Gynaecomastia
Sorting the wolves from the sheep

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In boys and men with breast enlargement, it is important to differentiate gynaecomastia from pseudogynaecomastia and male breast cancer and to identify any treatable or serious underlying conditions.

MedicineToday 2014; 15(11): 53-57

The challenge in patients with suspected gynaecomastia is to sort the wolves from the sheep – that is, to differentiate patients with male breast cancer or gynaecomastia caused by serious underlying pathology from patients with physiological gynaecomastia or reversible aetiologies. Physiological gynaecomastia occurs in neonates, boys during puberty and older men. However, pathological gynaecomastia can present at any age and needs careful exclusion. If gynaecomastia is both longstanding and asymptomatic, and careful evaluation does not reveal abnormalities then reassurance may be the only management required.

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PATHOPHYSIOLOGY

Gynaecomastia is a benign proliferation of glandular tissue of the male breast.[1] It is caused by an imbalance in the ratio of free oestrogen to free androgen activity in breast tissue.[2] This may result from:

- increased oestrogen production
- increased conversion of androgens to oestrogens by raised aromatase activity
- reduced production of testosterone, or
- altered receptor responsiveness to these hormones.

Many conditions and drugs that cause gynaecomastia act through multiple mechanisms.[3] For example, spironolactone causes gynaecomastia by inhibition of androgen receptors, increased testosterone clearance, inhibition of testicular testosterone synthesis, displacement of oestrogen from sex hormone binding globulin (SHBG), and increased aromatase activity.[4] Box 1 lists the various factors that can increase the oestrogen to androgen ratio, causing gynaecomastia.

CAUSES

Physiological gynaecomastia

Physiological gynaecomastia occurs with a trimodal distribution: in neonates, in boys at puberty and in older men.[5] Up to 90% of neonates have gynaecomastia caused by exposure to maternal and placental oestrogens; this resolves spontaneously within a month.

About 40 to 50% of adolescent boys develop gynaecomastia during puberty, but only 4% have gynaecomastia with a diameter of 1 cm or more.[6] Typically, the onset of gynaecomastia is at least six months after the onset of male secondary sexual characteristics.[7] Pubertal gynaecomastia is most prevalent at age 13 to 14 years and usually regresses within 18 months; it is uncommon after the age of 17 years.[5,8] Pubertal gynaecomastia persisting into adulthood is termed 'persistent pubertal gynaecomastia'.

The mechanism of pubertal gynaecomastia is uncertain. It may be caused by a transient imbalance in the oestrogen to androgen ratio, increased breast tissue sensitivity to oestrogen,

1. FACTORS THAT INCREASE THE OESTROGEN TO ANDROGEN RATIO

Raised oestrogen activity

Exogenous oestrogen
- Prescription oestrogens
- Inadvertent oestrogen administration (e.g. aromatisable androgens in anabolic steroids)

Increased production of oestrogen
- Testicular source
  - Testicular tumour (Leydig or Sertoli cell)
  - LH-mediated stimulation of Leydig cells (e.g. primary hypogonadism, drugs such as gonadotrophins)
  - hCG-mediated stimulation of Leydig cells (hCG-producing tumour)
- Adrenal source: feminising adrenocortical tumour

Increased aromatase activity
- Ageing
- Obesity
- Pubertal gynaecomastia
- Drugs such as spironolactone
- Hepatic cirrhosis
- hCG-producing tumours
- Hyperthyroidism
- Familial or sporadic aromatase excess (rare)

Raised sex hormone binding globulin level*
- Hyperthyroidism
- Drugs such as spironolactone
- Alcohol

Reduced androgen activity

Reduced production of testosterone
- Primary hypogonadism
- Secondary hypogonadism
- Drugs
  - Spironolactone
  - Ketoconazole
  - GnRH analogues
  - Opioids
- Alcohol

Increased aromatase activity
- See left (raised oestrogen activity)

Raised sex hormone binding globulin level*
- See left (raised oestrogen activity)

Reduced androgen action at receptor
- Androgen receptor antagonists:
  - Spironolactone
  - Cimetidine
  - Flutamide
  - Bicalutamide
- Defective androgen receptor
  - Androgen insensitivity syndrome†
  - Kennedy disease (excess glutamine repeats in androgen receptor gene)
- 5-alpha-reductase inhibitors (finasteride, dutasteride)‡

ABBREVIATIONS:
LH = luteinising hormone
hCG = human chorionic gonadotrophin
GnRH = gonadotrophin-releasing hormone

* Oestradiol binds less avidly than testosterone to sex hormone binding globulin. Thus, an increased level of sex hormone binding globulin tends to bind relatively more testosterone than oestrogen. This reduces free testosterone levels and displaces relatively more oestrogen than testosterone, increasing free oestrogen levels.

† Undervirilised males with gynaecomastia may have partial androgen insensitivity syndrome. Note that patients with complete androgen insensitivity syndrome are usually phenotypically female.

‡ 5-alpha-reductase inhibitors reduce conversion of testosterone to the more potent androgen dihydrotestosterone.

2. CAUSES OF GYNAECOMASTIA IN ADULT MEN[2]

- Persistent pubertal gynaecomastia
- Drugs (see Box 3)
- Idiopathic (no detectable abnormality)
- Hepatic cirrhosis or malnutrition
- Male hypogonadism
  - Primary hypogonadism (e.g. Klinefelter syndrome, testicular enzyme defects)
  - Secondary hypogonadism (e.g. pituitary lesion, hyperprolactinaemia)
- Testicular tumours (germ cell, Leydig cell, Sertoli cell)
- Hyperthyroidism
- Renal disease and dialysis
- Rare causes
  - Partial androgen insensitivity syndrome
  - Enzymatic defects in testosterone production
  - Excessive extraglandular aromatase activity
  - True hermaphroditism
  - Feminising adrenal tumours
  - Ectopic hCG secreted by nontrophoblastic tumours (e.g. gastric cancer, renal cell carcinoma, large cell carcinoma of lung)

ABBREVIATION:
hCG = human chorionic gonadotrophin

enhanced aromatase activity or the action of leptin. Leptin directly stimulates the breast via receptors in intramammary tissue, activates breast oestrogen receptors and stimulates aromatase activity.[5] Leptin levels in non-obese boys with pubertal gynaecomastia are higher than in those without gynaecomastia.

In contrast to pubertal gynaecomastia, gynaecomastia appearing in childhood (before pubertal onset) is abnormal and warrants specialist evaluation for an underlying endocrine or neoplastic disorder.[9]

Physiological gynaecomastia also occurs commonly in older men and is found in about two-thirds of men aged between 50 and 70 years. It is caused by an increase in aromatase activity, resulting partly from an increase in adipose tissue. It is more common in obese men.[1,10,11]

Although physiological gynaecomastia is common in adolescent and older men, careful evaluation is still needed for an underlying pathological cause.

Pathological gynaecomastia

Persistent pubertal, drug-induced and idiopathic gynaecomastia account for

3. DRUG CAUSES OF GYNAECOMASTIA[12]*

Definite association

- Spironolactone
- Cimetidine
- Ketoconazole
- Human growth hormone
- Exogenous oestrogenic substances
- Human chorionic gonadotrophin
- Antiandrogens (e.g. flutamide, bicalutamide)
- Gonadotrophin-releasing hormone analogues
- 5-alpha-reductase inhibitors

Probable association

- Anabolic steroids
- Risperidone
- Verapamil
- Nifedipine
- Omeprazole
- Alkylating agents
- HIV medication (e.g. efavirenz)
- Alcohol
- Opioids

* Many other medications, illicit substances and herbal preparations have been associated with gynaecomastia, but because of either a low number of reported cases or poor quality published evidence, causality is not certain

4. KEY ASPECTS IN EVALUATION OF PATIENTS WITH GYNAECOMASTIA

History

- Is the breast enlargement of recent onset, or painful or tender?
- Is the patient taking medications that can cause gynaecomastia (see Box 3)?
- In adolescents, was the onset of gynaecomastia within months of the onset of puberty? (Note: prepubertal gynaecomastia is always abnormal)
- Are there symptoms or a history of renal failure, cirrhosis, malnutrition, hyperthyroidism or hypogonadism?
- Are there risk factors for male breast cancer (e.g. age over 65 years, family history of breast cancer, personal carrier of the *BRCA2* gene mutation, previous chest irradiation, Klinefelter syndrome, obesity, exogenous oestrogen, testicular disorder or injury, such as cryptorchidism)?

Examination

- Does the patient have gynaecomastia or pseudogynaecomastia (see the Figure)?
- Are there any features of breast cancer (e.g. unilateral, painless, firm or hard, fixed eccentric mass, ± nipple discharge, nipple retraction, nipple ulceration, inflammatory skin change)?
- Is virilisation (body hair, muscle bulk, testicular size) appropriate for age?
- Are there any testicular masses?

Investigations

- Initial laboratory tests include measurement of oestradiol, morning testosterone, SHBG, LH, FSH, hCG and prolactin levels, and renal, liver and thyroid function (TSH and fT4 levels). These tests may not be necessary if pubertal onset is clearly apparent and examination results are normal
- Imaging may be required if clinical examination cannot distinguish gynaecomastia from breast cancer; mammography is more sensitive and ultrasonography more specific
- Testicular ultrasound examination is indicated if a testicular mass is found on examination, or oestradiol, testosterone or hCG levels are elevated and LH level is suppressed

Referral

- If abnormalities are found on examination and/or laboratory testing then specialist referral is suggested.

ABBREVIATIONS:
FSH = follicle stimulating hormone
fT4 = free thyroxine
GnRH = gonadotrophin-releasing hormone
hCG = human chorionic gonadotrophin
LH = luteinising hormone
SHBG = sex hormone binding globulin
TSH = thyroid stimulating hormone

more than three-quarters of cases of all gynaecomastia in adult men (Box 2).[2] As many as 25% of cases are said to be idiopathic.

Drug causes of gynaecomastia are summarised in Box 3.[12] Gynaecomastia is common in patients undergoing androgen deprivation therapy for prostate cancer.

Klinefelter syndrome (47XXY karyotype) is an important cause of primary gonadal failure in males, and more than 50% with this condition have gynaecomastia. Klinefelter syndrome also confers a significantly increased risk of breast cancer.[13]

Testicular tumours are an uncommon but serious cause of gynaecomastia.[2] Most of these are germ cell tumours that produce human chorionic gonadotrophin (hCG), leading to Leydig cell dysfunction and increased aromatase activity, thus increasing the oestrogen to androgen ratio.

EVALUATION

Important aspects of the evaluation of the patient with gynaecomastia are summarised in Box 4.

History

A full drug history should be taken, including herbal medications, over-the-counter preparations and illicit substances. Boys are more susceptible than men to the effects of exogenous oestrogens.[14] Gynaecomastia can occur with both pharmacological preparations and herbal preparations, as illustrated by reports of cases in prepubertal boys exposed to lavender and tea tree oil.[15]

Examination

The first step in examination is to distinguish gynaecomastia from pseudogynaecomastia, which is a benign increase in subareolar fat without increased glandular tissue, often associated with obesity.[16] A suggested examination technique for the breast is shown in the Figure. Clinically, gynaecomastia is the presence of firm rubbery tissue that extends concentrically from the nipple. It may have a fine granular-like

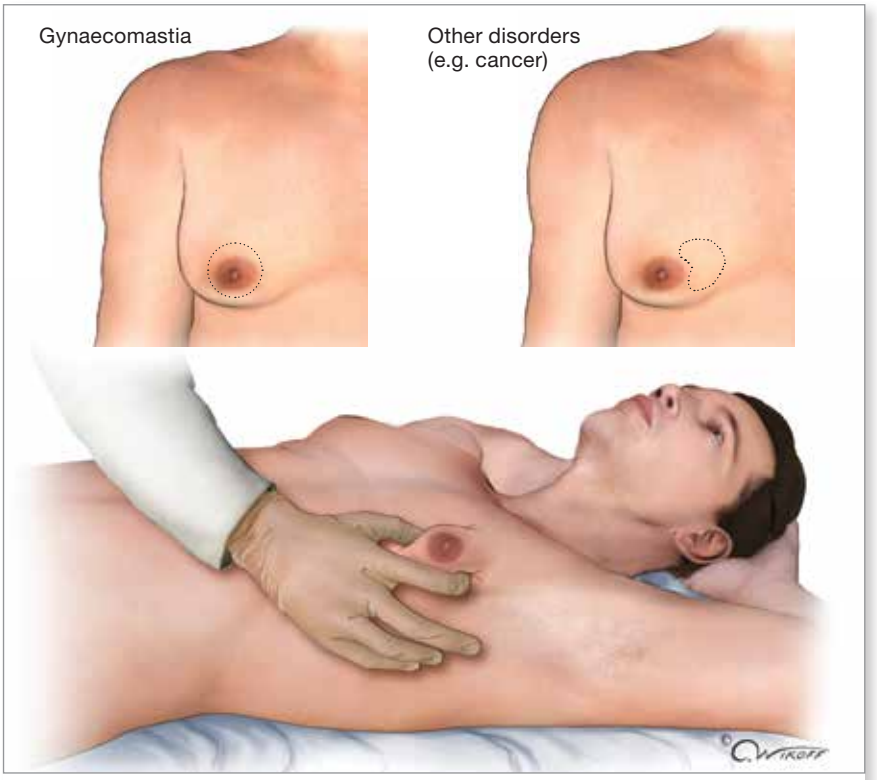


Figure. Examination for gynaecomastia. The thumb and forefinger are drawn together towards the areola. In gynaecomastia, a concentric mass with a rubbery or firm consistency is felt under the areola (top left). In disorders such as male breast cancer the mass is eccentric to the nipple and has a hard or firm consistency (top right).

texture. It may be bilateral, unilateral or asymmetric. Gynaecomastia is often tender within six months of its onset, when glandular proliferation is more active. After six to 12 months there is increasing fibrosis and less tenderness.[9]

Features of breast cancer should be sought, such as a unilateral, painless, firm or hard, fixed mass, located eccentrically to the nipple.[17] Male breast cancer often presents with at least one other suspicious feature in addition to the breast mass, such as nipple retraction, bleeding, discharge, ulceration, inflammatory skin changes or breast pain. Two-thirds of tumours are greater than 2 cm on presentation.[18]

The examination should also look for features of androgen deficiency, hepatic cirrhosis and thyroid overactivity. It is important to examine the testes carefully in all patients with gynaecomastia. Very small pea-like testes are typical of Klinefelter syndrome whereas a testicular mass may indicate a germ cell tumour.

Investigation

Whether laboratory testing is warranted in every patient presenting with gynaecomastia is controversial. In an adequately virilised adolescent with pubertal gynaecomastia and normal history and examination results (including normal testes), laboratory testing is probably not warranted.[1,9] Other patients should be investigated, as outlined in Box 4. A guide to interpretation of laboratory results is given in the Flowchart.

TREATMENT

Pubertal gynaecomastia

For an adolescent with suspected pubertal gynaecomastia, age-appropriate sexual development, including testicular size, and no abnormal findings on history or examination, treatment involves reassurance, as there is a high rate of spontaneous regression.[9]

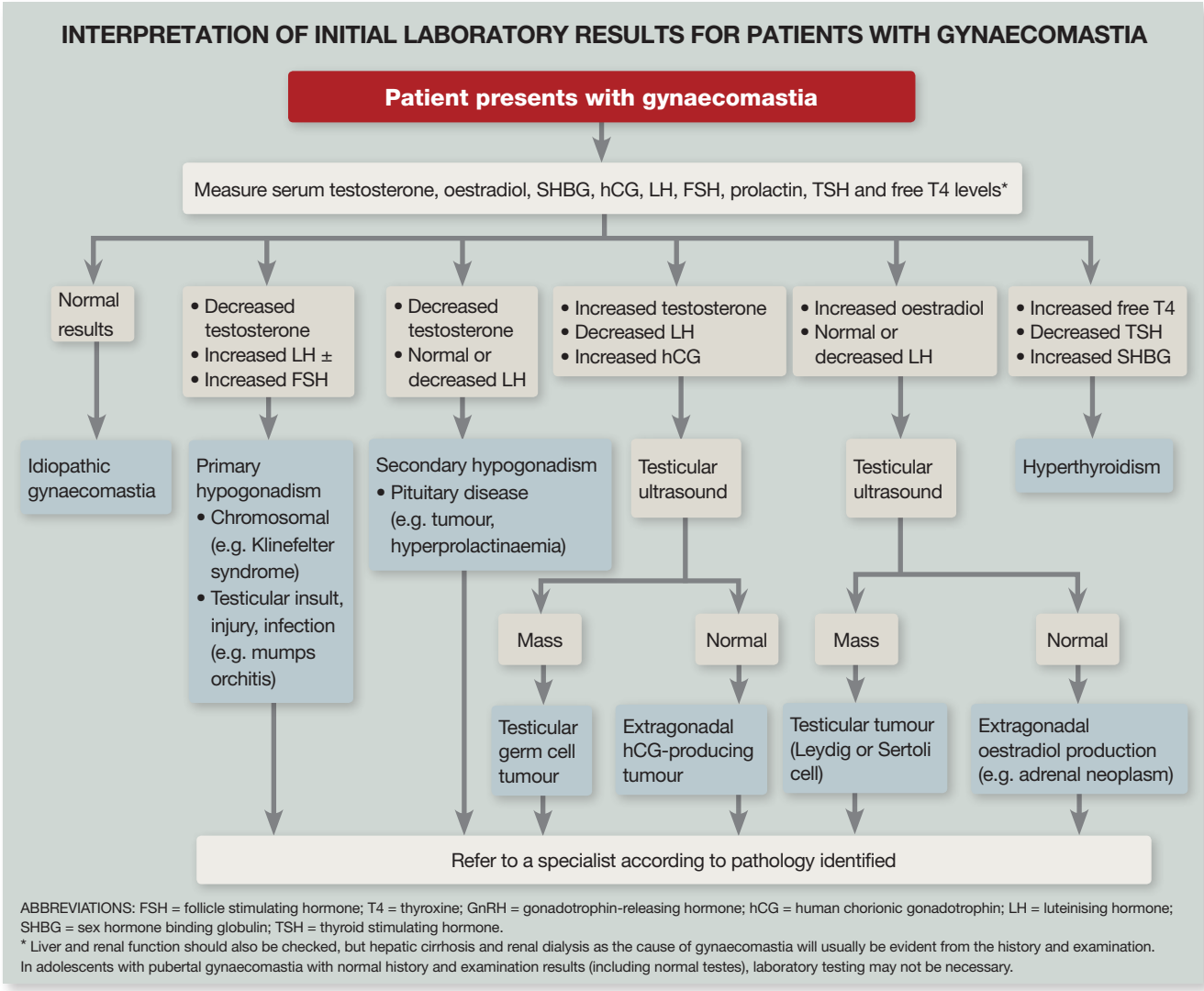
5. PRACTICE POINTS ON GYNAECOMASTIA

- GPs have an important role in the evaluation of patients presenting with gynaecomastia.
- Differentiating gynaecomastia from pseudogynaecomastia and from the rare entity of male breast cancer is essential.
- Although most cases of gynaecomastia are persistent pubertal, drug-induced or idiopathic, it is important not to miss treatable underlying conditions such as hypogonadism and hyperthyroidism.
- Uncommonly, gynaecomastia may be the first sign of a serious condition such as a testicular or adrenal tumour.

Adult gynaecomastia

In adults, if the evaluation does not reveal abnormalities and the gynaecomastia is longstanding and asymptomatic then treatment involves reassurance. Reversible causes should be treated where possible. In drug-induced gynaecomastia of short duration, improvement is expected within one month of ceasing the offending drug.[16] Anabolic steroids containing aromatisable androgens are the exception as their adverse effects often persist for many months after the drug is ceased.

When a causative medication cannot be stopped or the gynaecomastia is causing significant discomfort then a trial of tamoxifen (20 mg daily for 12 weeks) might help (off-label use).[19] As with any selective oestrogen receptor modulator, tamoxifen should not be taken by men with a personal or family history of venous thromboembolic disease. It is only effective if the gynaecomastia has been present for less



ABBREVIATIONS: FSH = follicle stimulating hormone; T4 = thyroxine; GnRH = gonadotrophin-releasing hormone; hCG = human chorionic gonadotrophin; LH = luteinising hormone; SHBG = sex hormone binding globulin; TSH = thyroid stimulating hormone.
* Liver and renal function should also be checked, but hepatic cirrhosis and renal dialysis as the cause of gynaecomastia will usually be evident from the history and examination. In adolescents with pubertal gynaecomastia with normal history and examination results (including normal testes), laboratory testing may not be necessary.

than six months, and it may be only partially effective.[20]

Surgery is the only option for longstanding gynaecomastia that causes significant discomfort or distress.[20] This involves open excision of glandular tissue via periareolar incision, suction lipectomy and skin reduction if necessary.[21] It is best delayed until the gynaecomastia reaches the fibrotic stage and after treatment of reversible causes. It should not be undertaken before completion of puberty.[22]

In patients receiving androgen deprivation treatment for prostate cancer, prophylactic radiotherapy or tamoxifen will often prevent the development of gynaecomastia.[23] Tamoxifen is probably more effective than radiotherapy in this setting.[23]

Aromatase inhibitors are not effective in patients with gynaecomastia, with the exception of those with the rare aromatase excess syndrome.[24,25]

CONCLUSION

Gynaecomastia can occur in males of all ages and may be distressing for patients. Some practice points regarding gynaecomastia are summarised in Box 5. Differentiation of true gynaecomastia from pseudogynaecomastia and male breast cancer is essential. Uncommonly, gynaecomastia may be the first sign of an hCG-producing tumour. A careful evaluation can usually identify the most common as well as the serious causes. As many as 25% of cases are said to be idiopathic. Some cases are self-limiting, and others are reversible following treatment of the underlying condition or withdrawal of a causative drug. Options for treatment include tamoxifen (off-label) if used soon after onset and surgery for longstanding gynaecomastia. MT

REFERENCES

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

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