CLINICAL PRACTICE

Gynecomastia

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

During an evaluation for low back pain, a 67-year-old man is found to have gynecomastia on the right side that is nontender on palpation. Other than a body-mass index (the weight in kilograms divided by the square of the height in meters) of 32, the physical examination is normal. His medical history is notable only for hyperlipidemia; his only medication is a statin. How should his gynecomastia be evaluated and managed?

THE CLINICAL PROBLEM

Asymptomatic gynecomastia, or enlargement of the glandular tissue of the breast, is common in older men; it is found on examination in one third to two thirds of men and at autopsy in 40 to 55% of men.[1-7] The condition has usually been present for months or years when it is first discovered during a physical examination. Histologic examination of the breast tissue in this setting usually shows dilated ducts with periductal fibrosis, stromal hyalinization, and increased subareolar fat.[6-9] In contrast, patients who present with symptoms of pain and tenderness generally have gynecomastia of more recent onset, and pathological findings include hyperplasia of the ductal epithelium, infiltration of the periductal tissue with inflammatory cells, and increased subareolar fat.[6-9]

The pathophysiological process of gynecomastia involves an imbalance between free estrogen and free androgen actions in the breast tissue; this imbalance can occur through multiple mechanisms (Fig. 1).[10] During mid-to-late puberty, relatively more estrogen may be produced by the testes and peripheral tissues before testosterone secretion reaches adult levels, resulting in the gynecomastia that commonly occurs during this period. The testes may directly secrete too much estradiol from a Leydig-cell or Sertoli-cell tumor. They may also secrete estradiol indirectly through the stimulatory effects of a human chorionic gonadotropin (hCG)–secreting tumor of gonadal or extragonadal germ-cell origin (also called eutopic hCG production) or a tumor derived from a nontrophoblastic tissue, such as a large-cell carcinoma of the lung or some gastric or renal-cell carcinomas (also called ectopic hCG production). In addition, the testes may secrete too little testosterone; this occurs in primary or secondary hypogonadism. The prevalence of these conditions increases with advanced age, and one study indicated that 50% of men in their 70s have a low free testosterone concentration.[11]

An adrenal neoplasm may overproduce the weak androgen androstenedione and other androgen precursors such as dehydroepiandrosterone, which are converted into estrogens in peripheral tissues. An increase in aromatase activity has been reported in a number of patients with gynecomastia associated with a variety of disease processes, including thyrotoxicosis, Klinefelter's syndrome, and adrenal and testicular tumors.[12] Aromatase activity increases both with age and with an increase

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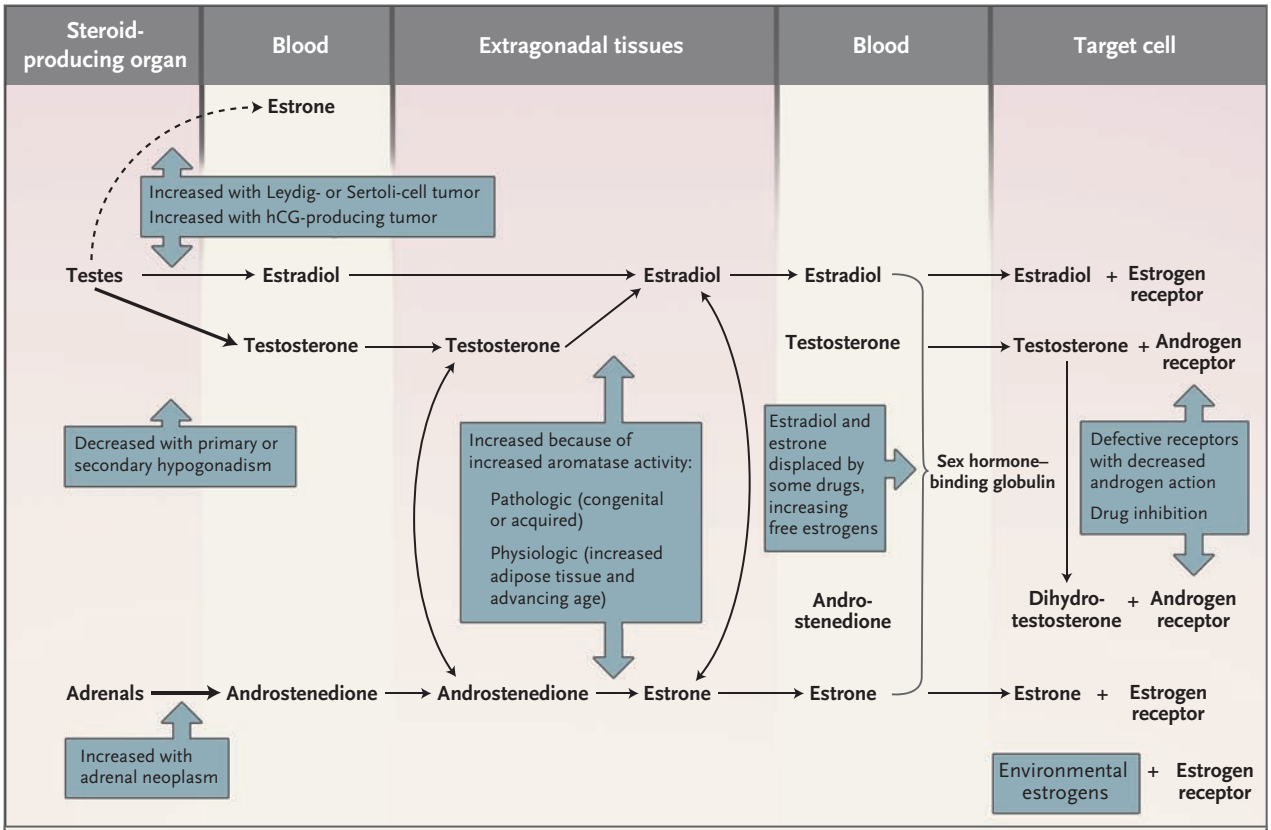

Figure 1. Estradiol and Estrone, Displaced by Some Drugs, Resulting in an Increase in Free Estrogen.

Most testosterone and approximately 15% of estradiol are secreted directly by the testes.[10] Both bind to sex hormone–binding globulin and, to a lesser extent, albumin, and a small amount of each hormone circulates in the free state. The free and albumin-bound steroids (the "bioavailable" fraction) enter extragonadal tissues, many of which contain the aromatase enzyme complex, which converts some of the testosterone to estradiol. This enzyme complex also converts androstenedione of adrenal origin to estrone, which may be further converted to the more potent estrogen estradiol through the action of 17β-hydroxysteroid dehydrogenase. The bioavailable testosterone, estradiol, and estrone, derived from direct glandular secretion and extraglandular production, enter target tissues, where they bind to their respective receptors and initiate gene activation and transcription. In addition, some of the testosterone is converted to the more potent metabolite dihydrotestosterone through the action of 5α-reductase. Dihydrotestosterone binds to the same androgen receptors as testosterone. Multiple processes can alter the pathways of estrogen and androgen production and action, resulting in gynecomastia from an enhanced estrogen effect or a diminished androgen effect at the target-tissue level. Figure was modified from Mathur and Braunstein.[10]

in body fat. Since body fat also increases with age, it is likely that a physiologic increase in the activity of the aromatase enzyme complex with normal aging is responsible for many cases of asymptomatic gynecomastia in older men. Indeed, there is a progressive increase in the prevalence of gynecomastia with an increase of the body-mass index, probably reflecting the local paracrine effects of estradiol production in the subareolar fat on the breast glandular tissue.[4,5]

Since estradiol and estrone bind less avidly to sex hormone–binding globulin than does testosterone, drugs such as spironolactone may displace relatively more estrogen than testosterone from this protein, increasing the bioavailable fraction of estrogen to a greater extent than bioavailable androgen. Similarly, an increase in the sex hormone–binding globulin concentration, which occurs with hyperthyroidism and some forms of liver disease, may be associated with greater binding of testosterone relative to estrogen, leading to a decrease in free testosterone relative to free estrogen. Androgen-receptor abnormalities, either due to a genetic defect or blockade by an antagonist such as bicalutamide or due to stimulation of the estrogen receptor by medications or environmental estrogens, may also result in gynecomastia.

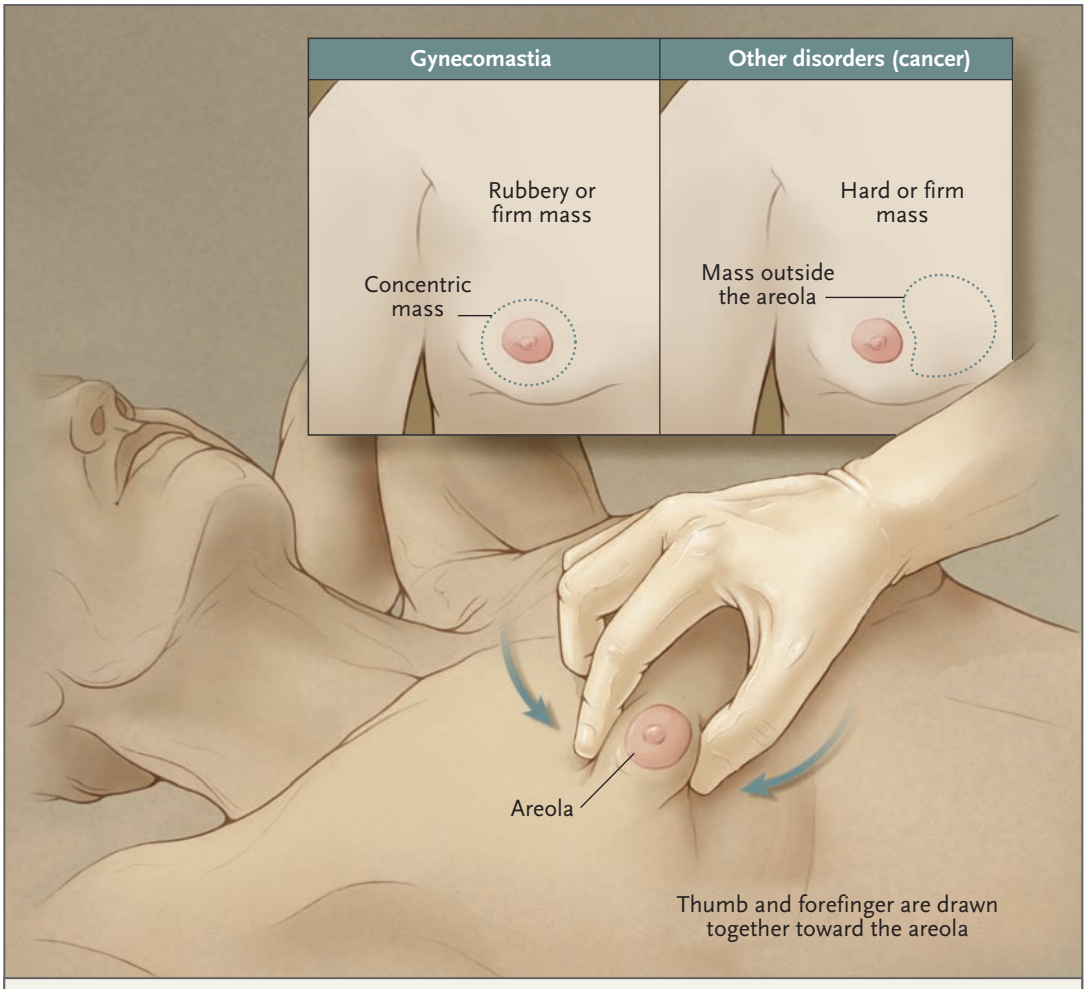

Figure 2. Differentiation of Gynecomastia from Pseudogynecomastia and Other Disorders by Physical Examination.
The patient lies flat on his back with his hands clasped beneath his head. Using the separated thumb and forefinger, the examiner slowly brings the fingers together from either side of the breast. In patients with true gynecomastia, a rubbery or firm mound of tissue that is concentric with the nipple–areolar complex is felt, whereas in patients with pseudogynecomastia, no such disk of tissue is found.

STRATEGIES AND EVIDENCE

DIAGNOSIS

The first step in the clinical evaluation of patients is to determine whether the enlarged breast tissue or mass is gynecomastia. Pseudogynecomastia is characterized by increased subareolar fat without enlargement of the breast glandular component. The differentiation between gynecomastia and pseudogynecomastia is made on physical examination, as shown in Figure 2. The other important differentiation is between gynecomastia and breast carcinoma. The tissue in gynecomastia is soft, elastic, or firm but generally not hard, the affected area is concentric to the nipple–areolar complex, and it is clinically bilateral in approximately half of patients. Breast carcinoma is usually hard or firm, is located outside the nipple–areolar complex, and is most often unilateral. In addition, skin dimpling and nipple retraction are not present with gynecomastia, but they may be seen in patients with breast carcinoma. Tenderness may be present in gynecomastia of less than 6 months' duration, but it is unusual with breast carcinoma. Nipple bleeding or discharge is present in approximately 10% of men with breast cancer, but it is not expected with gynecomastia.[13] If the differentiation between gynecomastia and breast carcinoma cannot be made on the basis of clinical findings alone, the

patient should undergo diagnostic mammography, which has 90% sensitivity and specificity for distinguishing malignant from benign breast diseases.[14]

EVALUATION

Once the diagnosis of gynecomastia is established, it is important to review all medications, including over-the-counter drugs such as herbal products, that may be associated with gynecomastia. Ingestion of sex steroid hormones or their precursors may cause gynecomastia through bioconversion to estrogens. Antiandrogens used for the treatment of prostate cancer, spironolactone, cimetidine, environmental estrogens or antiandrogens, and one or more components of highly active antiviral therapy used for human immunodeficiency virus infection (especially protease inhibitors) have been clearly shown to be associated with gynecomastia.[15-25] Several cancer chemotherapeutic drugs, particularly alkylating agents, can damage the testes and result in primary hypogonadism. Other drugs, including phenytoin and metoclopramide, have also been associated with gynecomastia, but a cause-and-effect relationship has not been proved.[15]

An adolescent presenting with gynecomastia usually has physiologic pubertal gynecomastia, which generally appears at 13 or 14 years of age, lasts for 6 months or less, and then regresses. Less than 5% of affected boys have persistent gynecomastia, but this is the apparent cause in a large proportion of young men in their late teens or 20s presenting for evaluation. Other conditions to consider in adolescents and young adults with gynecomastia are Klinefelter's syndrome, familial or sporadic excessive aromatase activity, incomplete androgen insensitivity, feminizing testicular or adrenal tumors, and hyperthyroidism.[26-28] Drug abuse, especially with anabolic steroids, but also with alcohol, marijuana, or opioids, also should be considered.[29]

If an adolescent or adult presents with unilateral or bilateral gynecomastia that is painful or tender, and if the patient's history and physical examination do not reveal the cause (Table 1), hCG, luteinizing hormone, testosterone, and estradiol should be measured (Fig. 3).[30] Many of the available measurements of testosterone have poor accuracy and precision, especially in men with testosterone levels at the low end of the normal range.[31] Measurement of these levels in the morning is recommended, since testosterone and luteinizing hormone secretion have a circadian rhythm (with the highest levels in the morning) as well as secretory bursts throughout the day. If the total testosterone level is borderline or low, free or bioavailable testosterone should be measured or calculated to confirm hypogonadism. Although such laboratory evaluation is prudent, no abnormalities are detected in the majority of patients.

Laboratory tests to determine the cause of asymptomatic gynecomastia in an adult without a history suggestive of an underlying pathologic cause, with an otherwise normal physical examination, are unlikely to be revealing, and the extent of hormonal evaluation that should be performed in such patients remains controversial. The likelihood of discovering a pathologic abnormality is low in patients with long-standing asymptomatic gynecomastia in the fibrotic stage, and the long duration of the condition without other evidence of disease is reassuring; thus, many clinicians take a minimalist approach to evaluation. Nevertheless, measurement of the morning testosterone level and free or bioavailable testosterone and luteinizing hormone levels, if the morning testosterone level is low, is reasonable to detect hypogonadism, which is increasingly common with advanced age.[11] A finding of a low free or bioavailable testosterone level and an elevated luteinizing hormone level indicates primary testicular failure, whereas a low free or bioavailable testosterone level and a normal or low luteinizing hormone level may indicate secondary hypogonadism.

TREATMENT

If a specific cause of gynecomastia can be identified and treated during the painful proliferative phase, there may be regression of the breast enlargement. This regression most often occurs with discontinuation of an offending drug or after initiation of testosterone treatment for primary hypogonadism. If the gynecomastia is drug-induced, decreased tenderness and softening of the glandular tissue will usually be apparent within 1 month after discontinuation of the drug. However, if the gynecomastia has been present for more than 1 year, it is unlikely to regress substantially, either spontaneously or with medical therapy, because of the presence of fibrosis. In such circumstances, surgical subcutaneous mastectomy, ultrasound-

Table 1. Signs and Symptoms of Pathologic Processes That Cause Gynecomastia.

Condition	Symptoms	Signs
Tumor		
Testicular		
Leydig-cell or Sertoli-cell	Testicular pain, enlargement, or both; decreased libido	Testicular mass or enlargement, contralateral testis with some atrophy, signs of feminization
Germ-cell	Testicular pain, enlargement, or both; symptoms of metastases (e.g., back pain, hemoptysis)	Testicular mass
Adrenocortical	Weight loss, decreased libido, possible symptoms of coexisting Cushing's syndrome or mineralocorticoid excess	Abdominal mass, signs of Cushing's syndrome or mineralocorticoid excess (hypertension)
Ectopic hCG-secreting	Weight loss; respiratory symptoms with lung carcinoma; abdominal symptoms with hepatocellular, gastric, or renal-cell carcinoma	Dependent on location of primary tumor and presence or absence of metastases
Hypogonadism		
Primary	Decreased libido, erectile dysfunction, vasomotor symptoms	Decreased testicular size, hard texture with Klinefelter's syndrome, soft texture if acquired; incomplete development of secondary sexual characteristics with prepubertal onset; possible findings of a systemic disorder (e.g., hemochromatosis)
Secondary	Decreased libido, erectile dysfunction, symptoms of other pituitary hormone deficiency, headache, visual symptoms	Decreased testicular size; possible visual-field cuts from a pituitary or parasellar tumor; signs of hypothyroidism, excess or deficiency of growth hormone; galactorrhea (rare)
Hyperthyroidism	Weight loss, palpitations, increased sweating, increased frequency of defecation, nervousness, insomnia, heat intolerance	Goiter, tremor, tachycardia, upper-eyelid retraction
Liver disease	Anorexia, nausea, vomiting, weight loss (or weight gain with ascites), edema, jaundice, pruritus	Jaundice, enlarged or shrunken liver, ascites, edema
Renal disease	Anorexia, fatigue, nausea, vomiting, oliguria or polyuria, pruritus, yellowish skin	Lethargy, asterixis, uremic hue, hypertension
Androgen insensitivity	Decreased libido, infertility	Possible hypospadias or ambiguity of genitalia, possible neurologic findings (e.g., proximal muscle weakness with fasciculations and tremor in X-linked spinal and bulbar muscular atrophy)
Familial or sporadic aromatase excess syndrome	None	Prepubertal onset of gynecomastia; accelerated increase in height in childhood, reduced final height; incomplete virilization

assisted liposuction, and suction-assisted lipectomy are the best options for cosmetic improvement, as described in several case series.[32,33]

During the rapid, proliferative phase, manifested clinically as breast pain and tenderness, medical therapy may be attempted. Most studies of drugs — including testosterone (in patients without hypogonadism), dihydrotestosterone, danazol, clomiphene citrate, tamoxifen, and testolactone — have been uncontrolled and thus difficult to interpret because gynecomastia may resolve spontaneously.[34,35] The few randomized, double-blind, placebo-controlled trials generally have been limited by small samples.

Although not approved for the treatment of gynecomastia, the selective estrogen-receptor modulator tamoxifen, administered orally at a dose of 20 mg daily for up to 3 months, has been shown to be effective in randomized and nonrandomized trials, resulting in partial regression of gynecomastia in approximately 80% of patients and complete regression in about 60%.[36-45] Patients in whom tamoxifen is effective usually experience a decrease in pain and tenderness within 1 month. In a retrospective analysis of a series of patients with idiopathic gynecomastia, 78% of patients treated with tamoxifen had complete resolution of gynecomastia, as compared with only 40% of patients receiving danazol.[42] In case series describing the use of tamoxifen for this condition in more than 225 patients, adverse events were uncommon; they included epigastric distress in 2 pa-

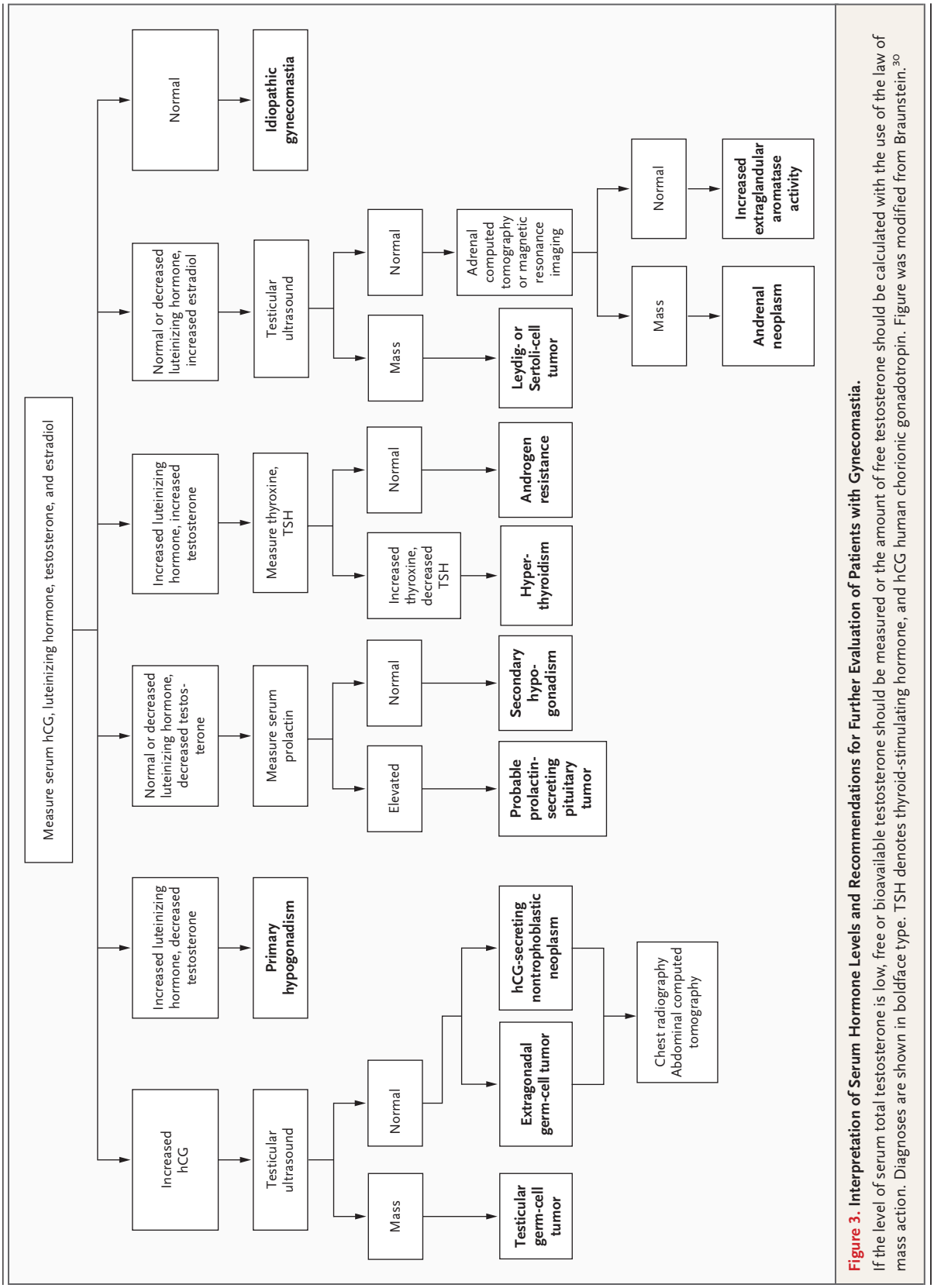

Figure 3. Interpretation of Serum Hormone Levels and Recommendations for Further Evaluation of Patients with Gynecomastia.
If the level of serum total testosterone is low, free or bioavailable testosterone should be measured or the amount of free testosterone should be calculated with the use of the law of mass action. Diagnoses are shown in boldface type. TSH denotes thyroid-stimulating hormone, and hCG human chorionic gonadotropin. Figure was modified from Braunstein.[30]

tients[38] and a post-traumatic deep-vein thrombosis in 1 patient.[43]

The aromatase inhibitor anastrozole was not shown to be more effective than placebo in a randomized, double-blind, placebo-controlled trial in boys with pubertal gynecomastia.[46] Although in an uncontrolled study of 10 patients with pubertal gynecomastia, the selective estrogen-receptor modulator raloxifene was shown to result in more than a 50% decrease in the size of the gynecomastia in the majority of the boys, there are insufficient data to recommend its use at this time.[44]

It has also been suggested that therapy with tamoxifen may prevent the development of gynecomastia in men receiving monotherapy with high doses of bicalutamide (Casodex) for prostate cancer. In a randomized, double-blind, controlled trial involving men receiving high-dose bicalutamide (150 mg per day),[47] gynecomastia occurred in 10% of patients who received tamoxifen at a dose of 20 mg daily, but it occurred in 51% of those who received anastrozole at a dose of 1 mg daily and in 73% of those who received placebo, over a period of 48 weeks; mastalgia occurred in 6%, 27%, and 39% of these patients, respectively. In another trial[48] involving 3 months of therapy, gynecomastia, mastalgia, or both occurred in 69.4% of patients receiving placebo, 11.8% receiving tamoxifen ($P<0.001$ for the comparison with placebo), and 63.9% receiving anastrozole (not significantly different from the rate in the placebo group). Another randomized trial showed efficacy of a 10-mg dose of tamoxifen as prophylaxis against gynecomastia. Among patients treated with bicalutamide alone, gynecomastia occurred in 68.6% and mastalgia occurred in 56.8%. These rates were significantly lower among patients receiving one 12-Gy fraction of radiation therapy to the breast on the first day of treatment with bicalutamide (34% and 30%, respectively), and they were further reduced among patients receiving bicalutamide and tamoxifen (8% and 6%, respectively).[49] Although it has been used in men treated for prostate cancer, tamoxifen is not approved by the Food and Drug Administration for this indication.

AREAS OF UNCERTAINTY

The high prevalence of asymptomatic gynecomastia among older men raises the question of whether it should be considered to be pathologic or a part of the normal process of aging. It is likely, but unproved, that many cases of asymptomatic gynecomastia are due to the enhanced aromatization of androgens in subareolar fat tissue, resulting in high local concentrations of estrogens, as well as to the age-related decline in testosterone production.[11,12,50] Another possible cause is unrecognized exposure over time to unidentified environmental estrogens or antiandrogens.[18,19,21]

There is no uniformity of opinion regarding what biochemical evaluation, if any, should be performed in a patient with asymptomatic gynecomastia. The diagnostic tests for patients with symptomatic gynecomastia of recent onset for which no cause is discerned on the basis of the history or physical examination (Fig. 3) have a low yield; however, a prospective cost–benefit analysis in this population has not been performed. In a retrospective study of 87 men with symptomatic gynecomastia, 16% had apparent liver or renal disease, 21% had drug-induced gynecomastia, and 2% had hyperthyroidism, whereas 61% were considered to have idiopathic gynecomastia. Forty-five of the 53 patients in the group with idiopathic gynecomastia underwent endocrine testing, of whom only 1 patient (2%) was found to have an endocrine abnormality — an occult Leydig-cell testicular tumor.[51]

Finally, since the excessive aromatization of androgens to estrogens has been shown to be present in many patients with gynecomastia, it is unclear why aromatase inhibitors have not been more successful in the treatment of these patients or in the prevention of the development of gynecomastia in patients with prostate cancer treated with antiandrogens.

GUIDELINES

No professional guidelines are available for the management of gynecomastia.

CONCLUSIONS AND RECOMMENDATIONS

Asymptomatic gynecomastia is a relatively common finding on physical examination, and a careful history taking and physical examination are usually sufficient to identify pubertal gynecomastia, drug-induced causes, or an underlying pathologic process, with the possible exception of mild

hypogonadism. Pubertal gynecomastia resolves with time in the majority of adolescent boys, and reassurance and follow-up physical examination usually suffice. In adults who present with the acute onset of painful gynecomastia without an obvious cause, hormonal evaluation, including measurements of serum hCG, testosterone, luteinizing hormone, and estradiol levels, should be performed in order to rule out serious and treatable causes, although serious disease is unlikely in this setting. During the acute florid stage of gynecomastia, a trial of tamoxifen, at a dose of 20 mg per day for up to 3 months, may be attempted. If the gynecomastia has not regressed by 1 year, or in patients who present with long-standing gynecomastia who are troubled by their appearance, surgical removal of the breast glandular tissue and subareolar fat is an option that has a good cosmetic result in the majority of patients. For a patient such as the man in the vignette, who is asymptomatic, is not bothered by his gynecomastia, and does not have a suggestive history or physical examination, a more minimalist evaluation (i.e., measurements of testosterone and luteinizing hormone levels, although even the use of these tests might be debated[52]) is recommended, and treatment other than weight reduction is not warranted for the gynecomastia.

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