ETIOPATHOGENESIS AND TREATMENT PRINCIPLES OF GYNECOMASTIA

Xasanova Nargis Qodirovna

Department of Fundamental Medical Sciences of the Asian International University, Bukhara, Uzbekistan.

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Abstract. *Gynecomastia (GM) is characterized by enlargement of the male breast, caused by glandular proliferation and fat deposition. GM is common and occurs in adolescents, adults and in old age. The aim of this review is to discuss the pathophysiology, etiology, evaluation and therapy of GM. A hormonal imbalance between estrogens and androgens is the key hallmark of GM generation. The etiology of GM is attributable to physiological factors, endocrine tumors or dysfunctions, non-endocrine diseases, drug use or idiopathic causes. Clinical evaluation must address diagnostic confirmation, search for an etiological factor and classify GM into severity grades to guide the treatment. A proposal for tailored therapy is presented. Weight loss, reassurance, pharmacotherapy with tamoxifen and surgical correction are the therapeutic options. For long-standing GM, the best results are generally achieved through surgery, combining liposuction and mammary adenectomy.*

Keywords: *adolescent, gynecomastia, breast, surgery, IGF-1, aromatase.*

ЭТИОПАТОГЕНЕЗ, КЛИНИКА И ПРИНЦИПЫ ЛЕЧЕНИЯ ГИНЕКОМАСТИИ

Аннотация. *Гинекомастия (ГМ) характеризуется увеличением мужской груди, вызванным разрастанием железистой ткани и отложением жира. ГМ является распространённым явлением и встречается у подростков, взрослых и пожилых людей. Цель этого обзора — обсудить патофизиологию, этиологию, диагностику и терапию ГМ. Гормональный дисбаланс между эстрогенами и андрогенами является ключевым признаком возникновения ГМ. Этиология ГМ может быть связана с физиологическими факторами, эндокринными опухолями или нарушениями, неэндокринными заболеваниями, употреблением препаратов или идиопатическими причинами. Клиническая оценка должна включать подтверждение диагноза, поиск этиологического фактора и классификацию ГМ по степеням тяжести для выбора подходящего лечения. Представлено предложение по индивидуализированному лечению. Терапевтические варианты включают снижение массы тела, успокоение пациента, фармакотерапию с использованием тамоксифена и хирургическую коррекцию. Для длительно существующей ГМ наилучшие результаты обычно достигаются с помощью хирургии, сочетая липосакцию и аденэктомию молочной железы.*

Ключевые слова*: Подросток, Гинекомастия, Грудь, Хирургия, Инсулиноподобный фактор роста 1 (ИФР-1).*

Gynecomastia is a relatively common disorder. Its causes range from benign physiological processes to rare neoplasms. To diagnose the etiology of the gynecomastia, the clinician must understand the hormonal factors involved in breast development. Parallel to female breast development, estrogen, growth hormone (GH), and IGF-1 are required for breast growth in males. Since a balance exists between estrogen and androgens in males, any disease state or medication that increases circulating estrogens or decreases circulating androgens, causing an elevation in the estrogen to androgen ratio, can induce gynecomastia. Due to the diversity of possible etiologies, including a neoplasm, performing a careful history and physical is imperative. Once gynecomastia has been diagnosed, treatment of the underlying cause is warranted. If no underlying cause is discovered, then close observation is appropriate. If the gynecomastia is severe and of recent onset, medical therapy can be attempted, and if ineffective, glandular tissue can be removed surgically.

Etiological factors of Gynecomastia

1. Physiological causes:

- Neonatal gynecomastia – due to transplacental maternal estrogens.
- Pubertal gynecomastia – common and usually transient, caused by temporary hormonal imbalance.
- Aging – decreased testosterone production and increased peripheral conversion of androgens to estrogens.

2. Pathological causes:

a. Endocrine Disorders

- Primary hypogonadism (e.g., Klinefelter syndrome, testicular failure)
- Secondary hypogonadism (e.g., pituitary tumors)
- Hyperthyroidism – increases sex hormone-binding globulin (SHBG) and alters estrogen/testosterone ratio.
- Adrenal tumors or Leydig/Sertoli cell tumors

b. Systemic diseases

- Liver disease (e.g., cirrhosis) – impaired metabolism of estrogens.
- Chronic kidney disease – associated with hormonal imbalances and sometimes medications used in dialysis.

3. Drug-induced:

- Anti-androgens: flutamide, spironolactone, bicalutamide.
- Estrogens or estrogen-like compounds.
- Anabolic steroids (especially during withdrawal).

- Medications: Cimetidine, Ketoconazole, Digoxin, Calcium channel blockers (e.g., verapamil), Antipsychotics (e.g., risperidone), Antidepressants (e.g., tricyclics), Chemotherapy agents

4. Idiopathic:

In many cases, especially in pubertal males, no definitive cause is found.

5. Obesity

Increased peripheral aromatization of androgens to estrogens in adipose tissue.

Physiologic gynecomastia:

Gynecomastia, breast development in males, can occur normally during three phases of life. The first occurs shortly after birth in both males and females. This is partly caused by the high fetal blood levels of estradiol and progesterone (produced by the mother) that stimulate breast tissue in the newborn. Another mechanism is the increased conversion of steroid hormone precursors to sex steroids and increased aromatization of androgen as a result of neonatal surge of luteinizing hormone (LH).

Puberty marks the second period when gynecomastia can occur physiologically. In fact, up to 60% of boys have clinically detectable gynecomastia by age 14. Although it is mostly bilateral, it is often asymmetrical and can occur unilaterally. Pubertal gynecomastia usually resolves within 3 years of onset.

The third age range in which gynecomastia is frequently seen is during older age (>60 years). The reported prevalence varies from 36 to 57%, possibly because of different selected populations and different diagnostic criteria. Although the exact mechanisms by which this occurs have not been fully elucidated, evidence suggests that it may result from increased peripheral aromatase activity secondary to increased total body fat, relatively elevated LH concentrations, and decreased serum testosterone concentrations associated with male aging.

Pathologic gynecomastia:

Breast development requires the presence of estrogen. Androgens, on the other hand, have anti-proliferative effects on breast tissue. Thus, an equilibrium exists between estrogen and androgens in the adult male to prevent growth of breast tissue, whereby either an increase in estrogen or a decrease in androgen can tip the balance toward gynecomastia.

Also, Testicular tumors can lead to increased blood estrogen levels by the following mechanisms: estrogen overproduction, androgen overproduction with extragonadal aromatization to estrogens, and secretion of hCG that stimulates normal Leydig cells (via the LH receptor).

Tumors causing an overproduction of estrogen represent an unusual but important cause of estrogen excess. Examples of estrogen-secreting tumors include Leydig cell tumors, Sertoli cell tumors, granulosa cell tumors, and adrenal tumors.

Drugs:

About 20% of gynecomastia is caused by medications or exogenous chemicals. Some drugs may increase estrogen effect by several mechanisms: 1) they possess intrinsic estrogen-like properties, 2) they increase endogenous estrogen production, or 3) they supply an excess of an estrogen precursor (e.g., testosterone or androstenedione) that can be aromatized to estrogen.

Treatment:

Treatment of the underlying endocrinologic or systemic disease that has caused gynecomastia is appropriate when possible. Testicular tumors, such as Leydig cell, Sertoli cell, or granulosa cell tumors should be surgically removed. In addition to surgery, germ cell tumors are further managed with chemotherapy involving cisplatin, bleomycin, and either vinblastine or etoposide.

If no pathologic etiology is detected, then appropriate treatment is close observation. A careful breast exam should be done initially every 3-6 months until the gynecomastia regresses or stabilizes, after which a breast exam can be performed yearly. It is important to remember that most cases of pubertal gynecomastia may resolve spontaneously within one to two years, around 20% of patients have residual gynecomastia at the age of 20

If the gynecomastia is severe, does not resolve, of recent onset (less than 6 months) and does not have a treatable underlying cause, some medical therapies may be attempted. There are 3 classes of medical treatment for gynecomastia: androgens (testosterone, dihydrotestosterone, danazol), anti-estrogens (clomiphene citrate, tamoxifen), and aromatase inhibitors such as letrozole and anastrozole.

Conclusion: Gynecomastia is a common clinical condition resulting from an imbalance between estrogen and androgen activity, with a wide range of physiological, pathological, pharmacological, and idiopathic causes. Understanding its etiopathogenesis is essential for accurate diagnosis and appropriate management. While many cases, especially during puberty, are benign and self-limiting, others may indicate underlying systemic or endocrine disorders requiring further evaluation. Effective treatment begins with identifying and addressing the underlying cause, discontinuing causative drugs when possible, and monitoring for spontaneous resolution. In persistent or psychologically distressing cases, medical therapies—such as selective estrogen receptor modulators—and surgical interventions may be considered. A tailored, patient-centered approach ensures optimal outcomes and minimizes unnecessary interventions.

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