Gynecomastia is the breast enlargement in males, due to increased glandular proliferation. This is a very common condition and mostly physiological in neonates, pubertal boys and elderly persons. Some cases are pathologic and secondary to drugs, chronic liver and kidney disease or hyperthyroidism. Majority are asymptomatic and do not need treatment. If treatment is needed, it should be tailored against the etiology of gynecomastia. Symptomatic gynecomastia that does not resolve with treating the cause can respond to antiestrogens or aromatase inhibitors. Finally, surgical intervention should be offered only to severely symptomatic cases.

Definition of Gynecomastia

**Gynecomastia:** It is the benign enlargement of breasts in males due to glandular proliferation, giving breasts a characteristic rubbery nature.

**Pseudo-gynecomastia:** It is the benign breast enlargement in obese males due to excessive deposition of fat and not glandular proliferation. It is important to differentiate between gynecomastia and pseudo-gynecomastia.

Epidemiology of Gynecomastia

Gynecomastia is a very common condition that has a prevalence of approximately 40% in males. Gynecomastia is common in three main age groups.
Neonates can have transient physiological gynecomastia at birth due to elevated estrogen concentrations in fetal blood. It should regress by the age of 3 weeks of life.

Pubertal boys may have gynecomastia due to a transient increase in estradiol concentration at the onset of puberty which should regress within 18 months of puberty and is not common after the age of 17 years. In some boys, gynecomastia may persist after puberty into adulthood, resulting in persistent gynecomastia.

The third age group is in the elderly. The elderly have an increased body fat content which is responsible for the increased conversion of androgens to estrogens.

**Prognosis**

Apart from its association with risk of breast cancer, gynecomastia does not cause any long-term complications. In most cases, pubertal gynecomastia resolves within a short period to several years. However, macromastia rarely resolves completely and often requires surgery.

Gynecomastia that occurs secondary to an underlying, treatable cause (e.g. drug-induced gynecomastia) usually responds to treatment or removal of the primary cause.

Research sheds light on psychological effects of gynecomastia. This includes depression, anxiety, reduced self-esteem and disordered eating.

**Etiology of Gynecomastia**

The most cases of gynecomastia are physiological having trimodal distribution (as explained above) and regress spontaneously, but it can also be a pathologic consequence of certain disease processes and factors, which are enlightened as follows:

**Drugs**

Several drugs have been associated with the development of gynecomastia and the strong associations are with spironolactone, estrogens, antiandrogens, anabolic steroids, ketoconazole, cimetidine, and 5-alpha-reductase inhibitors.

Digitalis, even though not an estrogen, still has an estrogen-like effect and can cause gynecomastia. Diazepam, heroin, tricyclic antidepressants, captopril, and methyldopa might cause gynecomastia by unknown mechanisms.

**Metabolic disorders**

Liver disease and cirrhosis are associated with increased production of androstenedione from the adrenals which is then aromatized to estrogen, resulting in gynecomastia. It is estimated that about two-thirds of cirrhotic persons have gynecomastia.

The type 1 diabetes, hyperthyroidism, and chronic renal disease have also been linked to gynecomastia.

**Hypogonadism**

Male hypogonadism is associated with a decrease in testosterone levels which results in an imbalance in estrogen to androgen ratio leading to gynecomastia.
Testicular tumors

Men with testicular tumors secreting excessive female hormones, such as Leydig or Sertoli cell tumors (stromal tumors) or with human chorionic gonadotropin tumors such as seminomas and nonseminomas are at the risk of developing gynecomastia due to elevated serum estrogen level.

Pathologic Causes

<table>
<thead>
<tr>
<th>Drug-induced</th>
<th>Tumors</th>
<th>Endocrine causes</th>
<th>Organ dysfunction</th>
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<tr>
<td>Anabolic steroids, antipsychotics, spironolactone, marijuana, ketoconazole</td>
<td>• Testicular • Adrenal</td>
<td>• Hyperthyroidism • Primary hypogonadism – Klinefelter syndrome</td>
<td>• Cirrhosis • Renal insufficiency</td>
</tr>
</tbody>
</table>

Other causes

- Malnutrition
- Testicular trauma
- Viral orchitis
- Klinefelter syndrome
- Kallmann syndrome
- Pituitary tumors/Hyperprolactinemia
- Ectopic hCG production (e.g., lung cancer, gastric carcinoma, renal cell carcinoma, hepatoma)
- Environmental pollutants

Pathophysiology

Most of the etiologies described above for gynecomastia share a common pathophysiology in which there is an estrogen-to-androgen imbalance. Either there is:

1. An increase in the production and/or action of estrogen
2. A decrease in the production and/or action of androgens
3. An Increase in aromatization of androgens into estrogens

The end result is an estrogen-to-androgen imbalance in the favor of excess estrogen production and/or activity. Estrogen is a potent growth hormone for the breast’s glandular tissue and its excess will lead to increased glandular tissue proliferation.

Clinical Presentation

An accurate data on history is obtained, aiming to addresses the following signs and symptoms:

- Family history of gynecomastia.
- Age of onset and duration of the condition.
- History of mumps, testicular trauma, alcohol use, or drug use.
- Any recent changes in nipple size and any pain or discharge from the nipples.
- History of sexual dysfunction, infertility, or hypogonadism.

Apart from the breast enlargement which can be appreciated by inspection and palpation, most of the patients with gynecomastia are asymptomatic. The breast enlargement may be unilateral or bilateral. Although some persons may complain of painful breasts, it is more common to have nipple sensitivity due to rubbing against a
The other associated symptoms should be sought in a patient presenting with gynecomastia. For example, weight changes (malignancy, thyroid disorders), nipple discharge (hyperprolactinemia), and infertility (hypogonadism).

Physical examination is important to differentiate between gynecomastia, pseudo-gynecomastia and possible breast carcinoma.

The thumb and index finger are placed on opposite sides of the breast and slowly brought together towards the areolar area. Gynecomastia presents as a concentric, rubbery mobile tissue, present directly beneath the areolar area. No such discrete mass is present in pseudo-gynecomastia. The breast cancer tends to be eccentrically positioned and firm-to-hard in consistency.

Further, physical examination should be performed to look for the pathologic etiology. Abdominal examination to look for signs of liver disease. The signs of hyperthyroidism such as tremors, thyroid gland nodules, hypertension and/or tachycardia should be looked for. The testes should be palpated for the testicular mass.

Diagnostic Work-up

Laboratory investigations

Laboratory investigations are of most importance when the cause of gynecomastia is unknown at the time of presentation. Common etiologies should be excluded by evaluating the liver, kidney, and thyroid function status.

The next step would be to evaluate serum hormone levels. Estradiol, testosterone, and DHEA should be checked to exclude excess estrogen or low androgen etiologies. Luteinizing hormone and follicle stimulating hormone levels should be also checked to exclude hypogonadism due to a decrease in gonadotropins. Human chorionic gonadotropins are elevated in certain tumors and should be checked.

Imaging

Patients with suspicion of breast cancer should undergo a mammography. Breast ultrasonography can be used to visualize the glandular nature of the enlarged breast. Testicular ultrasound might be indicated to exclude testicular tumors.
Abdominal computed tomography scans or ultrasonography can be used to exclude liver tumors and/or liver cirrhosis.

Histologic examination

When mammography is not sufficient to exclude breast cancer as the cause of gynecomastia, breast tissue biopsy is usually indicated and histologic examination is needed to rule out breast cancer.

Treatment

The treatment of gynecomastia depends up on the underlying etiology.

The physiologic gynecomastia should not be treated in pubertal boys or in neonates because it regresses in most cases. Patients with gynecomastia secondary to estrogen-androgen imbalance should be followed up for six months because the glandular tissue is known to be spontaneously replaced by fibrous tissue in a significant number of cases.

When gynecomastia is a side effect of a drug, the drug should be discontinued if possible.

Specific treatment for secondary causes of gynecomastia such as liver disease, kidney disease, hyperthyroidism, testicular tumors, adrenal tumors or obesity, should be provided according to the current recommendations and guidelines and is not going to be covered in this article.

Patients with tumors, once they have their tumor resected, are likely to have a regression in their gynecomastia. Patients with hemodialysis related gynecomastia should be reassured that the condition is very likely to regress spontaneously without any intervention. Men with hypogonadism might benefit from testosterone administration.

If gynecomastia is very symptomatic, i.e. breast tenderness with significant enlargement, medical treatment should be initiated within the first 12 months of onset.

Aromatase inhibitors are very potent drugs that prevent the peripheral aromatization of testosterone to estrogen and are known to be at least partly effective in inducing regression. Unfortunately, aromatase inhibitors are known to have several side effects and are not well tolerated by a significant number of cases. Patients with breast tenderness might also benefit from anti-estrogens.

After one year of onset, if gynecomastia persists and is symptomatic, or if the patient is psychologically distressed and embarrassed about his physical appearance that interferes with his normal daily activities, a surgical treatment might be needed. Surgery involves removing breast glandular tissue by a subcutaneous mastectomy approach.

Several complications are associated with subcutaneous mastectomy in males which include hematoma, nipple numbness, and breast asymmetry. Unfortunately, 50% of the surgical patients are not satisfied with the cosmetic results of the procedure. Because of these complications, surgery should be offered only as a last resort in patients with severely symptomatic gynecomastia that is longstanding.
Management

General management of gynecomastia are as follows:

- There is no treatment required for physiologic gynecomastia.
- For patients with idiopathic gynecomastia or with residual gynecomastia after treatment of the primary cause, medical or surgical treatment may be considered.
- Pubertal gynecomastia resolves spontaneously within several weeks to several years in most patients with breasts larger than 4 cm in diameter not regressing completely.
- If medical therapies are used, they should be tried early in the condition’s course.
- Identifying and managing an underlying primary disorder often alleviates breast enlargement.

Pharmacologic agents used to treat gynecomastia include the following:

- Danazol
- Clomiphene
- Tamoxifen

Surgical approaches that may be considered include the following:

- Endoscopic subcutaneous mastectomy, without skin excision.
- Reduction mammoplasty: in cases of macromastia, long-standing gynecomastia, or failed medical therapy.
- More extensive plastic surgery: in cases of marked gynecomastia or excessive sagging of the breast tissue from weight loss.

Surgical complications of gynecomastia

- Contour irregularity.
- Sloughing of tissue due to a compromised blood supply.
- Hematoma or seroma formation.
- Permanent numbness in the nipple-areolar area.

References


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