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CLINICAL, IMAGING AND PATHOLOGICAL SPECTRUM OF GYNECOMASTIA

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ABSTRACT

Gynecomastia, the most common abnormality of the male breast, is caused by benign proliferation of ductal and stromal tissue elements, resulting in breast symptoms and imaging findings that may be unilateral or bilateral. Patients typically present with unilateral or less commonly bilateral breast pain, a breast mass or masses, or breast enlargement. The three characteristic patterns of gynecomastia seen at mammography are nodular, dendritic, and diffuse glandular. The nodular and dendritic forms correspond to the florid and fibrous stages of proliferation, respectively, whereas the diffuse glandular type corresponds to epithelial proliferation and is often linked to the use of exogenous hormones. The ultrasound examination reveals a subareolar hypoechoic mass, which may have typical nodular features and a long axis that is parallel to the skin (nodular gynecomastia), or it may be triangular with extensions that radiate into the subareolar fat (dendritic gynecomastia), or it may resemble a female breast (diffuse gynecomastia). The colour-Doppler evaluation reveals moderate, harmonious intralesional vascularisation. Ultrasonography is more important in the diagnosis of true gynecomastia, which has a clinical presentation very similar to that of other nodular diseases. Ultrasonography, together with history, physical examination and image guided FNAC can provide a preliminary diagnosis for further evaluation. Image guided core biopsies would be reserved for definite diagnostic purposes.

INTRODUCTION

Gynecomastia is derived from the Greek word gyne (female) +mastos (breast). It is a condition characterized by an increase in the ductal tissue, stroma and/or fat of the male breast resulting in male breast enlargement. It is believed to result from an imbalance in the estrogen to androgen ratio, causing proliferation of breast tissue cellular components [1].

- **Physiological gynecomastia**: It has a trimodal age distribution, occurring in neonatal, pubertal, and elderly males.

- **Neonatal breast hypertrophy** is a common transient condition seen in 90% of all newborns. It may be due to transplacental passage of hormones. It is due to action of prolactin, placental estrogens, and progesterone on the neonatal breast parenchyma. Another mechanism could be due to the increased conversion of steroid hormone precursors to sex steroids and a neonatal surge of gonadotropins. It can persist for several weeks after birth and can cause mild breast discharge called "witch's milk". With decline in these hormones, this breast enlargement usually regresses within a few weeks.
- **Pubertal gynecomastia** can be seen in 3.9-64.6% of boys. It is generally seen in boys aged 10-13years, with typical onset 6 months after the appearance of secondary sex charecteristics. It is a benign process that regresses within 2 years of onset. In early puberty, the pituitary gland releases gonadotropins at night and stimulates testicular production of testosterone during the very early morning hours. Estrogens, however, rise throughout the entire day. The mechanism by which pubertal gynecomastia occurs may be due to either decreased production of androgens or increased aromatization of circulating androgens, thus increasing the estrogen to androgen ratio. Leptin may play a role in its development of pubertal gynecomastia. Leptin is found in mammary epithelial cells and can enhance aromatase enzyme activity in fatty tissue and breast tissue, resulting in an increase in estrogen concentrations. Leptin can also activate oetrogen receptors in breast tissue.
- **Senile Gynecomastia** It results from increased peripheral aromatase activity secondary to the increase in total body fat, relatively elevated LH concentrations, and a decrease in serum testosterone concentrations associated with male aging. Besides increase in total body fat with age there may also be an increase in aromatase activity in the adipose tissue already present resulting in increase of circulating estrogens even further. Sex hormone binding globulin (SHBG) increases with age in men. Since SHBG binds estrogen with less affinity than testosterone, the ratio of bioavailable estradiol to bioavailable testosterone may increase in the obese older male. Lastly, elderly patients may take multiple medications associated with gynecomastia. [2].

Pathological gynecomastia: It is due to an increase in the circulating and/or local breast tissue ratio of estrogen to androgen. In post-pubertal boys and adult men, the testes secrete approximately 15% of the estradiol and less than 5% of the estrone in the circulation, whereas extragonadal tissues produce 85% of the estradiol and more than 95% of the estrone through the aromatization of precursors. The principal precursor of estradiol is testosterone, 95% of which is derived from the testes. Androstenedione, an androgen secreted primarily by the adrenal gland, serves as a precursor of estrone formation. The important extraglandular sites of aromatization are adipose tissue, liver and muscle. In addition, a substantial degree of interconversion between estrone and estradiol takes place through the action of the widely distributed enzyme 17-ketosteroid reductase, which also catalyzes the conversion of androstenedione to testosterone. Thus, any cause of estrogen excess from overproduction or peripheral aromatization of androgens can initiate the cascade to breast development. [3].

Pathological causes include

- Tumors causing gynecomastia
- Drugs causing gynecomastia
- Hypogonadism
- Klinefelter syndrome (XXY)
- Pituitary hormone deficiency
- Androgen resistance syndromes
- Liver Cirrhosis
- Hyperthryoidism
- Chronic Renal disease and dialysis
- Idiopathic causes

Tumors causing Gynecomastia

Testicular tumors can lead to increased blood estrogen levels by estrogen overproduction, androgen overproduction with aromatization in the periphery to estrogens, and by ectopic

secretion of gonadotropins which stimulate otherwise normal Leydig cells. Following Table shows list of tumors causing gynecomastia and their corresponding hormone production.

Table 1 Tumors Causing Gynecomastia

Tumor Type	Hormone Produced
Leydig cell tumor	Testosterone, estrogen
Sertoli cell tumor	Estrogen
Granulosa cell tumor	Estrogen
Adrenal tumor	Estrogen, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S), and androstenedione which are converted in the periphery to estrogens.
Gonadal germ cell tumor	hCG and β-hCG
Extragonadal germ cell tumor (lung, gastric, renal cell and hepatocellular carcinoma	hCG and β-hCG (ectopic)

Drugs Causing Gynecomastia

Drugs may cause gynecomastia by several mechanisms: [4].

- By having intrinsic estrogen-like properties
- Increasing endogenous estrogen production
- Supplying an excess of an estrogen precursor (e.g. testosterone or androstenedione) which can be aromatized to estrogen.
- Direct testicular damage
- By blocking testosterone synthesis
- By blocking androgen action

Table 2 Drugs That May Induce Gynecomastia by Known or Proposed Mechanisms

Mechanism	Drugs
Estrogen-like, or binds to estrogen receptor	Estrogen vaginal cream Estrogen-containing embalming cream Delousing powder Digitalis Clomiphene
Stimulate estrogen synthesis	Gonadotropins Growth Hormone
Supply aromatizable estrogen precursors	Exogenous androgen Androgen precursors (i.e. androstenedione and DHEA)
Direct testicular damage	Busulfan Nitrosurea Vincristine Ethanol
Block testosterone synthesis	Ketoconazole Spironolactone Metronidazole Etomidate
Block androgen action	Flutamide Bicalutamide Finasteride Cyproterone Zanoterone Cimetidine Ranitidine* Spironolactone
Displace estrogen from SHBG	Spironolactone Ethanol

Table 3 : Drugs That Cause Gynecomastia by Uncertain Mechanisms

Cardiac and antihypertensive medications:
Calcium channel blockers (verapamil, nifedipine, diltiazem)
Amiodarone
Methyldopa
Reserpine
Nitrates
Psychoactive drugs:
Neuroleptics
Phenytoin
Tricyclic antidepressants
Haloperidol
Atypical antipsychotic agents
Drugs for infectious diseases:
Antiretroviral therapy for HIV/AIDS (e.g. efavirenz)
Isoniazid
Ethionamide
Griseofulvin
Minocycline
Drugs of Abuse:
Amphetamines
Heroin
Methadone
Others:
Theophylline
Omeprazole
Auranofin
Diethylpropion
Domperidone
Penicillamine
Sulindac
Heparin
Methotrexate

Hypogonadism

- **Primary hypogonadism:** Is associated with reduction in serum testosterone and increase in serum LH levels which increases aromatization of testosterone to estradiol and is associated with an increased estrogen to androgen ratio. Any acquired testicular disease resulting in primary hypogonadism such as severe, postpubertal viral and bacterial orchitis, or scrotal trauma or radiation can result in gynecomastia.
- **Klinefelter syndrome:** It occurs in 1 in 600-700 males and is due to supernumerary X chromosomes (XXY or XXXY karyotype). Mainly presents with primary testicular failure and often prominent gynecomastia, due to decreased testosterone production, compensatory increased LH secretion, overstimulation of the Leydig cells and relative estrogen excess.
- **Secondary hypogonadism:** Results in low serum testosterone and unopposed estrogen effect due to increased conversion of adrenal precursors to estrogens. Therefore, patients with Kallmann syndrome which is a type of congenital secondary hypogonadism with anosmia, also develop gynecomastia.

Androgen Resistance Syndromes [5]

In these diseases the peripheral tissues, including the breast and pituitary, are less responsive to testosterone and other androgens. It includes complete and partial testicular feminization (e.g. Reifenstein's syndrome) characterized by gynecomastia and varying degrees of pseudohe rmaphroditism. Kennedy disease, a neurode generative disease, is also associated with decreased effective testosterone due to a defective androgen receptor. Androgen resistance at the pituitary results in elevated serum LH levels and increased circulating testosterone. The increased serum testosterone is then aromatized peripherally, resulting in gynecomastia.

Gynecomastia of Liver disease

The gynecomastia is the result of estrogen overproduction, possibly secondary to increased extraglandular aromatization of androstenedione, which may have decreased hepatic clearance in cirrhotics. although the association of gynecomastia with liver disease is apparent. Current data in this regard is conflicting and the mechanism remains unclear still.

Gynecomastia of Thyroid lesions

Thyrotoxicosis may be associated with gynecomastia. Patients often have elevated estrogen levels that may result from a stimulatory effect of thyroid hormone on peripheral aromatase. Untreated thyrotoxicosis is often associated with high or high normal total testosterone, very high SHBG and low or low-normal free testosterone. Since SHBG binds testosterone more avidly than estradiol, there is a higher ratio of free estradiol to free testosterone.

Congenital testicular hypoplasia or aplasia, testicular trauma or torsion, viral orchitis and other congenital anomalies may lead to pathological gynecomastia.

Approach to evaluate Gynecomastia

- Clinical and Physical examination
- Imaging
- Cytology/Biopsy Confirmation

Table 4 : Clinical and physical evaluation of gyneco mastia

History • Duration of symptoms • Localized symptoms, like a palpable mass, breast tenderness or enlargement and nipple discharge • History of an undescended testis, mumps or liver or kidney disease • Detailed history of medications, supplements, illicit drugs, anabolic steroids
Physical Examination • Height/ weight • Anthropometric measurements (body mass index) • Signs of feminization • Stigmata of liver disease • Breast and overlying skin • Regional lymph node • Thyroid • Scrotum • Varicoceles

Pseudogynecomastia:

Careful history taking and physical examination often helps in identifying patients with pseudogynecomastia. Pseudogynecomastia is more commonly seen in overweight or obese individuals, manifesting as unilateral or bilateral breast enlargement rather than a discrete mass, since this condition is caused by benign diffuse proliferation of normal fatty tissue rather than stimulation of ductal and stromal elements which means accumulation of subareolar fat without actual proliferation of glandular tissue. These patients do not need additional work-up and only require reassurance. [6].

Gynecomastia is usually bilateral, but patients may present with asymmetrical or unilateral findings. **(Figure 1)** Palpation usually demonstrates a palpable, tender, firm, mobile, disc-like mound of tissues that is not as hard as breast cancer and is located centrally under the nipple-areolar complex. When palpable masses are unilateral, hard, fixed, peripheral to the nipple, and associated with nipple discharge, skin changes, or lymphadenopathy then breast cancer should be suspected and thorough evaluation is recommended.

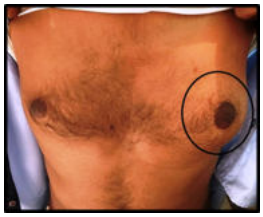

Figure 1 Unilateral enlargement of left breast

The American Society of Plastic Surgeons classifies male breast enlargement into four grades based on clinical appearance:.

- Grade I: Small breast enlargement with a localized collection of periareolar tissue.
- Grade II: Moderate breast enlargement exceeding areolar boundaries, with indistinct borders from the chest.
- Grade III: Moderate breast enlargement exceeding areolar boundaries, with distinct borders from the chest and associated with excess skin.
- Grade IV: Marked breast enlargement and feminization associated with excess skin.

Role of Imaging

Mammography can differentiate true gynecomastia from a mass that requires tissue sampling to exclude malignancy. Three mammographic patterns of gynecomastia have been described representing various degrees and stages of ductal and stromal proliferation.

They are: [7].

- Nodular pattern
- Dendritic pattern
- Diffuse glandular pattern

Early nodular gynecomastia (florid phase) is seen in patients with gynecomastia for less than 1 year. At mammography, there is often a nodular subareolar density.

Chronic dendritic gynecomastia (quiescent phase) is seen in patients with gynecomastia for longer than 1 year. Fibrosis becomes the dominant process and is irreversible. Mammograms in this phase typically show a dendritic subareolar density with posterior linear projections radiating into the surrounding tissue towards the upper-outer quadrant.

Diffuse glandular gynecomastia is commonly seen in patients receiving exogenous estrogen. At mammography, there is enlargement of the breast and diffuse density with both dendritic and nodular features.

Ultrasonography: The US appearances of gynecomastia in a subareolar location can include nodular, poorly defined, or flame-shaped masses, the majority of which will have a hypoechoic echotexture and potentially spiculated margins. **(Figure 2)** Other US features may include a parallel growth pattern, lack of posterior acoustic enhancement, variable vascularity depending on the phase of gynecomastia. USG allows verification of normal appearing breast tissue and also helps in revealing a lack of breast tissue in cases of pseudogynecomastia. Imaging of the scrotum is only recommended if palpable masses are present. Testicular neoplasms can also be evaluated by USG[8].

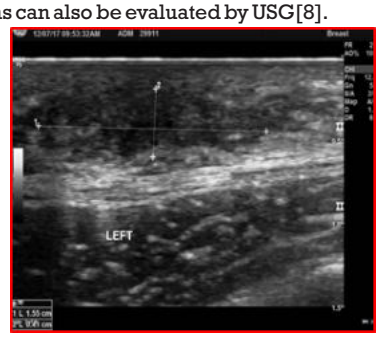

Figure 2 USG shows diffuse glandular gynecomastia in which glandular tissue is diffusely distributed within adipose tissue in a pattern resembling female breast

Clinically, it can present as unilateral or bilateral ill-defined swellings or as discrete nodules. Cases with bilateral presentation do not pose a clinical problem most of the time. However, unilateral cases may raise the clinical suspicion of malignancy and therefore biopsy may be requested.

Table 5 Differential diagnosis of Gynecomastia with male breast carcinoma[9].

Features	Gynecomastia	Breast carcinoma	Both Gynecomastia and breast carcinoma
Patient age	Bimodal prevalence; peripubertal and >50 yrs	>60 yrs	Approx 60yrs
Clinical appearance	Soft tender mass; mobile	Soft or firm nontender mass; mobile or non-mobile mass	
Relationship of lesion to the nipple	Central	Eccentric	Subareolar
Laterality	Most commonly bilateral	Usually unilateral	
Mammographic appearance	Fan or flame shaped density	Discrete mass, calcifications, skin thickening, nipple retraction, axillary adenopathy	Irregular margins
Ultrasound appearance	Hypoechoic irregular mass; usually no axillary adenopathy	Most commonly a hypoechoic mass, similar to breast Ca of females; suspicious axillary lymph nodes	Vascular, complex, cystic mass
Histology Cytology	Ductal epithelial hyperplasia and increased periductal stromal cellularity Sparsely to moderately cellular smears composed of clusters of bland epithelial and stromal fragments in a background of naked bipolar nuclei.	Mostly poorly differentiated infiltrating ductal carcinoma. Can also be in situ or lobular carcinoma. Dispersed epithelial cells with atypical features and high N/C ratio.	

Laboratory investigations:

- Liver, kidney, and thyroid function tests exclude the respective medical conditions.
- Hormonal testing measures levels of total and bioavailable testosterone, estradiol, prolactin, luteinizing hormone, and hCG

Cytology

The FNAC features of gynecomastia include three components such as cell-poor to cell-moderate, cohesive sheets or groups of bland cells, bipolar bare nuclei and single tall columnar cells. Cytologically, the aspiration of gynecomastia typically shows moderately cellular smears with a biphasic population of epithelial and stromal fragments. **(Figure 3)** Naked bipolar to oval myoepithelial nuclei are also seen in the background. The epithelial fragments are often large, tightly cohesive, appearing as flat somewhat monolayered sheets or show mild to marked epithelial atypia in the form of cellular crowding with nuclear overlap, nuclear hyperchromasia, occasional mitotic figures, loss of architecture, and some cellular discohesiveness. Because of this occasional cytological atypia, the differentiation from malignancy may be difficult in some cases. However, in cases of carcinoma the smears tend to be more cellular with a predominant population of discohesive single malignant cells. Nuclear abnormalities are more striking and include high nuclear/cytoplasmic ratio, and nuclear hyperchromasia with occasional prominent nucleoli. Occasionally, attempts of glandular formation and intracytoplasmic mucin vacuoles may also be seen. [10].

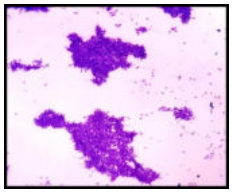

Figure 3 Smears with cohesive monolayered sheets of benign ductal epithelial cells admixed with myoepithelial cells (Giema 40x)

Diagnostic dilemmas

- Gynecomastia may be significantly painful and many patients refuse additional FNAB passes due to the associated pain.
- The fibrotic nature of the lesion makes adequate sampling difficult, therefore a significant number of insufficient cases may be encountered.

Patients with a FNAB diagnosis of gynecomastia can avoid surgical intervention, while patients with the diagnosis of malignancy will follow routine breast carcinoma management protocols already established for female patients.

Histopathology

Tissue sections showed the usual histologic features of gynecomastia characterized by fibromyxoid or collagenous stroma and duct hyperplasia.**(Figure 4)**

- **Type 1 (florid type):** Characterized by a large number of ducts with irregular lumens and three or more epithelial layers surrounded by loose connective tissue that is well demarcated from the surrounding stroma. This type is most common in immature 'young' gynecomastia of <4 months duration.
- **Type 2 (fibrous type):** Exhibits only a slight increase in the number of ducts with greater stromal fibrosis, and is most common in mature 'older' gynecomastia of >1 year duration.
- **Type 3 (intermediate type):** Appears between 4 and 12 months, and is believed to represent the transition from florid to fibrous type.

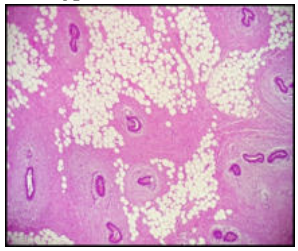

Figure 4 Section shows benign ducts embedded in stroma (40x HxE)

Management and Prognosis

Overall, gynecomastia is a benign condition and is usually self-limited. Over time, fibrotic tissue replaces symptomatic proliferation of glandular tissue and tenderness resolves. If the appropriate work-up does not reveal considerable underlying pathology, reassurance and periodic follow-up are recommended. Causative medications should be withdrawn or the underlying causative medical conditions (e.g. hyperthyroidism) should be addressed. Most cases of pubertal gynecomastia usually resolve in less than a year. Gynecomastia has a favorable prognosis but if it persists and is associated with pain or psychological distress and if the patient wishes to pursue treatment, pharmacological and surgical options are available. Psycological concern is generally to rule out breast cancer and cosmetic correction. Breast cancer is adequately addressed by following the appropriate diagnostic evaluation. Pharmacotherapy is likely beneficial if implemented early before fibrous tissue replaces glandular tissue, whereas surgery can be performed at any time.

Surgical Correction; Surgery is the standard treatment for gynecomastia. [11] The most commonly used technique is subcutaneous mastectomy that involves the direct resection of the glandular tissue using a periareolar or transareolar approach with or without associated liposuction. Liposuction alone may be sufficient if breast enlargement is purely due to excess fatty tissue without substantial glandular hypertrophy. Skin resection is needed for more advanced cases. In general, surgical treatment produces good cosmesis and is well tolerated.

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