REVIEW PAPER

Gynecomastia: Clinical Review and Endocrinology Perspectives

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Abstract

Gynecomastia is the term used to describe the benign growth of glandular breast tissue in men. The most common causes are pubertal gynecomastia, hypogonadism, and drugs. An imbalance in the actions of free estrogen and androgens in the breast tissue is the root cause of gynecomastia. Physiologic or pubertal gynecomastia is a common finding in mid-puberty, with pubic hair present in Tanner stage III–IV. Gynecomastia is commonly bilateral, however, 20% of pubertal boys have unilateral disease. In gynecomastia, evaluation needs history – onset, progression, associated pain, medication history, and symptoms of hypogonadism. True gynecomastia and pseudogynecomastia should be distinguished by the feel of glandular or fat tissue. The testis and abdomen examination is an essential part of the examination. It is reasonable to measure the levels of serum testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), prolactin, thyroid stimulating hormone (TSH), serum estradiol, serum human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), liver function test, and renal function test in peripubertal boys with macromastia (Tanner stage III or greater) and adult males with newly developing gynecomastia, fast growth, and eccentric or hard, irregular masses or gynecomastia larger than 4 cm inch. Physiologic gynecomastia usually resolves on its own. In 75–90% of adolescents, pubertal gynecomastia resolves independently after 1–2 years. Aromatase inhibitors, e.g., letrozole and estrogen receptor modulators, e.g., tamoxifen (10–20 mg daily), are recommended for painful pubertal gynecomastia or macromastia (Tanner staging III or more). If the gynecomastia is persevering (>2 years) and very disturbing to the boy, surgical reduction, mammoplasty by an experienced surgeon can be pursued.

Keywords: Gynecomastia, Klinefelter syndrome, Lipomastia, Mammoplasty, Tamoxifen.

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Definition

Gynecomastia is the term used to describe the benign growth of glandular breast tissue in men.[1] When there is more than 2 cm of palpable breast tissue in adult males, gynecomastia is typically regarded as significant.

Prevalence of gynecomastia in the general population varies from 30 to 60% due to different age group presentation.[2–4] In clinical practice, the most common causes are pubertal gynecomastia, hypogonadism, and drugs.

Pathophysiology

Gynecomastia results from an imbalance in the activities of free estrogen and androgens in breast tissue.[5]

Etiology[6–8]

Physiological

Pathological

I. Estrogen excess
   - A. Exogenous estrogens:
     Exposure to estrogenic compounds, such as lavender and tea tree oils, as well as aromatizable androgens.
   - B. Endogenous estrogens:
     - From testis – Leydig cell or Sertoli cell tumors.
     - From adrenals – feminizing adrenocortical tumors.
     - Increased androgen aromatization to estrogens (obesity, liver failure, hyperthyroidism, drugs, hCG-secreting tumors, and aging).
     - Constitutively active autosomal-dominant mutations in the aromatase (CYP19A1) gene.

II. Androgen deficiency: Hypogonadism either primary or secondary, due to disease, radiation, trauma, or drugs

III. Altered serum androgen/estrogen ratio (puberty, aging, gynecomastia, hepatic failure, chronic kidney disease, hyperthyroidism, pharmaceuticals such as tricyclic antidepressants, chemotherapy medications, and cardiovascular therapies (e.g., digitalis).

IV. Decreased androgen action
   - A. Androgen receptor antagonists (cimetidine, spironolactone, bicalutamide, and flutamide), GnRH analogs, and 5α-reductase inhibitors, GH.
   - B. Kennedy disease – expansion of cytosine, adenine, guanine (CAG) repeats in androgen receptor.

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In neonates, adolescents, and elderly men, physiologic gynecomastia is frequent. It is self-limiting, but it can be treated to alleviate emotional and physical pain.

Physiologic or pubertal gynecomastia is a common finding in mid-puberty, with pubic hair present in tanner stage III–IV. Gynecomastia is commonly bilateral, although in 20% of pubertal males, it is unilateral. The relative and transient imbalance in the testosterone-to-estradiol ratio has been implicated as the cause of pubertal gynecomastia.[9] Gynecomastia usually resolves or at least stabilizes as puberty progresses and testosterone concentrations rise.

History

The following are the most important questions: (1) the onset, progression rate, and severity of pain associated with gynecomastia; (2) androgen deficiency symptoms; (3) medication, prescription and over-the-counter pharmaceuticals, "nutritional" supplements, and skin care goods; (4) the presence of a severe systemic ailment, such as poorly managed diabetes, severe renal, hepatic, or cardiac disease, or pulmonary sickness that inhibits the hypothalamic–pituitary–adrenal axis; (5) manifestations of underlying malignancy, particularly testicular cancer; (6) symptoms caused by with estradiol, prolactin, growth hormone, cortisol, or thyroxine excess; (7) gynecomastia in the family; and (8) history of chest trauma.

Physical Examination

True gynecomastia and pseudogynecomastia should be distinguished. The examiner can progressively press the breast region between the fingers and thumb, commencing from the sides of the breast, while the patient is recumbent with his hands clasped under his head. Breast tissue with true gynecomastia is typically bilateral, rubbery, or firm, and concentrically located under the nipple–areolar complex. Pain or tenderness as a result of the periductal inflammation is linked to this early proliferation. Lipomastia, also known as pseudogynecomastia, is defined by breast fullness and the lack of a nipple–areolar complex mound, lipomastia, also known as pseudogynecomastia, is defined by breast fullness and the lack of a nipple–areolar complex mound, which allows the rib cage to be palpated behind the areolae. Breast carcinoma is typically hard or firm, located exterior of the nipple–areolar complex, and unilateral.[1,10]

Upper and lower segment ratios (US/LS ratios) and arm span-height differences are essential criteria to consider while evaluating gynecomastia. Upper and lower segment ratio in patients with Klinefelter syndrome is decreased. Arm span is increased than height in Klinefelter syndrome. Careful testis examination is an important part of gynecomastia evaluation because of Sertoli or Leydig cell tumor present with testicular enlargement/mass.

Investigation

It is reasonable to measure the levels of serum testosterone, FSH, LH, prolactin, TSH, serum estradiol, serum HCG, AFP, liver function test, and renal function test in peripubertal boys with macromastia (Tanner stage III or greater) and adult males with newly developing gynecomastia, fast growth, and eccentric or hard, irregular masses or gynecomastia larger than 4 cm in diameter.

Ultrasound breast may be used when the clinical examination is equivocal to differentiate pseudo-or true gynecomastia. If a breast tumor is surmised, ultrasonography, mammography, fine-needle aspiration, or core biopsy should be performed.[11]

Treatment of Pubertal Gynecomastia

A prepubertal boy's gynecomastia is pathologic and should be investigated. Physiologic gynecomastia typically resolves on its own. In 75–90% of adolescents, pubertal gynecomastia resolves on its own after 1–2 years.[12]

Aromatase inhibitors, e.g., letrozole and estrogen receptor modulators, e.g., tamoxifen (10–20 mg daily), are recommended for painful pubertal gynecomastia or macromastia (Tanner staging III or more).[13,14] If the gynecomastia is persevering (>2 years) and very disturbing to the boy, surgical reduction or mammoplasty by an experienced surgeon can be pursued.

A skilled surgeon may perform a surgical reduction or mammoplasty if it persists for more than 2 years and very disturbing to the boy.

Treatment of Adult Gynecomastia

Treatment of the underlying causes like stoppage of offending drug, e.g., spironolactone, treatment of hyperthyroid, and replacement of male hormone in hypogonadism. Some patients with recently developed, highly symptomatic idiopathic gynecomastia may benefit from treatment with tamoxifen 20 mg once daily for three months.[15] Reduction mammoplasty may be required if gynecomastia lasts for more than a year and is very irritating cosmetically.[16]

Guideline

One guideline of gynecomastia management is available – European Academy of Andrology (EAA) clinical practice guidelines – gynecomastia evaluation and management.[17]

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