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Gynecomastia: Its features, and when and how to treat it

ABSTRACT

Gynecomastia is common, being present in 30% to 50% of healthy men. A general medical history and careful physical examination with particular attention to features suggestive of breast cancer often suffice for evaluation in patients without symptoms or those with incidentally discovered breast enlargement. Men with recent-onset gynecomastia or mastodynia need a more detailed evaluation, including selected laboratory tests to search for an underlying cause. Treatment depends on the cause and may include observation, withdrawal of an offending drug, therapy of an underlying disease, giving androgen or antiestrogen drugs, or plastic surgery.

KEY POINTS

Gynecomastia is probably not associated with an increased risk of breast cancer, except in Klinefelter syndrome.

Most cases of gynecomastia result from an imbalance between estrogenic (stimulatory) and androgenic (inhibitory) effects on the breast.

Drug-induced gynecomastia accounts for 20% to 25% of cases. Even with detailed evaluation, there is no identifiable cause in about 25% of cases.

GYNECOMASTIA (enlargement of the male breast) is usually benign. Yet, it causes much anxiety, psychosocial discomfort, and fear of breast cancer.

In this article we briefly review the causes of gynecomastia, the key features to look for in the history and the physical examination, who needs a more detailed evaluation, and when and how to treat this condition.

PREVALENCE AND OCCURRENCE

Gynecomastia is common. In two case series, palpable breast tissue was detected on physical examination in 36% of healthy younger adult men, 57% of healthy older men,[1] and more than 70% of hospitalized elderly men.[2] In autopsy studies, its prevalence was as high as 55%.[3]

Gynecomastia has three peaks of occurrence during the life span:

The neonatal period. An estimated 60% to 90% of infants have transient gynecomastia due to transplacental transfer of maternal estrogens. It usually regresses completely by the end of the first year.

Puberty. Gynecomastia may occur in 48% to 64% of boys at puberty. It may first appear as early as 10 years of age, with a peak onset between ages 13 and 14, followed by a decline in late teenage years.

Late in life. The highest prevalence is among men ages 50 to 80.[1,2]

HISTOLOGY

Histologic studies reveal a proliferation of ductules embedded in a connective tissue stroma; glandular acini are rare. In the early or florid

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

stage, ductal hyperplasia and proliferation are extensive while the stroma is loose and edematous.

Usually, over about 12 months, the breast tissue evolves into a quiescent stage, in which the amount of stroma and fibrosis increases and the ductules become less prominent. This distinction seems to be unimportant diagnostically, as these microscopic findings are the same regardless of the cause of the gynecomastia.[3,4]

CLINICAL CHARACTERISTICS

Pseudogynecomastia (fatty breasts) is common in obese men and needs to be differentiated from true gynecomastia. In true gynecomastia, there may be a button of firm subareolar tissue, or there may be a more diffuse collection of fibroglandular tissue that resembles that of the female breast, and which may be difficult to distinguish from simple adiposity. Comparing the subareolar tissue with the anterior axillary fold or other subcutaneous tissue may help in differentiating true gynecomastia from pseudogynecomastia.[5]

Gynecomastia is present in one third to one half of healthy men

Although commonly bilateral and symmetric, gynecomastia of any cause may be unilateral or asymmetric. Unilateral gynecomastia seems to be more common on the left side.[4]

Gynecomastia is often asymptomatic and may be an incidental finding on routine examination, but breast pain or tenderness may be present, particularly if the onset of the condition is recent.

Breast cancer accounts for only 0.2% of all malignancies in men,[5] and generally presents as a unilateral firm mass, often eccentric in location rather than centered beneath the areola. Skin dimpling, nipple retraction, nipple discharge, and axillary lymphadenopathy may be seen.

AN IMBALANCE OF ESTROGENS OVER ANDROGENS

Estrogens stimulate breast tissue growth, whereas androgens inhibit it.[6,7] Most cases of gynecomastia appear to result from an imbalance between estrogenic and androgenic effects on the breast.

Local tissue factors in the breast may be important. These may include excessive local production of estrogen due to increased aromatase activity, decreased estrogen degradation, or changes in androgen or estrogen receptors.[5]

Hyperprolactinemia is not believed to play a direct role in gynecomastia, although prolactin receptors have recently been demonstrated in gynecomastia tissue.[8] Most patients with gynecomastia have normal serum prolactin levels.[9] Moreover, not all patients with hyperprolactinemia have gynecomastia. Elevated prolactin levels may, however, suppress gonadotropin release, producing secondary hypogonadism, which then contributes to the development of gynecomastia.

Absolute estrogen excess

Exogenous estrogens. The simplest mechanism underlying gynecomastia is absolute estrogen excess, as with the use of diethylstilbestrol in the treatment of advanced prostatic carcinoma.[6] Cases have also resulted from unintended exposure to exogenous estrogens in vaginal creams and hair lotions.[10,11]

Leydig cell tumors are rare testicular tumors that secrete estradiol; about 90% are benign. Most patients are young to middle-aged.[12,13] The increased serum estradiol level suppresses pituitary luteinizing hormone (LH), leading to decreased serum testosterone. Elevated serum estradiol also stimulates the production of sex hormone-binding globulin (SHBG), which preferentially binds testosterone, leading to decreased free testosterone with normal or elevated free estradiol. Leydig cell tumors are small and, in some cases, nonpalpable. If they are nonpalpable, testicular sonography or thermography may be needed to detect them. Treatment remains surgical.

Estrogen-producing adrenal tumors, although rare, are usually malignant and are often quite large when discovered.[14] In about one half of cases, there is a palpable abdominal mass. They tend to secrete large amounts of estrogen precursors such as androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate, and some directly produce estradiol and estrone.[15] Two thirds of patients have elevations of urinary 17-ketosteroids, and some have elevated serum DHEA sulfate, both of which are useful tumor markers.

Tumors producing chorionic gonadotropin. The placental hormone human chorionic gonadotropin (hCG) is similar to LH in both its structure and its action on the testis. Thus, elevated serum levels of hCG disproportionately stimulate normal Leydig cells of the testis to secrete increased amounts of estradiol. In addition, many hCG-secreting tumors can take up estrogen precursors from the circulation and aromatize them into active estrogens.

A variety of tumors can secrete hCG, including testicular germ cell tumors and bronchogenic, liver, and gastric carcinomas.[13] Measurement of serum beta-hCG by immunoassay is used for diagnosis. Normal men have undetectable serum levels of hCG in commercially available assays.

Relative estrogen excess

Aging seems to be associated with progressive testicular dysfunction, with low or low-normal serum testosterone levels and, in some cases, elevated LH.[16] Total and free serum estradiol concentrations remain normal. The exact mechanism of testicular failure remains unknown.

Aging is also associated with accumulation of adipose tissue, which maintains normal serum estrogen levels, since adipose tissue is an important site of aromatization of androgens to estrogens.

Primary hypogonadism from any cause (eg, mumps orchitis, trauma, cytotoxic chemotherapy) is commonly associated with gynecomastia. Several factors may contribute to an altered estrogen-to-androgen ratio. First, levels of total and free testosterone decrease. Second, the resulting increase in serum LH stimulates the aromatase enzyme in testicular Leydig cells to produce more estrogen. In addition, peripheral aromatization of the adrenal androgen androstenedione to estrogen remains unaffected.

Klinefelter syndrome is associated with gynecomastia in about 80% of Klinefelter cases, perhaps due to primary hypogonadism. It is the only cause of gynecomastia that clearly carries an increased risk of breast cancer—10-fold to 20-fold greater than normal.[13]

Klinefelter patients typically carry an extra X chromosome. Whether the extra X chromosome plays a role in the development of breast cancer is uncertain, although some studies suggest it; a plausible mechanism is that expression of genes on the noninactivated portions of the second X chromosome facilitates the development of the cancer. Fibroblasts from patients with the XXY genotype have also been shown to have an increased rate of transformation after exposure to simian virus 40.

Secondary hypogonadism. Although less common, gynecomastia may also be a consequence of androgen deficiency in secondary hypogonadism due to partial hypopituitarism. In this situation, peripheral aromatization of adrenal androgens to estrogens remains unaffected and maintains normal serum estrogen levels.

Puberty. Gynecomastia develops in about two thirds of boys during puberty. There are periods during puberty when the balance of sex hormone secretion favors estrogen,[12] despite an increase in androgen production. This ratio returns to more normal adult values as puberty advances. The condition is usually asymptomatic and self-limited and regresses spontaneously after about 2 years.

Refeeding gynecomastia was first noted in World War II, when men liberated from prison camps developed gynecomastia within a few weeks of resuming an adequate diet; the condition persisted for about 1 to 2 years and then regressed spontaneously. The mechanism is not known but may be similar to that of pubertal gynecomastia.[5] Significant weight loss and malnutrition are often accompanied by hypogonadism, due to decreased gonadotropin secretion. With weight gain, gonadotropin secretion and gonadal function return to normal, resulting in a "second puberty."

Gynecomastia in puberty is usually asymptomatic and regresses spontaneously

Renal failure and dialysis. Men with chronic renal failure have a variety of hormonal abnormalities, including low levels of serum testosterone, raised estradiol and LH levels, and modest increases in serum prolactin. The hormonal abnormalities are often reversed with renal transplantation but are not altered by dialysis.[12]

Dialysis-associated gynecomastia may be pathogenetically similar to refeeding gynecomastia. Before dialysis, renal failure patients must follow restricted diets, often are anorec-

TABLE 1

Drugs that can cause gynecomastia

DRUG	MECHANISM
Amiodarone	Unknown
Calcium channel blockers (diltiazem, verapamil, nifedipine)	Unknown
Central nervous system agents (amphetamines, diazepam, methyldopa, phenytoin, reserpine, tricyclic antidepressants)	Unknown
Cimetidine	Androgen receptor antagonism
Cytotoxic agents (alkylating agents, vincristine, nitrosoureas, methotrexate)	Primary hypogonadism due to Leydig cell damage
Flutamide	Androgen receptor antagonism
Hormones	
Androgens	Aromatization to estrogens; other mechanisms?
Estrogens	Direct stimulation of the breast
Human chorionic gonadotropin	Stimulation of testicular Leydig cell estrogen secretion
Isoniazid	Possibly refeeding
Ketoconazole, metronidazole	Inhibition of testosterone synthesis
Marijuana	Androgen receptor antagonism
D-penicillamine	Unknown
Phenothiazines	Elevated serum prolactin
Spironolactone	Androgen receptor antagonism; at high doses, interference with testosterone biosynthesis
Theophylline	Unknown

Drug-induced gynecomastia may account for up to 25% of all cases

tic, and tend to lose weight. With dialysis, diet is liberalized and patients often regain weight.

Dialysis-associated gynecomastia has been reported to improve spontaneously after 1 to 2 years.

Cirrhosis of the liver, especially alcoholic cirrhosis, is commonly associated with gynecomastia. A number of factors may explain this link: alcohol can inhibit the hypothalamic-pituitary-testicular axis, leading to low serum testosterone levels; peripheral aromatization of androgens to estrogens increases in liver disease; SHBG levels are often elevated, causing a further decrease in free testosterone levels; and some alcoholic beverages contain phytoestrogens that may contribute to relative estrogen excess.[5,12]

Hyperthyroidism. Gynecomastia has been reported in 10% to 40% of men with hyperthyroidism. SHBG is often increased in hyperthyroidism, resulting in high normal or elevated total serum testosterone and decreased free testosterone levels. Peripheral conversion of androgens to estrogens by aromatase may also be enhanced in hyperthyroidism.[5] Breast enlargement usually resolves after the euthyroid state is restored.

Stressful life events were linked to episodes of transient gynecomastia in a report of five cases.[17] Increased serum cortisol and estradiol levels with decreased serum testosterone were found during the stressful episode (though all measurements were within normal limits). It was proposed that the adrenal glands might increase their secretion of estrogen precursors in response to stress.

Drugs and gynecomastia

Drug-induced gynecomastia is common and may account for 20% to 25% of cases.[15] Mechanisms that have been reported include direct action of estrogens or estrogen-like substances, enhancement of testicular production of estrogens, and inhibition of testosterone synthesis or action (TABLE 1).

Therapeutic doses of testosterone can be peripherally aromatized to estrogen, which may result in gynecomastia, but other mechanisms may be involved, since nonaromatizable androgens such as methyltestosterone or dihy-

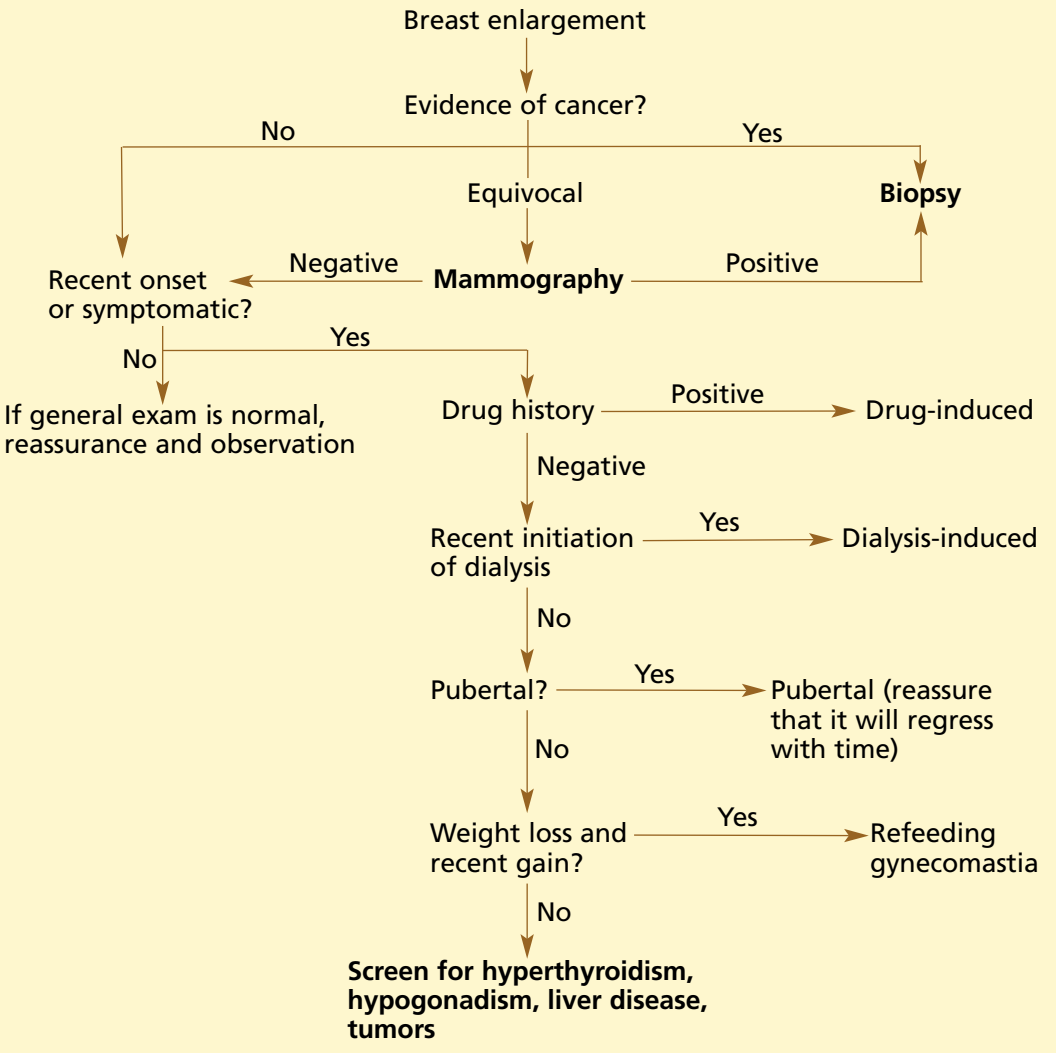

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FIGURE 1 Diagnostic approach to the evaluation of male breast enlargement

drotestosterone may also cause gynecomastia.

Some drugs can cause gynecomastia through multiple mechanisms. For example, spironolactone, in addition to being an androgen receptor antagonist, may also interfere with testosterone biosynthesis.[18] However, the mechanisms by which many drugs cause gynecomastia are still not known.

DIAGNOSTIC EVALUATION

Since palpable breast tissue is so prevalent in the normal male population, an otherwise healthy man with asymptomatic, incidentally discovered gynecomastia should not be subjected to an exhaustive endocrine evaluation.

The breasts should be examined in detail, however, to rule out the likelihood of breast cancer, and if the findings are suspicious, fine needle aspiration or excisional biopsy should be done (FIGURE 1). Ultrasonography or mammography may be helpful in evaluating men at high risk, such as those with Klinefelter syndrome.

Men with recent-onset breast enlarge-

TABLE 2

Diagnostic evaluation of gynecomastia

History
- Duration of breast enlargement
- Presence of breast pain or tenderness
- Drug history (prescription, over-the-counter, occupational, or recreational)
- Sexual functioning
- Changes in virilization
- Changes in weight
- Symptoms of hyperthyroidism

Physical examination
- Thyroid and signs of thyroid hormone excess
- Breast examination, suspicious findings suggestive of malignancy
- Abdominal examination for possible adrenal mass or hepatomegaly
- Examination of genitalia, testicular size, testicular mass
- Degree of virilization: body hair, voice, muscles

Laboratory evaluation
- Serum creatinine
- Liver enzymes
- Thyroid-stimulating hormone, free thyroxine
- Serum total and free or bioavailable testosterone, luteinizing hormone, follicle-stimulating hormone, estradiol, prolactin
- Beta-human chorionic gonadotropin
- Serum dehydroepiandrosterone sulfate or urinary 17-ketosteroids

ment or who present with breast pain and tenderness require a more detailed evaluation to search for a possible underlying cause (TABLE 2).

Laboratory screening should include measurements of:

- Thyroid function
- Liver enzymes
- Serum creatinine
- Serum total and free or bioavailable testosterone, estradiol, LH, follicle-stimulating hormone (FSH), and prolactin
- Serum beta-hCG
- Serum DHEA-sulfate or urinary 17-ketosteroids (may be added if a feminizing adrenal tumor is part of the differential diagnosis).

Imaging studies should not be ordered unless clinical signs or laboratory results dictate them. Imaging studies may include testicular sonography or thermography, computed tomography of the adrenal glands, magnetic resonance imaging of the sella turcica, and mammography.

TREATMENT

Treatment of gynecomastia depends on the underlying cause. If it is drug-induced, it may regress if the offending medication is stopped. Similarly, breast enlargement following cytotoxic chemotherapy may also resolve spontaneously.

Treatment of hyperthyroidism and surgical removal of testicular, adrenal, or other causative tumors may lead to regression. In patients with hypogonadism, treatment with testosterone may produce regression by providing androgen and suppressing LH-stimulated estradiol secretion.

Pubertal gynecomastia usually eventually resolves naturally, as does breast enlargement associated with dialysis or refeeding.

Drug treatment

Even with exhaustive evaluation, no underlying cause is identifiable in about 25% of patients.[15] In these cases, no treatment is necessary, unless the condition causes pain, embarrassment, or psychological discomfort. In these patients, drug therapy may be tried. Options include antiestrogens (clomiphene, tamoxifen), androgens (danazol), and aromatase inhibitors.

Clomiphene has been tried mainly in uncontrolled studies, in which it had variable efficacy.[19]

Tamoxifen, in an uncontrolled study, resulted in complete regression of gynecomastia in 70% of cases.[20]

Danazol is a weak androgen that inhibits pituitary secretion of LH and FSH. In a randomized, double-blind study, danazol significantly reduced breast tenderness and size compared with placebo.[21] In a head-to-head study, 78% of patients receiving tamoxifen 20 mg daily showed complete regression of gynecomastia vs 40% in patients receiving danazol 400 mg daily.[22]

Testolactone, an aromatase inhibitor, was tried in a small uncontrolled study in patients with pubertal gynecomastia, with good results.[19] There have been no studies of the newer aromatase inhibitors letrozole or anastrozole in the treatment of gynecomastia.

Radiation

Several studies have shown that prophylactic breast irradiation is effective in preventing gynecomastia and mastodynia in patients with prostate cancer scheduled to receive estrogen or antiandrogen therapy.[23]

Surgery

Due to limited experience and unknown long-term side effects, trials of medical therapy should be limited to only 6 months. When gynecomastia has been present for more than 2 years, medical therapy may no longer be effective, and surgery may be the only useful treatment. The usual method is to remove the glandular tissue through a periareolar incision with or without suction lipectomy. Results are cosmetically unsatisfactory in up to 50% of patients, however.[24]

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