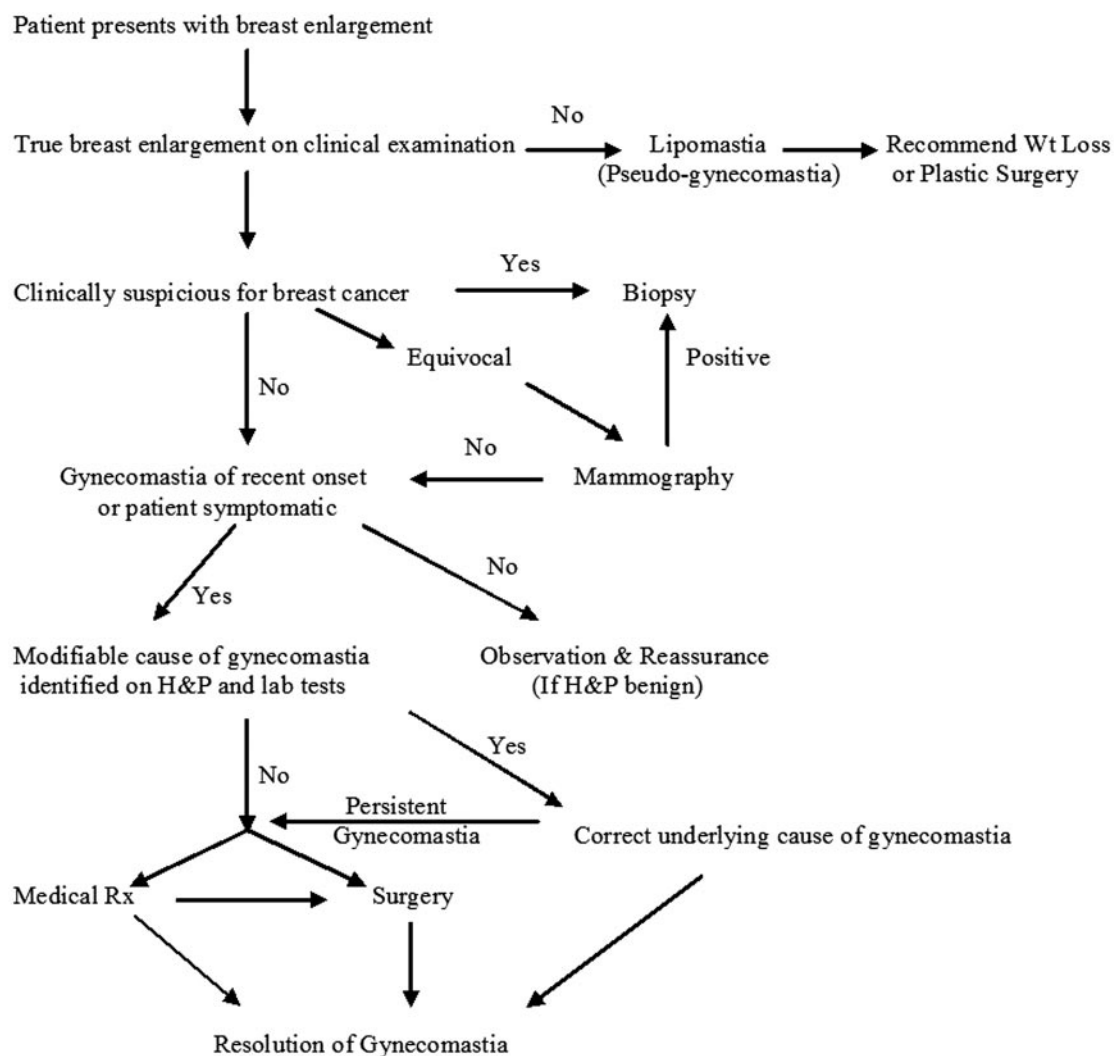


FIG. 1. Suggested algorithm for the management of gynecomastia. H&P, History and physical examination; Rx, therapy; Wt, weight. [Reprinted from H. S. Narula and H. E. Carlson: *Endocrinol Metab Clin North Am* 36:497–519, 2007 (13), with permission from Elsevier.]

Returning to the Case

Our patient developed tender bilateral breast enlargement in the setting of recent cytotoxic chemotherapy for lymphoma. Although his prior fertility history was normal, his total serum testosterone was in the low-normal range, with elevated serum LH, FSH, and estradiol but normal serum prolactin and negative β -hCG. There was no evidence of thyroid, renal, or hepatic disease. His compensated primary hypogonadism was most likely a consequence of his cancer chemotherapy. Stimulation of Leydig cells by LH (or hCG) increases aromatase activity and estradiol secretion (64). Literature reports suggest that many (although not all) such patients with chemotherapy-induced gynecomastia will have spontaneous recovery of Leydig cell function over several months, with gradual improvement or disappearance of the breast enlargement and tenderness (30, 65–67). Alternatively,

he could be offered testosterone supplementation or tamoxifen therapy, with a good chance that his gynecomastia would decrease in size and tenderness because his breast enlargement had been present for only a few months. Finally, surgery would probably be the most certain way to cure this man's gynecomastia. After an extensive discussion of all these options, he chose to forego active treatment, opting for continued observation. Over the next 6 months, his serum testosterone LH and FSH returned to mid-normal, and his breasts were no longer tender or enlarged.

This patient is in many ways typical of the sort of patient seen by endocrinologists for gynecomastia. Although his history suggested the ultimate cause, it was important to rule out other underlying diseases and neoplasms and then to offer the patient the appropriate therapeutic modalities from which to choose.

Conclusions

Patients with asymptomatic palpable breast tissue need only a careful history and physical examination; most of these patients have either persistent pubertal gynecomastia or age-related gynecomastia. Patients with symptomatic gynecomastia need, in addition to a careful history and physical examination, appropriate screening laboratory tests to detect underlying disorders and guide therapy. Most such cases have a benign etiology or are idiopathic. Underlying causes should be corrected, when possible; medical therapy or surgery can be offered to patients with persistent symptoms.

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Address all correspondence and requests for reprints to: Harold E. Carlson, M.D., Department of Medicine, Endocrinology Division, HSC T15-060, Stony Brook University, Stony Brook, New York 11794-8154. E-mail: harold.carlson@stonybrook.edu.

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