

CLINICAL VIGNETTE

Gynecomastia

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Case Report

A 27-year-old previously healthy male presented with a painful left breast mass which he had noticed for the past month. He denied the presence of either abnormal breast discharge or change in the breast mass since discovery. He did not recall any similar episode in the past. He did not take any over-the-counter or prescription medications. Upon further questioning, the patient admitted to smoking marijuana on a regular basis. He did not have any constitutional symptoms of fatigue, weight loss, fever or night sweats. Review of his family history did not reveal any history of breast cancer.

On examination, the patient had a distinct left subareolar mass, which was mildly tender to palpation. Approximately 3 cm in diameter, the mass felt rubbery and slightly mobile. His right breast was normal. Discharge was not expressed from the nipple. There was no cervical or axillary lymphadenopathy.

Fine needle aspiration biopsy of the mass showed gynecomastia. The patient also underwent a mammogram, which confirmed the diagnosis.

Discussion

Gynecomastia is defined as the enlargement of the male breast due to the benign proliferation of the glandular component of the male breast tissue. The condition frequently presents either as painful breast masses or an incidental finding on physical examination. In addition to causing physical discomfort, gynecomastia may raise cosmetic concerns and provoke anxiety. Primary care physicians often encounter patients with gynecomastia. Although gynecomastia is usually related to puberty or idiopathic, it is important to distinguish benign cases of gynecomastia from more serious illnesses. Because asymmetric gynecomastia is a common clinical finding, another challenge for the physician is differentiating it from pathological causes such as breast carcinoma.

The mammary gland is composed of glandular ductal epithelium and the periductal connective tissue. More recent onset gynecomastia is associated with the proliferation of the ductal epithelium as well as hyperplasia and edema of the surrounding stromal and connective tissue. Gynecomastia of longer duration,

on the other hand, results in the replacement of epithelial growth by periductal fibrosis and hyalinization.

Gynecomastia arises primarily from an imbalance between estrogen-androgen levels (e.g., an elevated estrogen-to-androgen ratio). Decreases in free serum androgen concentrations are found in older men as part of aging, primary or secondary hypogonadism, testicular enzymatic defects or drugs such as spironolactone or ketoconazole which inhibit the biosynthesis of testosterone. On the other hand, increases in serum estrogen concentrations result from testicular tumors and feminizing adrenocortical neoplasms as well as nonmalignant conditions such as obesity, liver disease, and hyperthyroidism. An increased level of estrogen also leads to negative feedback inhibition of the production of gonadotropins, which in turn further lower the levels of circulating androgens and increase sensitivity of the breast tissue to estrogen. Other less common mechanisms for gynecomastia include a relative insensitivity to androgen due to defective androgen receptors and an increased sensitivity of the breast tissue to a normal estrogen level.¹

Physiologic gynecomastia has three peaks in the age distribution. Outside the neonatal period in which the condition is transient due to the presence of transplacental estrogen, the incidence of the condition peaks in adolescent males and in older adult males age 50-80. The condition is most common in adolescent males. Studies have shown that the incidences range from as low as 10% to high of 65% in 14-year-old boys. The number of cases appears to decrease sharply after age 17. In normal adult males, the incidence ranges from 4% to 56%.¹

Given the high prevalence of gynecomastia, various medications and conditions are associated with clinically important gynecomastia. Exogenous androgen, anabolic steroids, chorionic gonadotropin, estrogen and antiandrogens all can lead to gynecomastia. In addition to these hormone-related agents, commonly prescribed drugs such as digoxin, ketoconazole, and cimetidine have been strongly related to gynecomastia. Medications, including isoniazid, metronidazole, omeprazole, ACE inhibitors, amiodarone, verapamil, phenytoin, diazepam, haloperidol, phenothiazines, and tricyclic antidepressants, have all been identified as possible causative agents. Cancer chemotherapeutic agents, especially alkylating agents, are also known to be related to gynecomastia. Lastly, alcohol, amphetamines, heroin, and marijuana contaminated with plant estrogens have also been associated with the condition.

A small percentage of gynecomastia is associated with tumors such as testicular carcinomas (germ-cell, Leydig-cell, or Sertoli-cell), adrenal adenoma or carcinoma. These cancers involve production of estrogen or estrogen precursors. Other cancers such as choriocarcinomas, lung, liver, and kidney cancers lead to the ectopic production of human chorionic gonadotropin. Gynecomastia may be also seen in systemic conditions such as cirrhosis, renal disease and dialysis, hyperthyroidism, and starvation, especially during the recovery phase. Familial causes have been shown to have either an autosomal dominant or X-linked recessive mode of transmission.² A mechanism of familial cases appears to be due to increased extraglandular aromatization of androgens to estrogens.³ Lastly, differential diagnoses of non-glandular breast masses such as breast carcinoma, mastitis, abscess, fibroma or papilloma should be considered.

The physician must determine whether the cause of the gynecomastia is physiologic or pathologic. The clinical evaluation begins with a thorough history including age of onset, associated pain, history of infertility or other chronic illnesses, family history of gynecomastia, and a comprehensive drug history including over-the-counter medications as well as illicit drug use. Painful, rapidly enlarging gynecomastia is more worrisome than long-term asymptomatic enlargement. Symptoms of decreased libido, erectile dysfunction should also be pursued. The physician should complete the assessment by reviewing the patient's general health, paying special attention to hepatic, pulmonary, and thyroidal symptoms.

In determining whether breast enlargement reflects true gynecomastia, the physician should squeeze the breast tissue between the index finger and the thumb with the patient in a supine position. While glandular tissue feels ropy, coiled, and rubbery, such texture is absent in adipose tissue.² In addition, gynecomastia often feels like a mobile disc rather than a hard, fixed, irregularly shaped, and eccentrically located mass of breast carcinoma. Additional signs of ulcerations, nipple retraction, skin dimpling or axillary lymphadenopathy should raise suspicion for malignancy. It is important to note that while breast cancer is mostly unilateral, asymmetric gynecomastia is fairly common. In addition to the breast examination, the patient's testicular size, secondary sexual characteristics, and any signs of feminization should be assessed.

If physical exam and history are unremarkable, reassurance and periodic follow-up are recom-

mended. Progressive gynecomastia, occurrence prior to puberty or new onset after age 26 should be followed by further evaluation. Moreover physical examination evidence of feminization, hypogonadism, and macrogynecomastia should similarly prompt further work-up. Laboratory levels of LH, FSH, testosterone, estradiol, beta HCG, 11-deoxycortisol, and DHEA-S may be helpful.

Mammograms can be used to distinguish adipose from glandular breast tissue. Fine needle aspirations are useful to confirm the diagnosis of a suspicious malignant mass. Other radiographic studies such as testicular ultrasonography, CT or MRI of the abdomen looking for adrenal mass, and chest radiographs should be performed as indicated.

Since the rate of spontaneous regression, especially during puberty, is high for gynecomastia, the patient often does not require any treatment. Whenever possible, treatment should be targeted towards the underlying cause of the particular condition (e.g. neoplasm, hypogonadism, and thyrotoxicosis). If gynecomastia is related to a particular drug exposure, the medication should be discontinued.

Therapy should be sought if pain is considerable or psychological stress is severe. Both medical and surgical options are available. In deciding between medical versus surgical therapies, the physician needs to take into account the duration of tissue proliferation. While early stages may respond to pharmacologic agents, gynecomastia present for greater than 1 year often results in fibrotic tissue which is less amenable to medical therapy.²

Medications aim at altering the balance between the estrogen and the androgen in a patient with gynecomastia. The number of studies on medical therapy has been limited. Furthermore, the outcome of these studies may be confounded by the lack of controlled subjects and the high rate of spontaneous resolution of breast tissue growth.⁴ Testosterone should be given in documented hypogonadal disorders. The weak androgen Danazol and topical dihydrotestosterone have shown some success in treating the condition. More commonly, anti-estrogens such as clomiphene and tamoxifen are used. Tamoxifen has been fairly effective for improving the pain associated with the breast tissue growth.

When reassurance or medical therapies are ineffective, surgical reduction mammoplasty with glandular breast tissue removal is effective. Liposuction is effective in removing the fatty but not necessarily the glandular component. In cases of macrogyneco-

mastia, surgery is often needed for cases in which the breast tissue is greater than 6 cm in diameter for more than 4 years.²

REFERENCES

1. **Braunstein GD.** Gynecomastia. *N Engl J Med.* 1993 Feb;328(7):490-495.
2. **Glass AR.** Gynecomastia. *Clin Andrology.* 1994 Dec;23(4):825-837.
3. **Leung AKC.** Gynecomastia. *Amer Fam Phys.* 1989 Apr;39(4):215-222.
4. **Neuman, JF.** Evaluation and treatment of gynecomastia. *Amer Fam Phys.* 1997 Apr;55(5):1835-1844, 1849-1850.