Imaging in gynecomastia

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Abstract

Background. Gynecomastia (GM) is the benign proliferation of glandular tissue of the male breast. It is a common condition, which may occur physiologically and shows three age peaks during a male's lifespan: infancy, puberty, and senescence. An underlying pathology may be revealed in 45–50% of adult men with GM, such as aggravating medications, systemic diseases, obesity, endocrinopathies or malignancy.

Objective. To discuss the role of imaging in the evaluation of GM and its contribution to therapeutic decision-making.

Materials/Methods. The current literature was reviewed through the PubMed, Scopus, and CENTRAL electronic databases to identify the best available evidence concerning imaging modalities in patients with GM.

Results. Most male breast lesions can be diagnosed on clinical grounds; however, in certain cases, when physical examination is inconclusive, imaging may be helpful.

Discussion. The main purpose of evaluating a patient with GM is to establish the diagnosis and differentiate true GM from pseudogynecomastia, exclude breast cancer, and detect the possible cause. GM is seen in mammography as a subareolar opacity and three mammographic patterns of GM are described: nodular, dendritic, and diffuse, corresponding to florid GM of early onset, fibrous persistent GM, and GM due to exogenous estrogen administration, respectively. In ultrasound, florid GM is depicted as a disk-shaped, hypoechoic area underlying the areola, whereas echogenicity of the lesions increases as fibrosis develops. Data on the use of MRI in the evaluation of the male breast and GM are still limited. Imaging findings can be classified according to the BIRADS (Breast Imaging Reporting and Data System) regarding their malignant potential.

Conclusion. Both mammography and US are sensitive and specific to diagnose GM and distinguish it from breast cancer. When clinical findings are suggestive of malignancy or imaging findings are inconclusive, a histological confirmation should be sought.

Keywords: Gynecomastia, pseudogynecomastia, breast cancer, ultrasound, mammography, MRI.

1. Introduction

Gynecomastia (GM) is a benign proliferation of glandular tissue of the male breast. It is a common condition as it affects one-third to two-thirds of the male population. It can be unilateral or, most commonly, bilateral, and often asymmetrical (Braunstein, 2007; Narula & Carlson, 2007; Mieritz et al., 2017). It must be differentiated from pseudogynecomastia (lipomastia), which refers to an excess of fat deposition without glandular proliferation. GM can be either the result of a physiological process ("physiological GM"), or a sign of an underlying endocrine or systematic disease ("pathological GM") (Narula & Carlson, 2014; Swerdloff & Ng, 2019; Braunstein & Anawalt, 2021a).

Physiological GM shows three age peaks during a male's lifespan **(Figure 1)** (Braunstein, 1993). The first peak occurs in the neonatal period, affecting 60–90% of neonates, due to the transplacental transfer of maternal estrogens (Nachtigall, 1965; Braunstein, 1993). Neonatal GM is usually regressing spontaneously two to three weeks after delivery, but it may persist or recur three to six months after birth, during the mini-puberty, due to a transient activation of the hypothalamic–pituitary–gonadal axis (HPG) (Nachtigall, 1965; McKiernan & Hull, 1981; Jayasinghe et al., 2010). However, it does not persist after the first year of life (Schmidt, 2002). The second peak is observed in puberty with a prevalence of 22–69%, reaching the highest incidence during mid-puberty (Moore et al., 1984; Biro et al., 1990; Braunstein, 1993; Kumanov et al., 2007; Mieritz et al., 2015). It is caused by a transient imbalance in the free androgen-to-free estrogen ratio caused by the earlier rise of serum estradiol (E_2) compared with serum androgen concentrations (Moore et al., 1984; Biro et al., 1990). Pubertal GM is characterized by gradual enlargement, usually not greater than 4 cm in diameter and generally regresses within 1–2 years; it may persist in up to 10% of affected adolescents till adulthood (Nydick et al., 1961; Ma & Geffner 2008). The third peak occurs in middle-aged and elderly men with an incidence of 30–65% (Nuttall, 1979; Niewoehner & Nuttal, 1984; Georgiades et al., 1994). It results either from increased peripheral aromatase activity, secondary to the increase in total body fat, elevated luteinizing hormone (LH) concentrations and a decrease in serum testosterone (T) concentrations associated with male aging or by an underlying pathology (45–50% of adult men with GM), such as medication, systemic diseases, obesity or endocrinopathies (Nuttall, 1979; Niewoehner & Nuttal, 1984; Georgiades et al., 1994; Mieritz et al., 2017; Swerdloff & Ng, 2019).

GM is usually asymptomatic and discovered incidentally during a physical examination, especially in adults, as a firm mass of at least 5 mm in diameter located concentrically beneath the nipple-areolar complex. However, in the early phase, it may be presented with breast tenderness and pain, especially in adolescents and cases of rapid progression (Braunstein, 2007; Gikas & Mokbel, 2007; Narula & Carlson, 2007).

Although GM is usually benign, it may cause physical and psychological stress and fear for breast cancer; in rare cases, it may be associated with severe underlying endocrine or systemic disease (Narula & Carlson 2014; Kipling et al., 2014; Rew et al., 2015). Thus, it is of clinical importance to clarify the etiology of GM. Imaging plays a pivotal role in this effort with mammography and ultrasound being the most used and magnetic resonance imaging (MRI) being employed in some special cases. This review aims to discuss the pathophysiology, evaluation, and management of GM, highlighting the prominent role of imaging in diagnostic and therapeutic decision-making.

2. Anatomy - Histology

The male breast is located craniocaudally between the second and sixth ribs and transversely between the mid-axillary line and the sternum. The male mammary tissue contains receptors for both estrogens and androgens (Sasano et al., 1996); its growth and differentiation depend on hormonal stimulatory or inhibitory effects in a way similar to that observed in women (Kanhai et al., 2000). However, the striking hormonal differences observed in the hormonal milieu between men and women during puberty result in certain histo-anatomical differences.

In women, estrogen secretion prevails over androgens evoking ductal proliferation, branching, and growth. Following ovulation, progesterone secretion ensues, resulting in stromal development and terminal ductal-lobular unit (TDLU) maturation. In contrast, the preponderance of T secretion in men favors involution of the ducts, while TDLU maturation is absent (Önder et al., 2020). As a result, the male breast, compared with the female may be considered as a rudimentary structure consisting mainly of subcutaneous adipose tissue, vestigial ductal tissue devoid of mammary lobules, and a small nipple-areolar complex. In addition, in the male breast, Cooper ligaments are absent, whereas pectoral muscles are more prominent (Omene & Tiersten, 2010) **(Figure 2)**.

Histopathologically, GM is characterized by ductal epithelial hyperplasia and increased stromal and periductal connective tissue; however, in contrast to the female breast, TDLU remains vestigial. (Nicolis et al., 1971; Braunstein, 2007; Narula & Carlson, 2007; Kornegooret al., 2012; Lapid et al., 2014). GM is classified in characteristic histologic patterns: florid, and fibrous:

- In the **florid pattern**, which corresponds to recent-onset GM (duration <6 months), hyperplasia of the ductal epithelium, infiltration of the periductal tissue with inflammatory cells and surrounding edema are observed. This is the stage of symptomatic GM, which is frequently accompanied by pain and tenderness and might be reversible if the underlying cause is withdrawn.
- On the other hand, the **fibrous pattern** may be observed after persistence of 6–12 months, when the glandular elements regress, and stromal fibrosis predominates. This quiescent stage is characterized by dilated ducts with periductal fibrosis, stromal hyalinization and increased subareolar fat; it is considered irreversible due to chronic changes and fibrosis (Nicolis, 1971; Narula & Carslon, 2007).

3. Pathophysiology

An imbalance of androgens-to-estrogens action on breast tissue is considered the principal mechanism that leads to GM, as male breast tissue has estrogen and androgen receptors. Estrogens stimulate, and androgens inhibit breast tissue proliferation (Sasano, 1996; Marthur & Braunstein 1997; Narula & Carlson, 2014). Thus, GM may result from androgen deficiency, deficient androgen

action, estrogen excess, increased estrogen action or a combination of them. Androgen deficiency and estrogen excess may be either absolute, when androgens are below and estrogens above the reference concentrations for young males, respectively, or relative, when both hormones are within the reference range, but the androgen-to-estrogen ratio is abnormal (Narula & Carlson, 2014).

Deficient androgen action in breast tissue might result from either decreased serum concentrations of androgens due to primary or secondary T deficiency or absent or defective androgen receptors. On the other hand, increased peripheral aromatization of androgens to estrogens by the enzyme aromatase may contribute to GM as it leads to estrogen excess. Moreover, estrogen excess may result from increased estrogen production by the testis or the adrenals, resulting from displacement from sex hormone-binding globulin (SHBG), or exogenous administration. In addition to the direct contribution to GM, increased estrogen concentrations enhance the production of SHBG, leading to a reduction in free T and, therefore, further decrease of the free androgen-to-free estrogen ratio. Finally, estrogens inhibit LH secretion by the pituitary through the negative feedback mechanism, resulting in secondary T deficiency (Braunstein, 1993; Narula & Carlson, 2014).

The local hormonal milieu in breast tissue plays a key role in the development of GM. Evidence suggests the contribution of local androgen deficiency or estrogen excess, locally decreased or increased number or activity of androgen or estrogen receptors, and locally increased action of aromatase in mammary tissue in the development of GM (Sasano et al., 1996; Narula & Carlson, 2014).

Additionally, progesterone, leptin, insulin-like growth factors-1 and -2 (IGF-1 and -2) and prolactin may constitute a different mechanism than secondary hypogonadism that may lead to GM (Sansone et al., 2017). Male breast tissue expresses LH, human chorionic gonadotrophin (hCG), prolactin, progesterone, IGF-1 and IGF-2 receptors; however, the role of the hormones and growth factors above mentioned in the pathogenesis of GM has not been clarified (Carslon et al., 2004; Narula & Carlson, 2014).

4. Causes

The etiology of GM ranges from a physiological process (neonatal, pubertal, aging) to pathological causes **(Table 1)**. In 10% of adults, more than one causative factor may coexist, while, in approximately 25–60% of cases, GM remains idiopathic as no causative factor can be identified (Mieritz et al., 2017; Narula & Carlson, 2014; Braunstein, 1993).

T deficiency, either primary or secondary, is one of the most prevalent causes. Primary testicular failure can be caused by chromosomal disorders, such as Klinefelter syndrome, radiation,

chemotherapy, alcohol abuse, trauma, infections, tumors, enzymatic defects and 46,XY dysgenetic syndromes. It is characterized by a compensatory increase of LH secretion, which stimulates aromatase activity leading to increased conversion of T to E_2, which, in turn, inhibits 17,20-lyase and 17-hydroxylase activities favoring further E_2 production (Forest et al., 1979; Braunstein, 1993; Marthur & Braunstein, 1997). On the other hand, in secondary hypogonadism, the continued peripheral aromatization of adrenal androgenic precursors to estrogens is responsible for an increase of estrogen-to-androgen ratio (Braunstein, 1993; Sansone et al., 2017). Cranial irradiation, chemotherapy, infections, drugs, trauma, pituitary surgery, adenomas including prolactinomas, systematic diseases, obesity and genetic defects, such as Kallmann syndrome and idiopathic hypogonadotropic syndrome, are causes of secondary androgen deficiency. In addition, renal insufficiency and medications for its management can cause both primary and secondary hypogonadism and hyperprolactinemia, and hence GM (Hou et al., 1985; Handelsman & Dong, 1993; Naroula & Carlson, 2014).

Androgen insensitivity syndromes can be either complete or partial and presented with a phenotype ranging from a female to an undervirilized male with a variable degree of GM (Hellman, 2012; Hughes et al., 2012; Hiort, 2013). Kennedy disease, a neurodegenerative disease, is associated with partial insensitivity of androgen receptor due to an increased number of CAG (polyglutamine) repeats in the androgen receptor gene (Dejager et al., 2002). Both conditions are characterized by increased T, E_2 and LH concentrations.

Approximately 40% of patients with hyperthyroidism may develop transient GM due to the increase of SHBG caused by thyroid hormones, which is bound more avidly to T compared with estrogens, leading to decreased free T and increased E_2 concentrations. Additionally, the consequent induction of LH pituitary secretion and the potential direct stimulation of aromatase activity by thyroid hormones increase further the E_2-to-free T ratio (Kidd et al., 1979; Ford et al., 1992; Krassas et al., 2010; Sansone et al., 2017). Similarly, liver disease may cause GM due to high SHBG concentrations and increased hepatic aromatization of T and the antiandrogenic effects of some medication used for its management (Narula, 2007).

Estrogen-producing tumors, either testicular or non-testicular, are another cause of GN. Leydig-cell tumors secrete both T and E_2, while estrogen excess is enhanced due to increased peripheral conversion of T to E_2 (Bercovici et al., 1984, Pozza et al., 2019). Approximately 10% of these tumors are malignant. Sertoli cell tumors have also been associated with GM through an increased aromatase activity (Gourgari et al., 2012) that occur as part of Peutz-Jeghers syndrome and Carney complex (Young et al., 1995; Stratakis et al., 2001). Germ cell tumors, testicular and non-testicular, especially those that secrete hCG, can lead to GM through induction of T and E_2 production by Leydig cells and triggering of aromatase activity (Hassan et al., 2008). In a similar mechanism, ectopic hCG production by non-trophoblastic tumors, such as large-cell carcinoma of the lung, gastric carcinoma, or renal cell carcinoma, may cause GM in rare cases (Ali, 2017; Sansone et al., 2017). Adrenocortical

neoplasms, especially carcinomas, have also been reported to cause rapidly progressive GM via direct secretion of estrogens or conversion of overproducing androgen precursors into estrogens in peripheral tissues (Zayed et al., 1994; Kidd et al., 2011; LaFemina & Brennan, 2012; Narula & Carlson, 2014).

A common cause of GM, characterized by high T and E_2 but low LH concentrations, are anabolic-androgenic steroids (AAS); the mechanism is the peripheral aromatization of excessive androgens to estrogens (Sjöqvist et al., 2008; Basaria, 2010; Nieschlag & Vorona, 2015).

GM due to unintentional exposure to estrogens (occupational or due to contact or intercourse with women using transdermal gel or vaginally administrated estrogen replacement therapy) has been reported (Di Raimondo et al., 1980). Despite the inconsistent literature, environmental exposure to endocrine-disrupting chemicals with estrogenic and anti-androgenic properties and dietary estrogen intake have been indicated as a possible cause of GM (Finkelstein, 1988; Henley et al., 2007; Messina, 2010).

Obesity often results in GM, mainly because of estrogen excess, the consequent secondary hypogonadism and increased peripheral androgen aromatization in the abundant adipose tissue (Matsumoto & Bremner, 2011; Sansone, 2017). In a relative mechanism, the rare syndrome of familiar aromatase excess, caused by overexpression of the aromatase gene, is characterized by secondary hypogonadism, and accelerated early linear growth and prepubertal GM (Stratakis et al., 1998; Ma & Geffner, 2008; Fukami, 2014). The re-feeding syndrome is a possible cause of GM due to the re-activation of the HPG axis, which was suppressed during starvation or severe illness; the mechanism is similar to what happened during early puberty (Sattin et al., 1984).

Finally, several drugs can cause GM via estrogen-like properties, disturbance of sex steroid production, metabolism, and action, increase in prolactin secretion, or multifactorial mechanisms (Deepinder & Braunstein, 2012; Krause, 2012). Despite the proven causative role of some drugs (e.g., estrogens, GnRH-agonists and antagonists and anti-androgens), the association of other medications with GM is mostly speculative according to a recent meta-analysis **(Table 2)** (Deepinder & Braunstein, 2012; Krause, 2012). GM caused by androgen ablation therapy for prostate cancer and antiviral therapy (especially protease inhibitors) used for human immunodeficiency virus infection (HIV) are the most representative examples of drug-induced GM; in the latter, the etiology is multifactorial (Krause, 2012; Narula, 2014; Sansone, 2017).

5. Evaluation

The main purpose of evaluating a patient with GM is to establish the diagnosis and differentiate true GM from pseudogynecomastia, exclude breast cancer, and detect the possible cause using history, physical examination, and laboratory tests.

The diagnosis of GM is based on physical examination with the patient in a sitting or lying supine position. It is felt as a palpable, symmetric, firm, subareolar disk of tissue while the examiner squeezes the breast between the thumb and forefinger (Braunstein, 1993; Braunstein, 2007). Physical examination is completed with the palpation of axillary regions with the patient in the supine position with his hands resting behind his head (Braunstein & Anawalt, 2021a; Kanakis et al., 2019).

In most cases, GM is easily differentiated from pseudogynecomastia or breast cancer. Pseudogynecomastia is characterized by the absence of the palpable firm disk of tissue mentioned above, whereas breast cancer is felt as a non-tender, unilateral, eccentric, hard and often fixed to underlying tissue mass. In some cases, skin changes, nipple retraction or bleeding, and axillary lymphadenopathy may be present (Braunstein, 2007; Kanakis et al., 2019).

Once the diagnosis has been established, the identification of the cause follows. A detailed history and a careful physical examination are enough to reveal the cause of GM in most cases, while laboratory investigation is mainly required for proving a clinical suspicion or unclear cases (Braunstein, 2007; Ali, 2017; Kanakis et al., 2019).

● 5.1. History

Information regarding the timing, onset and duration of GM and the presence of breast pain or sensitivity is essential to determine whether a further evaluation is needed. Consequently, a detailed medical history about medication use, androgenic anabolic steroids, herbal supplements, alcohol, illicit drugs, such as morphine, cannabis, or amphetamines, occupational or accidental exposure to estrogens and systemic symptoms pointing to an underlying general disease (e.g., thyroid, liver or kidney disease) should be obtained following by andrological history to detect signs and symptoms of hypogonadism (Ma & Geffner, 2008; Narula, 2014; Kanakis et al., 2019) **(Table 2)**.

● 5.2. Physical examination

Physical examination includes general, breast and genital examination. General physical examination should be focused on anthropometric measurements to detect obesity, the degree of virilization and secondary sexual development, eunuchoid appearance and signs of thyroid, chronic kidney, or liver disease. Breast examination might reveal the presence of pain or tenderness implying a recently

developed GM, unilateral or bilateral position and evaluate the size of GM according to Tanner staging (Kanakis et al., 2019) or Simon's classification (Simon et al., 1973), the latter usually applied in the field of surgical treatment of gynecomastia **(Table 3)**. On genital examination, pubic hair, penile size, scrotal development, testicular size, and consistency should be evaluated, and the presence of varicocele or testicular masses should be explored (Ma & Geffner, 2008; Kanakis et al., 2019).

5. 5.3. Laboratory evaluation

Hormonal and biochemical. Laboratory examination is usually not needed in pubertal GM, as most cases concern transient GM. Exception are cases of rapid progression and enlargement >4 cm in diameter, which may be associated with a serious underlying condition, or persistence for more than one year or after the age of 17 years (Machoney, 1990; Ali, 2017; Taylor, 2020). Laboratory examination is usually not needed for the long-standing asymptomatic GM, which is incidentally noted on physical examination of old men with a normal history and physical examination. On the contrary, it is necessary in cases of a suspected underlying pathological condition from history and physical examination, in cases of recent-onset and rapidly progressive or tender/painful breast enlargement and whenever it appears in an age different than the normally expected trimodal age distribution (e.g., prepubertal boys) **(Table 4)** (Ma & Geffner, 2008; Ali, 2017; Braunstein & Anawalt, 2021a).

First-line laboratory tests include measurement of T, follicular-stimulating hormone (FSH), LH and prolactin (PRL) to detect the presence of primary or secondary hypogonadism, thyroid-stimulating hormone (TSH) to evaluate thyroid function and basic liver and renal function tests to exclude their dysfunction. Measurements of E_2 are needed to evaluate the T-to-E_2 ratio and exclude estrogen secreting tumors, while hCG and fetoprotein-α (AFP) should be obtained to exclude testicular or extragonadal tumors, especially in cases of recent-onset or painful GM. Further laboratory tests, including measurement of androgen precursors [e.g., dehydroepiandrosterone sulfate (DHEA-S), Δ_4-androstenedione (Δ_4A)], cortisol and karyotype, could be carried out in selected cases according to clinical suspicion (Braunstein, 2007; Ma & Geffner, 2008; Narula, 2014; Kanakis et al., 2019).

6. Imaging

Most male breast lesions, including GM, are benign and can be diagnosed on clinical grounds; however, in certain cases, when physical examination is inconclusive, imaging may be helpful (Rahmani et al., 2011).

- **6.1. Mammography findings**

The normal findings of mammography in men include a homogenously radiolucent fat layer, which is transversed by sparse strand-like subareolar densities, representing residual ductal branches and overlaps a prominent radio-opaque pectoral muscle (Muñoz Carrasco et al., 2013) **(Figure 3A)**.

GM is seen in mammography as a sub-areolar opacity, which may vary in shape according to the underlying histological pattern. Three mammographic patterns of GM are described: nodular, dendritic, and diffuse (Appelbaum et al., 1999).

- **Nodular GM** is the most common (72%) and corresponds to the florid histological phase and normally obtains a fan-shaped form, which radiates from the nipple and gradually blends into the surrounding fat tissue. Occasionally, this density may be opaque resembling a sphere **(Figure 4A)**.
- **Dendritic GM** is less frequent (18%) and corresponds to the fibrous histological phase and is depicted as a flame-shaped opacity with projections (dendrites) that irradiate and penetrate the surrounding adipose tissue, which may extend to the upper-outer quadrant of the breast **(Figure 4B)**.
- **Diffuse GM** is the less common form (~10%) and is typically observed in the enlarged breasts of transgender females under exogenous estrogen administration for gender affirming hormonal therapy. In this case, the breast resembles a dense female breast in mammography; however, marked by heterogeneity and the absence of Cooper ligaments.

Modern digital acquisition systems have enhanced the spatial resolution of mammography to roughly 0.1 mm/pixel, increasing both sensitivity and specificity in detecting breast lesions. However, due to the small volume of the male breast and the prominence of the pectoral muscle, mammography can be technically more demanding compared with women, occasionally being inconvenient for the patient (Lawson et al., 2019; Önder et al., 2020).

- **6.2. Ultrasound findings**

Ultrasound (US) is a handy imaging modality, which has encompassed technological advancements in terms of image quality and resolution. It is readily available in outpatient clinics as an adjunct to clinical evaluation. In B-mode (grey-scale imaging), the male breast predominantly consists of a mesh of isoechoic lobules corresponding to the subcutaneous adipose tissue, whereas the nipple-areolar complex is depicted as a small triangular hypoechoic area which measures up to 8 mm **(Figure 5A)** (Chau et al., 2016; Muñoz Carrasco et al., 2013).

The US features of GM depend on its histological form: florid GM is depicted as a disk-shaped, hypoechoic area underlying the areola, which may extend into the breast acquiring a triangular

shape **(Figure 5B)**. On the other hand, fibrous GM expands in the surrounding tissues adapting a "spider leg" appearance and the echogenicity of the lesions increases as fibrosis develops **(Figure 5C)** (Draghi et al., 2011; Önder et al., 2020). In color-Doppler US imaging, the florid form is commonly associated with increased vascularity, representing an inflammatory process of recent onset. In contrast, the vascularity in the fibrous form, which represents a chronic process, is reduced and often absent, since the inflammation has ceased and replaced by fibrosis. The diffuse form of GM, is characterized by increased breast volume and echogenicity, features similar to the US findings of dense female breast that must be evaluated along with the medical history and clinical findings (Draghi et al., 2011; Muñoz Carrasco et al., 2013).

- **6.3. MRI findings**

Data on the use of MRI in the evaluation of the male breast and GM are still limited. It may be helpful in certain cases of invasive tumors to evaluate the possible involvement of the chest wall, or in the setting of oncologic surveillance to assess post-operative residual disease, and chemotherapy response. Data are not conclusive whether the imaging features and diagnostic criteria used in MRI of female patients can be accurately used for male patients as well. (Lawson et al., 2019; Shin et al., 2019).

7. Differential diagnosis

The main target of the evaluation of male breast enlargement is to distinguish GM from other resembling entities, which may be clinically non-important, such as pseudogynecomastia, or life-threatening, such as breast cancer. (Braunstein, 2007; Kanakis et al., 2019). A distinct clinical entity that may be included in the differential diagnosis is gynecothelia, a rare clinical condition describing the isolated enlargement of nipples, which usually has different etiologies from GM (Jaiswal & Subbarao, 2012).

- **7.1. Pseudogynecomastia**

Pseudo-GM, like GM, can be unilateral or bilateral and both entities are encountered more frequently among overweight and obese men (Niewoehner & Nuttal, 1984; Rahmani et al., 2011). In such a case, differential diagnosis is important since lipomastia normally warrants no further workup to reveal an underlying pathology. Moreover, this information may be helpful in designing the most appropriate treatment plan. Florid and painful GM of recent onset may be alleviated with medical treatment, while chronic GM requires surgical excision of glandular tissue. On the other hand, lipomastia may be treated with lifestyle modifications that aim at the reduction of fat body mass or liposuction in cases of persistent local fat accumulation (Rahmani et al., 2011).

In most cases, the clinical distinction between GM and pseudogynecomastia is evident, and there is no need to perform imaging (Chau et al., 2016). Imaging is reserved for men with severe obesity or

in cases with fibrosis/hyalinization, where physical examination may not be informative. In mammography, pseudogynecomastia is characterized by breast enlargement with a predominance of radiolucent fat and minimal retro-areolar opacity **(Figure 3B)**. US may demonstrate the increased thickness of the subcutaneous adipose tissue as a hypogenic area comparted by irregular echogenic striae (Muñoz Carrasco et al., 2010).

- **7.2. Male breast cancer**

Male breast cancer (MBC) accounts for about 1% of all breast cancers and less than 1% of all cancers in male patients; nevertheless, it is still the second most frequent breast pathology after GM (Brinton et al., 2010). Moreover, due to delayed diagnosis, MBC is detected at a more advanced stage compared with women, with the percentage of axillary lymphadenopathy reaching 50% at the time of diagnosis (Omene & Tiersten, 2010; Önder et al., 2020). Therefore, it is important to identify a suspicious lesion and timely intervene or else avoid unnecessary procedures when imaging findings are consistent with benign conditions such as gynecomastia.

Clinical suspicion of MBC may already be set by physical examination as described in the relevant section. Besides, GM and MBC do not share the same risk factors nor the same age distribution. The prevalence of GM is higher during infancy, puberty and senescence and is associated mainly with hormonal disorders and drug adverse effects (Braunstein & Anawalt, 2021b). On the other hand, MBC is mainly a disease of advanced age (>60 years) related to genetic factors (BRCA2 mutation, Klinefelter syndrome) and a history of irradiation (Fentiman et al., 2006). Current evidence does not support the notion that GM is a premalignant condition (Kanakis et al., 2018).

Nevertheless, there may be cases where clinical differentiation between GM and MBC can be challenging. The vast majority (~85%) of MBC are ductal infiltrating carcinomas, which, due to decreased ductal branching, are in close proximity to nipple-areolar complex, hampering thus the distinction of early breast cancer from GM (Fentiman et al., 2006). On the other hand, unilateral or asymmetric GM may mimic MBC, especially if the fibrous form has developed, which is firm and painless to palpation (Volpe et al., 1999). Besides, studies have shown that physical breast examination despite of being adequately sensitive for the detection of MBC, it is not equally specific (Muñoz Carrasco et al., 2010).

1. **7.2.1. Mammography**

In mammography, MBC appears usually as retro-areolar eccentric opacity with ill-defined or irregular margins (spiculated or lobulated) **(Figure 6A)**. Accompanying signs of malignancy are thickening or ulceration of the skin and retraction of the nipple (Appelbaum et al., 1999; Muñoz Carrasco et al., 2013). The presence of microcalcifications is less frequent (30%), and, when present, they tend to be more disperse compared with female breast cancer, probably due to the involution of ducts (Chau et al., 2016).

The mammographic findings can be classified for their malignant potential according to the BIRADS (Breast Imaging Reporting and Data System) introduced by the American College of Radiology (ACR) for women (Orel et al., 1999). When no irregular findings are present, the examination is classified as BIRADS 1, while examinations consistent with benign entities, such as GM and pseudogynecomastia are considered as BIRADS 2. Categories BIRADS 4 and 5 are similarly to the female breast suspicious of MBC. BIRADS 3, which includes well-defined masses, has a higher positive predictive value (PPV) for malignancy compared with women (17.4 vs. 2.0 %) and should be monitored closely (Muñoz Carrasco et al., 2010; Varas et al., 2002). This finding may be explained by the fact that benign proliferative changes, such as fibroadenomas, are rarely encountered in men; therefore, imaging findings, such as circumscribed or cystic masses or punctuate calcifications that might be considered benign in women, should raise suspicion in male patients (Omene & Tiersten, 2010).

2. **7.2.2. Ultrasound**

US examination may further elucidate the nature of a breast lesion. Findings supporting malignancy are nonparallel orientation (taller-than-wide), combined with hypogenicity, the presence of calcifications and irregular borders (Muñoz Carrasco et al., 2010). US may also be valuable in the evaluation of nipple-mass relationship and the detection of suspicious axillary lymph nodes **(Figure 6B)**. The examination is concluded with Color-doppler mode, which in the case of MBC may reveal increased and chaotic intra-lesion vascularization. Another US technique that may assist in the characterization of a lesion is sonoelastography, however still no robust data exist regarding the evaluation of its findings in the male breast (Önder et al., 2020).

3. **7.2.3. Fine needle aspiration cytology and needle core biopsy**

When clinical findings are suggestive of malignancy or imaging findings are inconclusive, a histological confirmation should be sought (Kanakis et al., 2019). Due to the anatomic characteristics of the male breast, CT guidance is unnecessary and impractical; therefore, US guidance is the preferred method. Regarding the optimal technique for evaluation, fine needle aspiration cytology (FNAC) has been shown to be inaccurate because sampling is often ‘‘inadequate’’ (up to 62.5%), while GM may occasionally be associated with findings such as micropapillary architecture and cytologic atypia, which can be confused with MBC (Martin-Bates et al., 1990; Muñoz Carrasco et al., 2010; Rahmani et al., 2011). On the other hand, needle core biopsy (FNB) has a diagnostic accuracy that reaches 100% and should be preferred for the evaluation of lumps of the male breast (Janes et al., 2006; Muñoz Carrasco et al., 2010).

- **7.3. Imaging algorithm**

Currently, there is no established protocol for the use of imaging in the evaluation of breast symptoms in the male patient. In the most recent clinical practice guidelines for the evaluation and management of GM published by the European Academy of Andrology (EAA), it is suggested that

breast imaging may be employed, where the clinical examination is equivocal (Kanakis et al., 2019). It is also stated that, in most cases, especially in young patients younger than 18-year-old, the clinical picture of GM is informative, and there is no need to perform further imaging. In the case that the clinical findings are suspicious for a malignant lesion, the diagnostic approach should opt directly to perform an FNB (Hines et al., 2007). EAA guidelines place a high value on deferring otherwise healthy men from unnecessary imaging studies, while avoiding delays in the histological diagnosis of a suspicious lesion.

ACR in the most recent appropriateness criteria for the evaluation of the symptomatic male breast states that imaging is not usually required for men with the typical clinical findings of GM or pseudo-gynecomastia (Mainiero et al., 2015). Similarly to EAA, imaging is suggested to be performed when the clinical picture is equivocal, while an age limit of 25 years old is set for the selection of the first-line imaging modality. For those <25-year-old, US is recommended as first-line imaging followed by mammography if the results of US are inconclusive or suspicious for malignancy, whereas for those ≥25-year-old the evaluation should start with mammography and be completed with US, if the findings of mammography are inconclusive. When clinical findings are suspicious for malignancy, the ACR recommends that imaging should precede biopsy. In this case, mammography is proposed as the first step regardless of the patient's age. FNB is the final step for a definite diagnosis when imaging modalities are suspicious for malignancy (BIRADS ≥3) or indeterminate.

ACR recommendations are based on data which demonstrate that clinical breast examination though very sensitive in the identification of malignancy, lacks the required specificity. Thus, further imaging studies may obviate unnecessary biopsies (Muñoz Carrasco et al., 2010). Mammography is highly sensitive and specific for the detection of malignancy (92–100 and 90–95%, respectively) and has been shown to be more sensitive compared with US; therefore, it is suggested as the first-line imaging modality in case of suspicious clinical findings (Evans et al., 2001; Muñoz Carrasco et al., 2010; Patterson et al., 2006). On the other hand, US is more convenient, and some studies have shown superior specificity; thus, it is preferred in patients with a low likelihood for malignancy (e.g., age <25-year-old) (Fentiman et al., 2006). US can also be helpful if mammography does not localize a palpable lesion, such as lipomas, which are obscured by subcutaneous fat (Appelbaum et al., 1999). In any case, both modalities could complement one another in equivocal lesions.

The imaging procedure, either US or mammography, is recommended to be performed bilaterally even if symptoms are unilateral, to assess for symmetry and detect possible asymptomatic pathology on the contralateral breast. Follow-up of benign lesions (BIRADS 1 and 2) for oncological purposes is not justified, as the risk of developing malignancy is <1%. In contrast, follow-up is suggested for men with previous mastectomy for MBC as they remain at risk for the disease in the contralateral breast (Muñoz Carrasco et al., 2010). Based on the above recommendations we provide an algorithm for imaging of the male breast **(Figure 7)**.

8. Management

The management of GM depends on etiology, duration, severity, tenderness and the emotional discomfort that it causes; it involves watchful waiting, medical treatment and surgical correction.

● 8.1. Watchful waiting

Most patients with GM require no treatment other than removing the underlying cause, such as endocrinopathy, systematic disease or drug, providing that it will take place early in the course of breast enlargement, before the development of fibrous tissue, usually during 6–12 months from the onset. Thus, a periodic follow-up is appropriate in these cases. Since most cases of pubertal and many of adult GM resolve spontaneously within a year from the onset, a follow-up at 3–6 months intervals is the preferable treatment option (Braunstein, 2007; Ma & Geffner, 2008; Narula, 2014; Kanakis et al., 2019; Swerdlof, 2019).

● 8.2. Medical treatment

Androgens, anti-estrogens, and aromatase inhibitors have been used. It must be pointed out that medical treatment may be effective only during the early active phase of GM; long-standing breast enlargement is unlikely to respond due to the development of fibrotic tissue (Braunstein, 2007; Gikas & Mokbel, 2007; Kanakis et al., 2019).

T treatment is justified only in hypogonadism cases, while in eugonadal has the opposite effect due to the aromatization to estrogens (Braunstein & Anawalt, 2021c; Kanakis et al., 2019). Although, according to uncontrolled studies, percutaneous administration of dihydrotestosterone (DHT) is effective, it cannot be recommended due to insufficient data (Kuhn et al., 1983; Kanakis et al., 2019).

Selective estrogen-receptor modulators (SERMs), such as tamoxifen (TMX), raloxifene, and clomiphene citrate, have been used in the treatment of GM, with the first being the most studied (Gikas & Mokbel, 2007; Ma & Geffner, 2008; Lawrence et al., 2014). Despite TMX's antiestrogenic action, its effectiveness in the treatment of GM is limited; only 10% of pubertal GM cases regress completely while the rest show a partial regression (low-quality data) (Derman et al., 2003; James et al., 2012; Lapid et al., 2013; Kanakis et al., 2019). Nevertheless, TMX results in the resolution of symptoms in approximately 80–90% of painful GM cases; although it is not licensed for this indication, it could be applied in severe, painful, recently appeared GM (Braunstein, 2007; Kahn et al., 2004; Johnson & Murad, 2009). Albeit the low-quality data for idiopathic GM, TMX has been used prophylactically in patients with prostate cancer to prevent GM caused by anti-androgenic therapy (Perdona et al., 2005; Boccardo et al., 2005; Braunstein & Anawalt, 2021c; Kanakis et al., 2019).

Evidence of aromatase inhibitors' (AI) effectiveness in the regression of GM is lacking (Plourde et al., 2004; Braunstein, 2007). For this reason, their use in the management of GM is not suggested. However, some data indicate their effectiveness in selected patients with increased aromatization of androgens to estrogens, as in familial aromatase excess syndrome, patients with Peutz–Jeghers syndrome or Carney complex with aromatase excess due to testicular tumors and in GM caused by T or hCG administration. On the contrary, current literature supports the prophylactic use of AI in patients with prostate cancer, which will be treated with anti-androgenic factors (Boccardo et al., 2005; Kanakis et al., 2019).

- **8.3. Radiotherapy**

Radiotherapy has been used efficiently to prevent androgen deprivation-induced GM in patients with prostate cancer (Widmark et al., 2003; Dicker, 2003; Tyrrell et al., 2004; Perdona, 2005). Considering the increased risk of breast cancer related to radiation and its lower efficacy, it considered an alternative to TMX in patients being at increased risk of developing adverse effects with the latter, such as venous thromboembolism (Braunstein & Anawalt, 2021c).

- **8.4. Surgical therapy**

Surgical correction is the treatment of choice in long-standing, persistent and embarrassing GM as it offers immediate correction. It must follow an appropriate period of close observation after the onset and removal of a possible underline cause (Kanakis et al., 2019; Swerdloff & Ng, 2019). Especially in the case of persistent pubertal GM, the period of observation may be extended to more than two years, until puberty has been completed, to avoid the possibility of relapse (Swerdloff & Ng, 2019). The surgical approach usually involves nipple-sparing subcutaneous mastectomy via a periareolar or trans-areolar incision (Cordova & Moschella, 2008; Johnson & Murad, 2009; Kanakis et al., 2019). Liposuction alone may be sufficient in mild GM, and skin resection may be needed in more advanced cases (Cordova & Moschella, 2008; Tashkandi et al., 2004; Kanakis et al., 2019). In general, surgery results in good cosmetic results with few complications, including numbness of the nipple and adherence of the areola to the pectoral muscle; minimally invasive surgical procedures, available in recent years, may result in even fewer complications and rapid recovery (Johnson & Murad, 2009; Swerdloff & Ng, 2019).

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Figures

Figure 1. Clinical images characteristic of the three age peaks of gynecomastia (GM): A) physiologic, bilateral GM of puberty in a 15-year-old boy; B) unilateral right GM in a 46-year-old man associated with systematic ketoconazole administration (Dr. G. Kanakis, personal archive) and C) gynecomastia of senescence associated with the administration of dutasteride for benign prostate hypertrophy (used with permission from Kanakis et. al., 2019.

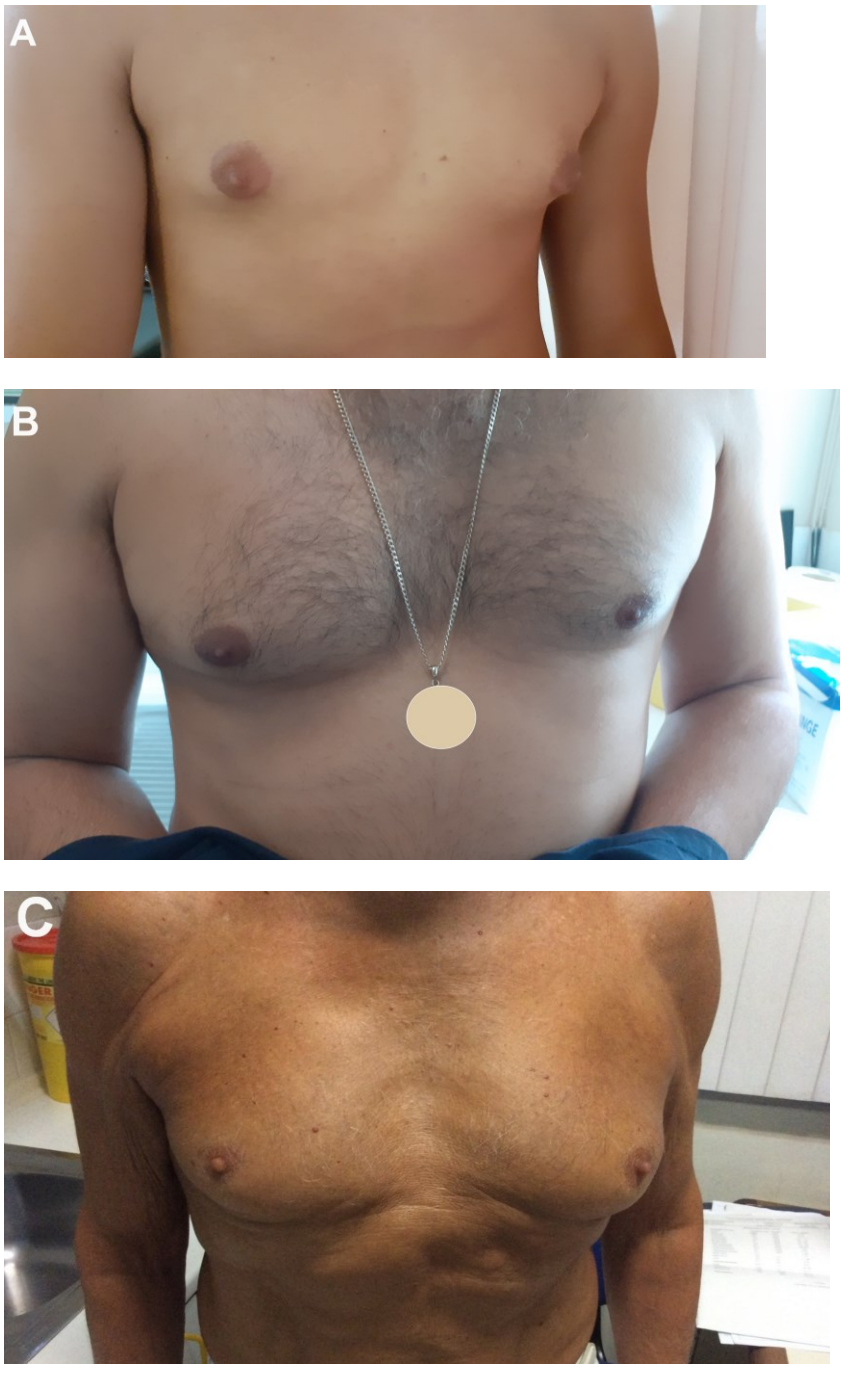


Figure 2. Anatomy of the normal male breast in comparison to the female breast and gynecomastia. The mature female breast is characterized by avid adipose and stromal tissue, and a prominent ductal network that ends in terminal mammary lobules. The whole structure is supported by Cooper ligaments. In contrast, the male breast consists mainly of adipose tissue, vestigial ductal network, devoid of mammary lobules, and a small nipple-areolar complex. In addition, in the male breast Cooper ligaments are absent, whereas pectoral muscle is more prominent. In gynecomastia, ductal and stromal proliferation are seen, retaining characteristics, such as the absence of mammary lobules and Cooper ligaments (https://plasticsurgerykey.com/gynecomastia-6).

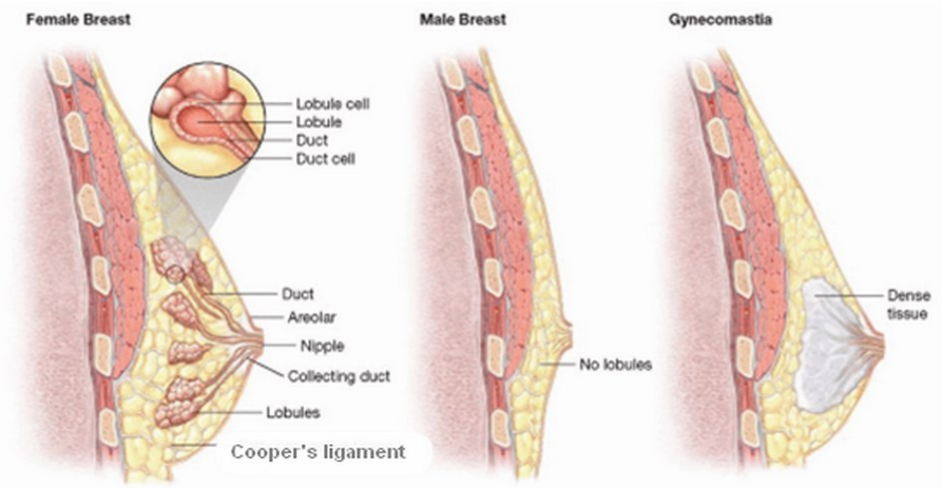


Figure 3. A. Mammography of normal male breast, mediolateral oblique view: the subcutaneous fat (SCF) lies on the prominent pectoral muscle (PM) and strand-like subareolar densities correspond to residual ducts B. Mammography demonstrating lipomastia, cranio-caudal view. Note the enlargement of the subcutaneous fat compared to the pectoral muscle and the absence of subareolar opacity (Panel A. adopted from https://radiologyassistant.nl; Panel B. archive of the Athens Naval and Veteran Affairs Hospital).

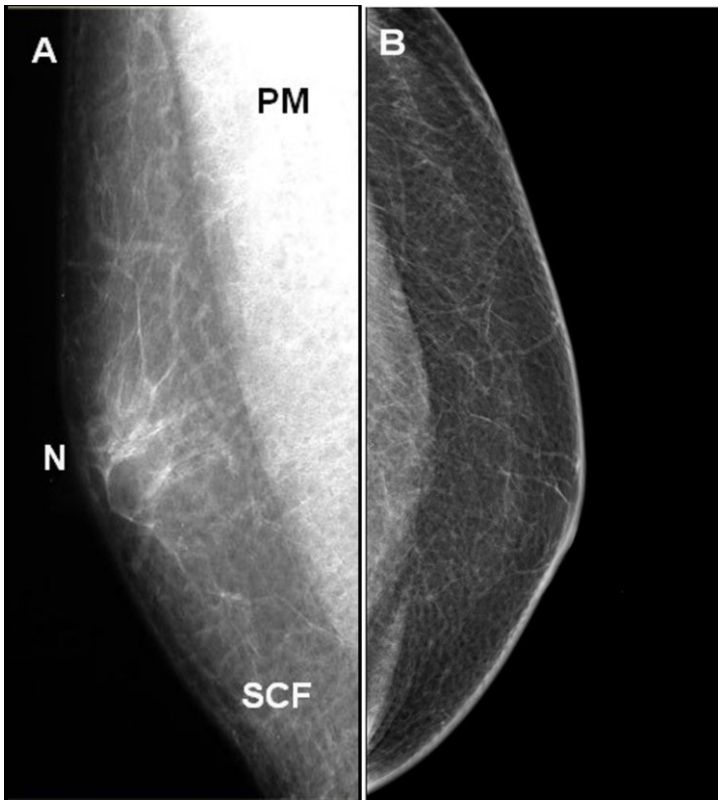


Figure 4. Mammography of the male breast (cranio-caudal view), showing: A) Nodular gynecomastia and B) Fibrous gynecomastia (archive of the Athens Naval and Veteran Affairs Hospital).

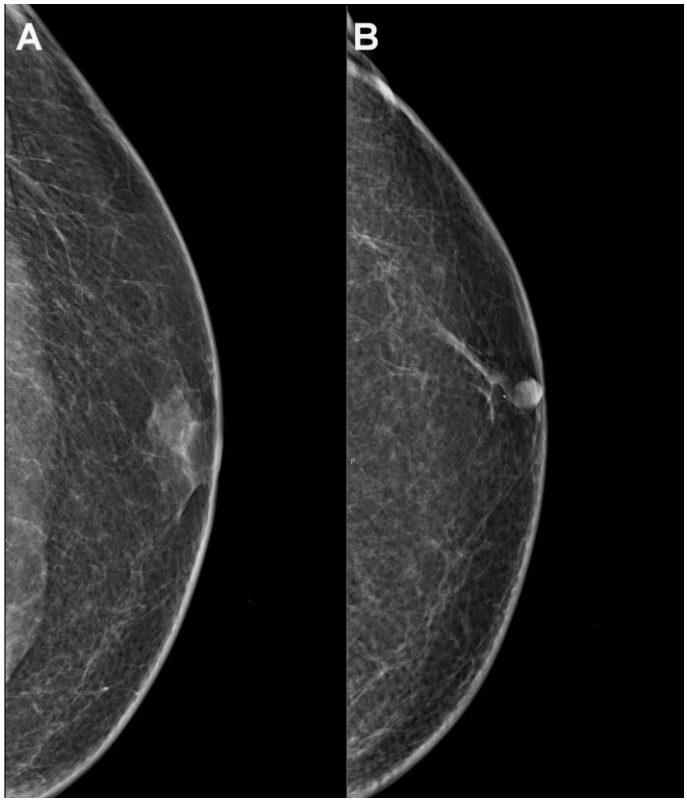


Figure 5. Ultrasound images of the male breast using high frequency (12 MHz), linear probe. Panel (A) shows a normal breast, while panel (B) nodular GM and panel (C) fibrous GM. (Dr. G. Kanakis, personal archive).

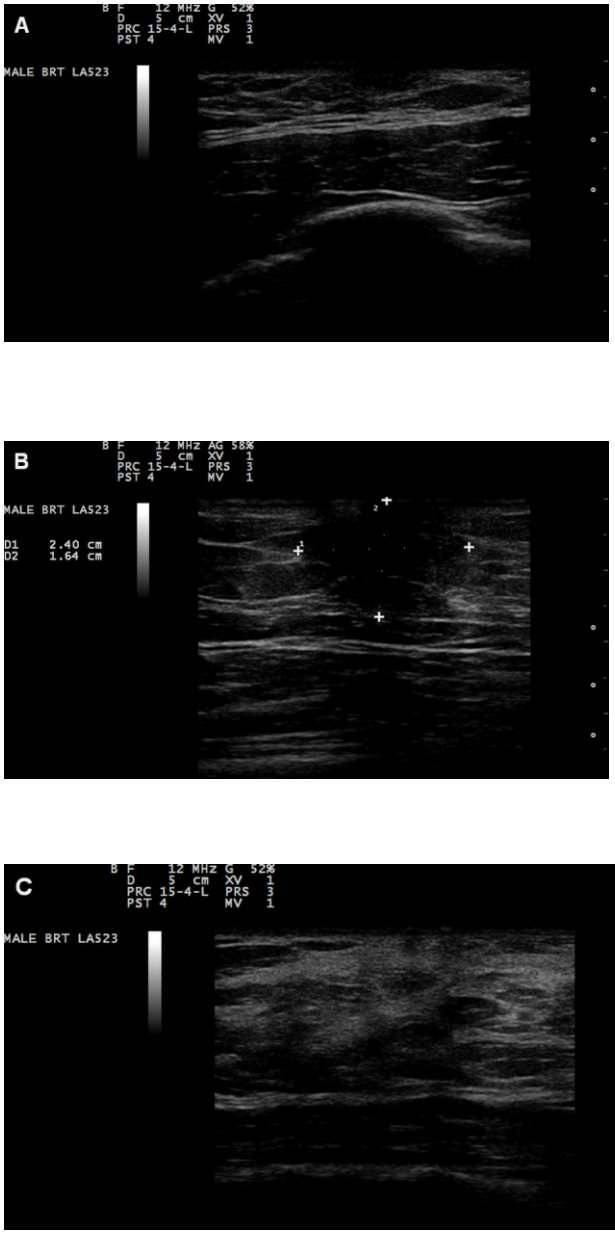


Figure 6. Invasive ductal carcinoma in a male patient. Note the eccentric localization of the lesion with respect to the nipple in mammography (A) and the lobulated margins observed in the ultrasound picture (B) (https://radiologyassistant.nl).

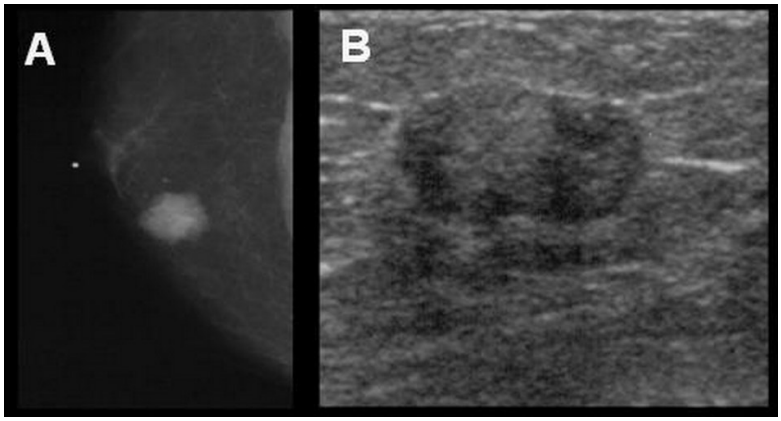
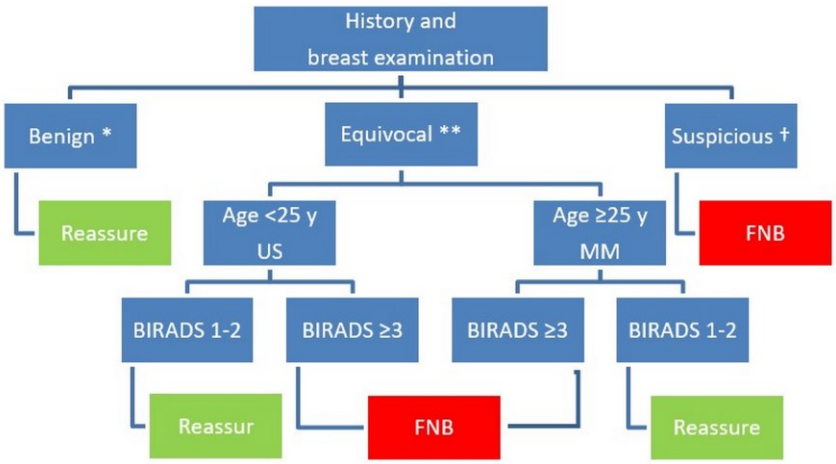


Figure 7. Proposed algorithm for imaging of the male breast. History and breast examination should be considered benign (*) in young patients <18-year-old with gynecomastia or when pseudogynecomastia is unequivocally diagnosed. Breast lumps associated with signs of malignancy should be treated as suspicious (†), while all other lesions, especially when presenting unilaterally in adult men, might be considered equivocal (**).

FNB: needle core biopsy; BIRADS: Breast Imaging Reporting and Data System; US: ultrasound; MM: mammography.



Tables

Table 1. Causes of gynecomastia.

Physiological
Neonatal
Pubertal
Aging
Pathological
Drugs
Hypogonadism
Primary
Secondary
Androgen receptor defects
Hyperthyroidism
Obesity
Renal failure and dialysis
Hepatic cirrhosis
Refeeding gynecomastia
Tumors
Testicular (from germ-cells, Leydig cells, Sertoli cells)
Ectopic production of hCG
Adrenocortical
Enzymatic defects of testosterone production
Aromatase excess syndrome
Occupational and environmental exposure to estrogens
Idiopathic

Table 2. Drugs associated with gynecomastia.

A	B	C
Anti-androgens	**Anti-androgens**	**Anti-androgens**
Flutamide	Eplerenone	Lavender oil
Bicalutamide	Ketoconazole	**Antibiotics**
Finasteride	**Antiulcer drugs**	Isoniazid
Dutasteride	Cimetidine	Metronidazole
Spironolactone	Ranitidine	**Cancer chemotherapeutics**
Hormones	Proton pump inhibitors	Imatinib
Estrogens	**Psychoactive drugs**	Methotrexate
Clomiphene citrate	Haloperidol	Alkylating agents
GnRH agonists	Phenothiazines	**Psychoactive drugs**
Others	Atypical antipsychotics	Diazepam
Metoclopramide	SSRIs (Fluoxetine)	**Cardiovascular drugs**
	Drugs of abuse	Calcium channel blockers
	Alcohol	Amiodarone
	Hormones	ACE inhibitors
	hCG	Digoxin
	Others	**Drugs of abuse**
	HAAT	Amphetamines
		Heroin
		Marijuana
		Drugs of abuse
		Methadone
		Hormones
		Anabolic steroids
		Growth hormone
		Others

	Phenytoin
	Penicillamine
	Theophylline

Causal role in gynecomastia by the level of evidence. A: proved causal role; B: highly probable role; and C: significant association could not be established (includes categories C and D of the original publication). Modified from: Krause (2012). ACE: angiotensin-converting enzyme; HAART: highly active anti-retroviral therapy; hCG: human chorionic gonadotropin; SSRIs: selective serotonin-receptor inhibitors.

Table 3.

A. Tanner classification of breast development.

Stage I	No breast tissue
Stage II	Development of retroareolar bud with an elevation of breast and papilla and enlargement or areola
Stage III	Further enlargement of breast and areola
Stage IV	Areola and papilla form a secondary mound above the breast tissue
Stage V	Recession of papilla and projection of papilla only

B. Simon's classification for the surgical correction of gynecomastia

Group 1	minor visible breast enlargement without skin redundancy.
Group 2	moderate breast enlargement without (2A) or with (2B) skin redundancy.
Group 3	gross breast enlargement with skin redundancy that simulates a pendulous female breast.

Table 4. Gynecomastia needing further evaluation.

● Non-tender, unilateral, eccentric, hard mass (for exclusion of breast cancer)
● Appearance in an age different than the normally expected trimodal age distribution (e.g., prepubertal boys)
Puberty
● Rapid progression and enlargement >4 cm in diameter
● Persistence for more than one year or after the age of 17 years
Adults
● Recent-onset and rapidly progressive
● Tender / painful breast enlargement
● Clinical suspicion for underlying pathology