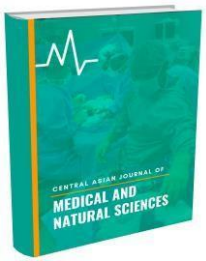

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Article

Comprehensive Study on Gynecomastia: Clinical Features, Pathophysiology, Morphologic, and Microscopic Features

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Abstract: Gynecomastia, a common benign enlargement of male breast tissue, results from an imbalance between estrogen and androgen levels. This study provides a comprehensive analysis of the clinical features, pathophysiology, morphological, and microscopic characteristics of gynecomastia. Clinically, the condition manifests as unilateral or bilateral breast enlargement, often accompanied by tenderness. The pathophysiological mechanisms involve hormonal fluctuations due to puberty, aging, medication use, liver or kidney dysfunction, and endocrine disorders. Morphologically, gynecomastia is characterized by fibroglandular tissue proliferation, with varying degrees of stromal and ductal changes. Microscopic examination reveals ductal hyperplasia, periductal fibrosis, and chronic inflammatory infiltration, distinguishing it from other breast pathologies. Diagnosis is primarily based on clinical assessment, supplemented by imaging and histopathological evaluation when necessary. Treatment options range from observation in transient cases to medical therapy or surgical intervention in persistent or severe cases. The study emphasizes the importance of early diagnosis to prevent unnecessary interventions and improve patient outcomes. Additionally, it highlights the need for further research to explore novel therapeutic approaches and the psychological impact of gynecomastia on affected individuals. Understanding the clinical, morphological, and microscopic features of gynecomastia enhances diagnostic accuracy and guides appropriate management strategies, ensuring better patient care.

Keywords: Gynecomastia, Hormonal Imbalance, Pathophysiology, Morphology, Microscopic Features, Male Breast Enlargement

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1. Introduction

Gynecomastia is a benign enlargement of male breast tissue. It may occur in one or both breasts, very frequently asymptomatically, and most commonly manifests during adolescent and old-age life. Gynecomastia, often meaning women-like breasts, is a clinical sign or disease with various meanings. Men can present with physiologic gynecomastia, pathologic gynecomastia, pseudogynecomastia, or can develop the shape of breasts secondary to obesity due to fast food, sedentarity and environmental pollution. Gynecomastia has a negative impact on male psychological conditions due to fear of breast carcinoma (mainly in old patients), rareness of the benign cases, feminization, reticence of the patients to describe their symptoms to their families or doctors [1], [2]. Since the enlargement can be asymmetric, pubertal boys may fear a tumor and even male patients tend to conceal it or remain under scrutiny due to their environment. This discretion brings the stigma easier to the disease. Hormone-induced gynecomastia can be benevolent with

observational follow-up but sometimes should be further evaluated [3]. Gynecomastia, one of the more prevailed conditions with its metaphysiological and pathologic causes increasing in today's and future's living conditions, needs to be defined, underlined as a clinical entity and evaluated with appropriate approaches. Consequently, in this essay, gynecomastia from 5 headings – as clinical features, pathophysiology, morphologic and/or IHC features, other causes of male breast enlargement, and conclusion – will be evaluated [4], [5].

2. Materials and Methods

2.1. Epidemiology of Gynecomastia

Gynecomastia, the benign proliferation of male breast tissue, is a common, albeit poorly recognized condition with a reported prevalence of 32%–65% in hospitalized males. The prevalence of gynecomastia was 32% in a study of 2057 general medicine male inpatients before endocrinological evaluation, and 65% in hospitalized males. This high prevalence raises awareness of the need for hospital staff, especially medical, surgical, and trauma surgeons who routinely evaluate males in the breast-bearing age group, to investigate the condition further. Despite its prevalence, only 17% of gynecomastia cases are recognized by physicians. A retrospective review demonstrated that only 27 of 1593 cases of breast cancer in men were considered gynecomastia, which suggested that poor recognition may have been a factor in the adverse outcomes observed [6].

Gynecomastia tends to occur at two different transitional phases in life, in adolescent males and in older males. A large study reported an overall gynecomastia rate of 22.8/1000 hospitalizations. In younger males aged 15–24, the admission rate was 11.3/1000 hospitalizations, and in older males, aged 65 years and above, it was 47.1/1000 hospitalizations. Developmental/pubertal gynecomastia is reported in 40–65% of adolescent males. Of adolescents needing admission to pediatric intensive care units, 91% of males had gynecomastia. The least number of male admissions due to gynecomastia were seen in the younger age group, consistent with the pattern of transient pubertal gynecomastia. The pathogenesis underlying the development of gynecomastia has been extensively researched. Gynecomastia is often related to an abnormal imbalance of the ratio of estrogens and androgens [7]. A normal physiological increase in estrogen can be seen in cirrhosis, and an increase in estrogens from androgens in testicular tumors. Cushing's syndrome, due to increased corticosteroids, also results in an increase in estrogen. Gynecomastia is one of the 25 most common endocrine symptoms/diseases seen in visiting outpatients. There was a relationship between gynecomastia and several other diseases. Psychopharmacological drugs, including neuroleptics, mood stabilizers, and selective serotonin reuptake inhibitors can induce gynecomastia symptoms. Out of all cases, 25–50% have an unknown cause, and these cases are principally referred to as idiopathic gynecomastia. Sociodemographic factors are noticeable causes [8]. Jobs that increase the likelihood of chemical exposure, such as paper mill work and the mining industry, also suggest a socioeconomic aspect of the causes. A study attempted to define gynecomastia by analyzing medical and lifestyle habits. Men with at least one hospitalization were considered as the case group, poor general health was used as a reference, and gynecomastia was defined as the presence of at least one hospital admission with a gynecomastia diagnosis. Participants with gynecomastia had lower social status. Moreover, men in the case group began smoking and consuming alcohol at a younger age than noninterred men. Early tobacco and alcohSol use significantly increased the risk of becoming hospitalized with gynecomastia. Gynecomastia is a condition that requires further examination, and the long-term condition is associated with higher social status and poor lifestyle habits, such as early smoking and consumption . The results have shown that physicians need to be aware of the symptoms and necessity to select an appropriate treatment regimen. In selected patients, gynecomastia can be an important objective in these particular groups of people with underlying health conditions and who consume

medication. It is common in males but less recognized compared to breast cancer. Virtually all populations showed a statistically significant increasing trend across all age ranges [9].

3. Results and Discussion

3.1 Anatomy and Physiology of the Male Breast

As a prelude to the discussion of gynecomastia, it is necessary to acquaint readers with the anatomy and physiology of the normal male breast. The glandular tissue of the breast is composed of lobules and ducts, woven in loose fibrous stroma that varies in quantity depending on the body mass index of the individual. The lobules DO NOT completely fill the stroma, especially in specimens of elderly patients with gynecomastia, in which the lobulates can be preserved as isolated nodular remainders localized in the central aspect of extensive adipose tissue. The bilateral edentation is connected by a small amount of soft adipose tissue, forming the pectoral fascia, that extends to the costal wall. Furthermore, this special study of the breast's overlap includes a series of (microphenistal): fistulous dilations in the lactiferous ducts that contain plugs of glandular tissue resulting from local prompting of apocrine hyperplasia, atrophy of the ductal epithelium, and accentuated sclerosis, with mild plasma cell infiltration. The growth of the breast is stimulated by estrogen and other growth factors. The effect of these hormones is bidirectional: ductolobular formation and prolongation, and regional adipose formation, as occurs in the subcutaneous tissue and interlobular stroma. Estrogen additionally promotes local response to repeatedly stimuli, with the ductolobular system always remaining ready for reactivation. The persistent imbalance between a large amount of fibroglandular component encased by its fibrous pseudocapsule and fat pressure can cause, in middle age or later in life, thoracic pain upon continuously compression [10].

Men, like women, are born with rudimentary nipples and extensively, undifferentiated mesenchyme ahead of the pectoral buds that are similar within both sexes until the fourth embryonic week. After this point, any sex-determining substance produced by the embryonic gonads will induce mullerian or wolffian duct development or stop the development of female or male internal genitalia. In females, the epithelial bud will proliferate as part of the mammary germinal system and will develop in the gland following the puberty estrogen peak. The unused mesenchyme surrounding the bud and indispensable for the supporting stroma will undergo involution. In the male breast, however, the testosterone burst during the first trimester of gestation halts the opposite intent to mullerian characteristic and, hence, gland ductal development [11]. Since adrenarche is physiologically more delayed than gonadarche, the first light from mammogenesis will come from that gland with exaggerated cipher of 5α-reductase receptors: the gonadal gland. It visibly enlarges first-as bilateral ocular hypertrophy- in early childhood, rendering a nubert real life representation of the female breast, although restrained in an attic of only fatty tissue outside quilted with areolar skin, without functional capability.

Later, testosterone triggered the desmientelisation of the residual fibroglandular rudiments, and the female-like appearance was irremediably lost by the age of 2, contrasting with the ongoing growth of the contralateral, prepubescent mons. In adulthood, they only remain as scarred rudimentary debris. The glutamatergic illumination of maleness contrasted with the somber murk of the half-slumbering unders and their content [12]. During straightforward extracts of the transgenic journey, Julius would become obsessed with the persistent lines of breast and transsexual operations intermingled within the various prescribed histologies. As far as the history of the world was considered, the main course of action in the library was to meticulously analyze all legal aspects of the "commodification-of-the-body well-fought arguments converging at severely blurred limits with echoes of the earliest aspirations for transcendence of sanguine and sensate constraints. On the other hand, fiction was not neglected, as it occasionally did provide him with new unexpected better conceptualizations of the persons he was

supposed to help. It was assumed that the most significant figures could only be those whose endeavours and downfall matched the somber Vestiges of a fallen breast.

3.2 Clinical Presentation of Gynecomastia

Gynecomastia is the ectopic proliferation of breast tissue in men, commonly as a consequence of increased estrogen levels relative to androgen action [13]. Patients may report a slow evolution of a firm subareolar mass with or without complaint of pain. Breast swelling, tenderness, and risk of painful complications, such as hematoma, lipomatosis or pseudoangiomatous stromal hyperplasia are common. These peculiarities are related to the pathophysiology and the growth of the lesions, which involves the formation of fibrous stroma, edema and the activation of inflammatory response [14]. The former is, in turn, dependent upon the balance of paracrine interactions among various cell types expressed in the breast. Commonly, patients recall smaller and firm breasts. However, there is a high variety in the set of clinical features reported in the anamneses, so, swelling and tenderness can be liberally mentioned. So are the risks and complications. Symptoms also can be poorly reported, as can be hurriedly mentioned ([15]. In some cases they are simply not expressive about them in the history of the disease. Thus, there is a bias in the set of registered anamneses. This general behaviour is responsible for the relatively poor evidentiary support concerning the duration and severity of the complaints, mostly coming from small series, ecological studies, personal impressions and casual registers. The psychological aspects and how it impact the patient's well being through the increase in the anxiety levels, and deterioration of the self-esteem of the individuals are frequently cited in persistent gynecomastias. The complaints related may be difficult to verbalize during the patient interview, or there might a varying degree of angust "per se" that the patient does not report to the health professional. Hence, as a rule, gynecomastia patients are more easily received hit in the physical examination of the thorax. These one should also encompass the evaluation of the lateral wall, of the areolar region, and a bimanual maneuver aiming to detect use of ectasia [16].

3.3 Diagnostic Evaluation of Gynecomastia

Gynecomastia is defined as benign enlargement of the male breast as a result of the growth of fibroglandular tissues. The diagnostic evaluation should focus on a thorough history, associated signs and symptoms, the use of medications, and the recency and duration of breast enlargement. Physical examination is always the initial diagnostic evaluation and includes the general appearance, body habitus, and other features. Additionally, determination is made about the contribution of fat and breast tissue to enlargement. Laboratory workup includes routine tests such as evaluation of the liver function, kidney function, sex hormone binding globulin, free and total testosterone, follicle-stimulating hormone, luteinizing hormone, estradiol, thyroid function tests, prolactin, and growth hormone. Specific hormone assays need to be individually evaluated. Patients with known liver disease or alcoholism may present with gynecomastia due to decreased metabolism of estrogen; in these cases an elevated estradiol level confirms the diagnosis. In certain diseases such as end stage renal disease, hematoma can result in overproduction of estrogen precursors. A lower estradiol to testosterone ratio (less than 10) indicates that the testes or adrenals are the sources of the estrogen [17], [18].

Gynecomastia is a frequent clinical condition. However, published information about its prevalence is scarce. Gynecomastia should be regarded as a symptom of an underlying disease, and its cause must be determined. Literature is limited concerning the patient's history and physical examination. Most articles on gynecomastia are case reports, surgical techniques for gynecomastia, and also epidemiologic and forensic issues. Although gynecomastia is seen in the male population at any age, antidepressant-induced gynecomastia is mostly prevalent in the pediatric and adolescent age groups during puberty to postpubertal period [19]. Evaluation is always recommended in the pediatric adolescent group, including not only hormonal assay but radiologic study as well. It is

important not to misinterpret pseudogynecomastia as true gynecomastia. Before medical treatment for gynecomastia, the physician should evaluate whether the patient has a genetic predisposition to breast cancer. This will be helpful for forensic issues of the concomitant use of anabolic steroids and gynecomastia. Atypical cases are frequently problematic. In these cases, the intensity of gynecomastia also plays a significant role. Gynecomastia is becoming an increasingly discussed issue in the daily clinical practice of plastic surgery, endocrinology, and oncology. It is important not to overlook an associated disease. Additionally, the concomitant use of a drug necessitates fuller evaluation [20].

3.3.1 History and Physical Examination

A comprehensive medical history should be obtained and a thorough physical examination should be performed. Many patients with gynecomastia may have a physiologic or familial etiology, whereas some may have an underlying pathologic condition that requires further evaluation. Medications, recreational drug use, possible exposure to environmental toxins, and numerous underlying conditions should be elicited. Attention should be paid to prior physiologic events and regression to eliminate certain drugs, particularly marijuana and anabolic steroids. Many causes of gynecomastia are associated with comorbid conditions. Additionally, a family history of gynecomastia, breast or testicular benign or malignant disease, or heritable conditions should be elicited. A drug, family, or other etiology may eliminate the need for surgical intervention. If a physician request letter is sent to a patient prior, a patient may provide laboratory results or other important tests which may be helpful [21].

Breast enlargement in men has many potential etiologies. The presence of mass or pain is concerning for neoplasm or infection. Gynecomastia beyond adolescence is much less likely to regress, and in the elderly it is likely pathologic. The onset and duration of enlargement, and accompanying symptoms should be inquired. Breast cancer in the male occurs most often in men over 60. Palpation of the breast tissue should be performed. It should be noted if the tissue is: strictly glandular or fatty, feels nodular or discoid, is bilaterally symmetric, fixed to the chest wall or skin, tender, warm, or erythematous. Discharge from the nipple should be noted and tested. Any nipple retraction, ulceration, or eruptions should be noted [22]. If lymphadenopathy is suspected, examination should include assessment for supraclavicular or infraclavicular adenopathy. All findings from the breast examination and surrounding tissues (pertinent skin change, chest or axillary nodes) should be noted. Composite data from the history and physical examination will define whether the gynecomastia is physiologic or pathologic. Observation is a critical aspect for evaluating the severity and duration of disease [23], [24].

3.3.2 Laboratory Investigations

Gynecomastia is a benign glandular enlargement of the male breast, caused by a proliferation of ductal, stromal, and/or periductal connective tissues. It is commonly seen in neonates, pubertal boys, and aging men but the central core of knowledge does never progress beyond simple clinical features. For most other patients, it serves as an excellent initial guide to etiology. Laboratory studies are less useful than one might think, as a small number of glandular enlargement will be reflected in abnormality, even when pathologic. Moreover, a focus on basal levels neglects the importance of how patients' tissues respond to provocative stimuli. These normative data show wide variations in the range of normality and suggest clinical investigation is restricted to atypical or severe instances. It is not possible to draw any broader or firmer conclusions than those above [25]. Still, the boy with asymmetric, painful pubertal gynecomastia in one breast only who is gaining weight very rapidly should be examined again! Gynecomastia may be a common phenomenon of little concern but the male breast is still open to the full gamut of medical and surgical pathology seen in the female breast. Thus a spectrum of disease may confront the physician. The goal of a successful outcome is to provide a useful picture of what needs to be done for whom, initially focusing on clinical and imaging evaluation [26]. Subsequent

articles will investigate the medical treatment of gynecomastia with the higher stage or histologically atypical and may require a biopsy. A small number of patients will have benign neoplasms. Broadly, the lesions will be those found in the female breast, but never carcinoma. In males, gynecomastia appears to be the only pathologic growth of the ductal system, reflecting the constrained secretory embryology. Hederos et al. found 38% of excisional biopsy showed male breast cancer. Majeski found just 0.77% of 6443 gynecomastia excisions had cancer, mostly in older men. The male breast does carry a lifetime risk and gynecomastia, like in females, is associated with an increased risk. Men with gynecomastia are hence twice as likely to develop a primary breast cancer. Combined with the demographic changes, surveillance and biopsy of suspicious lesions should therefore be part of the investigation and management of gynecomastia [27].

3.3.4 Imaging Studies

Gynecomastia is characterized by benign proliferation of the male glandular tissue and connective stroma, manifesting as a breast enlargement. It is a common finding with a prevalence of 40-50% among acquired breast abnormalities in males. Gynecomastia is commonly referred to as the male breast. In clinical practice, diagnosis of gynecomastia can be a challenge for radiologists. It can be incidental on imaging modalities performed for various reasons. Patients may present with mass, pain, or enlargement in the breast. Regardless of the reason, radiologists who display and interpret films should know the typical findings of gynecomastia and consider it while formulating their differential diagnosis. The knowledge of gynecomastia findings reduces the need for advanced breast imaging modalities such as diagnostic mammography or magnetic resonance imaging, as the diagnosis can be made directly from a typical finding. Since its underlying reason may have serious consequences such as breast cancer, incorrect many patients and their physicians request additional imaging studies or intervention [28,] [29].

Despite the benign nature and the signs that can easily be diagnosed with physical examination, the male breast can be the focus of anxiety and distaste for the patient. Attempting to improve the appearance of the breast with cosmetic methods is a rapidly growing area. Interestingly, the most obvious sign of the normal presence of a breast in the male gender is the presence of a breast in the female sex and it is possible to say that the signs on the outside have a great effect on gender perception. Since gynecomastia does not always present with a liver shape, understanding the imaging characteristics of this interesting entity is crucial for making an accurate diagnosis. For this reason, it is aimed to provide a review from the simplest to the most complicated knowledge levels of gynecomastia, which can be successfully treated with surgery. Because it is not a rare situation as well as with the increasing expectation of aesthetic appearance in men and an extensive examination together with the interpretation of various imaging methods in the differential diagnosis of the lesion in the breast [30].

The diagnosis of gynecomastia involves benign proliferation of the subareolar male breast tissue in the subareolar region, and the differentiation between malignant tumors is one of the most important tasks in the diagnostic approach. This benign breast pathology, frequently detected in male patients, is usually detected in patients aged 50-80, in patients using drugs affecting estrogenic and testosterone metabolism and in patients with chronic liver disease. A plethora of etiologies can be implicated in gynecomastia. The main category includes idiopathic, physiological (neonatal, puberty, and senescence related), endocrine (hypogonadism, hypergonadism, hyperprolactinemia, thyroid abnormalities), drug related, and pathology originating from the adrenal, renal, pulmonary, cardiovascular, neurological systems. Tumoral etiologies should be considered in the absence of one of these etiology findings [31].

3.4 Classification and Grading of Gynecomastia

Classification of gynecomastia is important in determining differential diagnosis and treatment plans. Gynecomastia is differentiated by its clinical form and is classified using

four grades. Grade I is defined as a minor lipomatous accumulation in male breast. Grade II type is characterized by an additional increase in fibroglandular tissue. Patients with grade III gynecomastia have a moderate fibroelastic increase. Marked skin excess is described in grade IV gynecomastia. It is important that the classification and grading of gynecomastia be done exactly and graded accurately, so that treatment planning is focused and standardized [32]. The development of common classification systems also contributes to standardizing the language between surgeons and healthcare professionals [33].

Determination of the classification of the disorder, which is seen around %55 in adult males, has drawn attention to its importance in the treatment process. Because it is important to differentiate between physiological and pathological gynecomastia in every classification, the classification made between non-physiological and physiological offers might change the pathway of the patients in diagnosis and treatment. Standardization of terms and concepts will both reveal research results and improve patient health. Classification of gynecomastia can affect the approach and also the frustration levels in patients [34]. For this reason, patients should be informed in every aspect, from the beginning of diagnosis to the end of treatment. In this sense, the classification of gynecomastia may affect the fall of the patients from the starting corners. Choosing the classification that is most appropriate for the patient will affect the success of the treatment and reduce the risk of the patient to fall [35], [36].

3.5 Pathophysiology of Gynecomastia

Gynecomastia usually occurs as a result of relative or absolute estrogen excess in comparison to androgens and androgen-to-estrogen imbalance. Such a hormonal profile may arise from diminished androgen production, increased local effects or increased systemic effect of estrogens, or other conditions leading to estrogen excess. The local role of estrogen in the development of gynecomastia is mainly accomplished by its receptor-dependent mechanism and growth factors involved in collagen fiber stimulation and myofibroblast proliferation. Estrogen and androgens are able to stimulate or inhibit some of the growth factors depending on their quantity and receptor type in the cell. In the case of androgen deficiency, gynecomastia can be developed by the increased local effect of estrogens and unopposed stimulatory activity on growth factors, despite normal or even lowered systemic levels of estrogen [37]. Growth factors showing positive immunohistochemical staining predominantly in the mammary stroma and their co-relation with sex steroid hormone receptor concentrations were further evaluated. Immunohistochemical expression of growth factors in both epithelial and stromal components of male gynecomastia as well as gynecomastia of male and female transgender individuals is shown with the minimal expression of ErbB2 and ErbB3 growth factor observed. Gynecomastia can also result from the reduced amount of growth factors produced because levels of receptor expression in gynecomastia did not differ from levels observed in controls. Anti-estrogens can both increase the receptor number in the cells and prevent the negative effect of estrogens on growth factor concentrations. Based on these findings, tamoxifen treatment can be called anti-estrogen not only because of its ERs blocking activity, but also because of its growth factor modulating influence [38]. Gynecomastia developed due to reduced androgen-to-estrogen ratio, reduction in the number of androgen receptor alpha and androgen receptor beta-containing cells followed by reduced stromal immunohistochemical expression of PDGF, its receptor alpha, and TGF-beta1 growth factor. This is also in accordance with the theory of increased breast sensitivity to estrogen in the development of gynecomastia [39].

The enlargement of male breasts can be the result of physiologic or pathologic conditions. Although these changes are usually benign and hormonal, a full evaluation is necessary because enlargement can be the presenting sign of a more serious disease [39]. The development of breast like tissue in males is commonly divided into 2 types: gynecomastia and pseudogynecomastia. Genuine gynecomastia is enlargement of the

male breast. It is considered physiologic if it develops in neonates, adolescent males, and elderly males [40]. Pubertal gynecomastia is due to physiologic changes in estrogen-testosterone levels and may be associated with nipple discharge due to local effects of these hormones. Elderly gynecomastia is a part of the aging process in males and jokes about "women with whiskers." Genuine gynecomastia has been associated with more than 20 conditions and numerous etiologies. Historically, the majority of patients had been staged into one of 3 groups: (1) Adolescents currently undergoing puberty, (2) Males taking pharmacologic agents, (3) Adult males with genuine gynecomastia. Pubertal gynecomastia is a consequence of the normal physiologic changes in pubertal hormones. Males produce estrogen via aromatase enzyme from cholesterol. In males the bulk of estrogen production is peripheral and is from the conversion of androgens to estradiol and estrone [40]. Gonadally, testosterone is converted to estradiol by the actions of the aromatase enzyme. Conversion of androstenedione to estrone is particularly important in postmenopausal women where this conversion in adipose tissue is the major source of estrogens. Testosterone is produced in both males and females from 2 sources: cholesterol in the adrenal gland and testosterone in the gonads. Testosterone production in males is almost exclusively from the testes. The development of breast tissue in neonates is due to the impact of maternal and placental estrogen as well as the impact of the 1st surge of maternal beta-hCG. Neonatal breast tissue formed either in-utero or due to this impact of maternal factors begins to regress in 2 to 3 weeks. Pseudogynecomastia is enlargement of the male breast-like tissue due to fat deposition. It most commonly occurs in obese males. Male breast enlargement is unusual in males. In the few published studies, between 25% and 65% of pubertal males are found to have gynecomastia and it usually self-resolves within 2 years [41]. There are also psychosocial effects reported in up to 35% of males and have told their fathers because of anxiety over developing breast tissue. Pseudo-gynecomastia is due to the conversion of peripheral androgens to estrogens by the actions of the aromatase enzyme. This process involves the conversion of testosterone to estradiol and 5 alpha-dihydrotestosterone to 5-alpha-androstene-17 beta-monoglucuronide. Pseudo gynecomastia is commonly associated with decreased sex hormone-binding globulin levels and lower testosterone to estrogen ratios while being obese. Because of this lower ratio, it is estimated that 87% of males who lose weight related to change in diet will experience regression of the breast tissue.

3.6 Endocrine Causes of Gynecomastia

There are a variety of endocrine causes of gynecomastia that the general public is not aware of. These include hyperthyroidism, hypogonadism, and tumors or other conditions that cause production of hormones or hormone-like substances that have an effect on the breast tissue. In the vast majority of cases, the etiology of gynecomastia and a review of the normal changes in breast tissue are performed, and the mammograms and breast ultrasonography for a normal male's breast tissue are obtained [42].

Gynecomastia is usually a physiologic condition that may regress over time. The etiology is often determined as a result of both thorough history and physical examination. If the gynecomastia involves breast tissue of 5 cm or more or if there is an atypical presentation, a hormonal and sometimes radiologic workup should be performed. Hormonal studies include total and free testosterone, estrogen, FSH, LH, and prolactin. These studies are frequently difficult to interpret and are based on age and Tanner staging in the adolescents and children. When there is a screening laboratory abnormality or if the etiology is in doubt, an endocrinologist should be consulted [43]. Medical treatments of gynecomastia are currently being studied, and antiestrogens may become the pharmacologic treatment of choice. Clinically, gynecomastia can be seen as an isolated finding in an otherwise healthy individual, or seen in a patient with a known medical or cancerous condition. In the pubertal male there are Tanner stages of breast development. When the endocrine pathway that mediates breast enlargement is reviewed, however, gynecomastia is enforced both as a marker of an underlying endocrine pathology and as a

potential direct contributor to future pathology [44]. There are many hormones circulating within the pubertal male and with increases in gonadal steroids, there is also an increase in estrogen and a subsequent increase in breast tissue. It is not surprising then that the most common time for pubertal gynecomastia is during the mid-teen years. In the older male, both testicular Leydig cell function decreases leading to androgen deficiencies and testosterone therapy for metabolic syndrome. This therapy can then increase the testosterone to estradiol ratio and subsequently increase the amount of breast tissue. Sports with high amounts of physical contact, and hence breast trauma, can lead to breast tissue formation. This was noted with Flo-Jo and the subsequent use of anabolic steroids in the males of that sport [45], [46].

3.7 Non-Endocrine Causes of Gynecomastia

When a man is described as having breast enlargement, known to some as a comedogenic glow, a search for the cause usually begins with an evaluation of his sex hormone balance and his peripheral hormone metabolism. This general approach is grounded in concepts such as that the breast is an androgen-dependent sex organ and that its development is mediated by an estrogen- and androgen-triggered process. It is true that the vast majority of cases of gynecomastia are due to an increase in the estrogen/androgen ratio in an individual. Estrogens, either endogenously produced or administered, can induce breast growth in the adult man [47]. Estrogens can be of testicular origin, though in the adult man much is derived from peripheral (and adrenal) conversion of androgens (in particular testosterone). As the spectrum of causes of breast enlargement is thought to be encompassed within this endocrine framework, it would seem that who has absolved the vast majority of cases. This would not be the case, however. The cause(s) of gynecomastia can be broadly classified into those from within this framework, endocrine and metabolic influences on breast growth, and those causes arising from outside this framework, nonendocrine or non-metabolic influences on breast growth [48]. Lists the wide spectrum of non-endocrine causes that can lead to the breast-tissue enlargement of gynecomastia.

The items within each of the four major headings in this list will be reviewed and some illustrative examples given. Some examples will involve a discussion of why something is considered a cause of gynecomastia as regards to breast growth, a task that, in some instances, is difficult. In general, the causes under these four major headings can be investigated by approaches even more straightforward than an understanding of peripheral androgen metabolism [49]. Many of either the listed pathological conditions produce substances that can promote the growth of breast tissue (predominantly fat and ductal and/or ductal-stromal tissue in the adult man). In other cases, the gynecomastia is a common presentation with the diagnosis. In all, cataloging and investigating diverse nonendocrine causes assists in the understanding and pursuit of comprehensive diagnostic evaluations [50].

3.8 Treatment Options for Gynecomastia

Gynecomastia is a common, benign enlargement of the male breast, usually secondary to glandular proliferation. Approximately 30% of males develop gynecomastia during their lifetime, associated with a peak period during adolescence. It may consist of a benign increase in the glandular breast tissue as part of the normal aging process or due to a variety of pathologic states, being further subdivided into physiological, pathological, and pseudogynecomastia. Gynecomastia can affect one or both breasts to varying degrees and may be due to an increase in glandular tissue or fat or a combination of both.

Gynecomastia can be a source of psychological and emotional distress for the affected male patient, regardless of its origin. However, it is important to preoperatively assess the patient's emotional status and his motivation for seeking a surgical solution and to provide all the necessary information regarding postoperative complications, especially concerning permanent or unfavorable scarring, to preclude subsequent dissatisfaction on

the part of the patient. Therapy includes conservative measures for mild cases or physiological gynecomastia, endocrinologic or chemotherapy for severe, symptomatic forms, while surgical excision represented the most common option in this series for moderate, non-resolving gynecomastia [51]. There is a wide range of surgical techniques for the management of gynecomastia depending on the type of gynecomastia, the preference of the surgeon, and the needed incision, where the most common intervention either gone through a sub-areolar resection or a circum-areolar resection [52].

3.8.1 Conservative Management

Management of gynecomastia ranges from no need for treatment in mild cases, symptomatic treatment in moderate cases, to therapeutic treatment in severe cases. General measures in mild grades are reassurance and periodic follow-up visits, lifestyle modification, weight reduction, alterations in drug regimens and anabolic agent withdrawal. Surgical treatment is indicated in patients with established fibrosis or adipous involution of the breast gland, cosmetic or psychological disturbances, and poor cosmetical outcome with medical therapy [53].

Gynecomastia must be clearly distinguished from other diseases with similar appearance, such as pseudogynecomastia and breast neoplasms, by means of medical history, clinical and laboratory examination, and mammography. Most cases of gynecomastia can be determined from clinical evaluation. As most cases are found to be idiopathic, routine clinical and laboratory examinations are usually sufficient to determine etiology. Mammography should be performed in older individuals, and surgical intervention should not precede this examination. Gynecomastia training involved the principal elements involving nipple, mammary gland, areola, chest hair, and color changes.

Gynecomastia is a benign breast epithelial proliferation or diffuse stromal growth relative to fat in males. It is a common benign cartilaginous disease in adolescent men and the elderly [54], [55].

3.8.2 Surgical Interventions

Surgical interventions may be considered in cases of gynecomastia requiring more definitive treatment. Indications for surgery may include painful or tender breasts with persistent symptoms, significant psychological distress and/or embarrassment associated with the condition, or if a patient has a strong preference for the surgical option. Various surgical techniques for the correction of gynecomastia have been devised, aimed at removing the glandular breast tissue. The most widely practised operative procedures are the excision of glandular tissue and liposuction. Both techniques might be combined to achieve the best results. The surgeon's experience and expertise in these operations are paramount in obtaining the desired results and in reducing risk of complications associated with these operations [56]. It is thus important that the treatment of gynecomastia be individualized because, as with any condition, techniques may vary in applicability, risk and outcome. A thorough physical examination of the patient is of paramount importance and helps in devising a surgical plan that best suits the individual patient. Hence, the management of patients with gynecomastia in the clinic setting commonly begins with a thorough physical examination and consultation. Pre-operative consultation and explanation of the problem, potential causes, the role of different options in the management and possible risks associated with these procedures is important. The risk of the condition recurring also needs to be addressed [57]. Long-term follow-up is an important part of the management of patients with gynecomastia. During postoperative care, complications such as blood collection, subcutaneous haematoma or seroma, superficial or deep infection pose an important risk and need to be closely monitored in the post-operative period. Early diagnosis and adequate management of complications are essential [58].

3.9 Complications and Prognosis of Gynecomastia

Gynecomastia is considered to be idiopathic in the vast majority of cases. The patient should be observed for reasons to suspect an endocrinologic or neoplastic etiology, and a treatment plan should not be instituted until an appropriate evaluation has been performed [59]. The great majority of cases that do not have a known cause presented as asymptomatic pubertal breast enlargements. Histologic examination of many such tissues generally reveals no intrinsic abnormalities, but in patients with gynecomastia, coarse periductal and interductal fibrosis may be seen as well as a notable increase in ductal epithelium and periductal stromal elements that extend out from the walls of the ducts and cross the fibrous tissue septa. Gynecomastia associated with known drug use usually persists as long as the patient is taking the medication but may also continue after cessation of the drug [59].

Being medical or surgical, the cosmetic correction of gynecomastia vastly increases the therapeutic costs. Hence the quali- and quantification of characteristics which may predict the evolution of breast enlargement in the pre-teen subject seem to be of particular interest in a preventive stance. Many gynecomastias regress spontaneously. The underlying metabolic disorders may induce distressing concomitant disease that will predomine in the preferred treatment [60]. Treatment is therefore more safe and efficient when applied early in the course of the gynaecomastia, i.e. from pre-puberty to beginning teenager. This is why early preventive measures concerning marked predispositions to puberty gynaecomastia may be warranted. Raloxifene caused a gynecomastia excess of 72%. In the tamoxifen group, 9 developed gynecomastia compared with 1 in the placebo group. There were four cases associated with drug therapy. Seven patients experienced gradual size reduction. At 3 year follow-up, 24 patients met the criteria for surgical treatment. There were no other significant different linear measures between the two groups, and the nipple to chest wall distance did not increase [61].

3.10 Morphologic Features of Gynecomastia

Pubertal gynecomastia is the most common form of breast tissue hypertrophy in males, often presenting as firm symmetric conical breast buds. However, breast tissue hypertrophy in males is not an uncommon disorder and various aspects of its morphologic features may become obscured over time. However, a thorough examination can identify changes in the proliferation of glandular elements, the deposition of fibrous tissue, or the composition of fat in the breast. Once recognized, the morphologic appearance of male breast tissue is useful in forming a differential diagnosis concerning benign versus life- or health-threatening pathologic conditions [62].

Gynecomastia is breast tissue overgrowth in males secondary to an imbalance in the production or activity of circulating sexual hormones. The macromorphology of breast tissue hypertrophy is influenced by both age- and hormone-related factors. In general terms, gynecomastic tissue changes can be separated into glandular proliferation, fibrous tissue changes, and changes in the fat composition. Examination of the morphologic features of gynecomastic tissue can yield information on the inciting cause. There are a number of morphologic presentations of male breast tissue hypertrophy including nodular, symmetrical, or diffuse presentations [63]. In addition, the presentation of male breast tissue hypertrophy is frequently asymmetric and can take more than twelve months to resolve. The significance of the morphologic features of male breast tissue is a bridge between the clinical presentation of gynecomastia and the botched pathology of the tissue, the recognition of which is essential for an accurate diagnosis and accurate classification [64].

3.11 Histopathological Findings in Gynecomastia

Histopathological examination of tissue remains the diagnostic reference standard for gynecomastia, irrespective of the radiologic findings. Gynecomastia with its wide spectrum of morphological presentations leads to a variety of histopathological results, even in the same specimen, so correct interpretation may be challenging. Knowledge of

both clinical data (duration, location, multifocality, symptoms) and histopathologic findings is imperative [65]. It is important for the histopathologist to be familiar with all the histological changes of gynecomastia, for an accurate and explicit histopathological report to be made, one that is informative and assists the clinician with patient management.

Gynecomastia demonstrates one of two phases of histological proliferative activity. The active evolving phase is a benign biphasic proliferation of epithelial and stromal component (Laimon et al., 2021). The ductal epithelial hyperplasia becomes prominent forming complex intraductal and interductal papillary processes with accompanying progressive increase in the fibroblastic cellularity and tissue edema. The hyperplastic ducts may appear normal sized or dilated. Stromal sclerosis or fibrosis are idealized processes. Periductal and interductal stromal oedema are common findings in active gynecomastia and this distinguishes it from involutional or idiopathic phase. The stroma in the latter is vastly more hyalinised and sclerotic and breast epithelia are fewer [66]. However, a direct progression from the active to the nodular phase without an intervening more fibrous stage may occur. Macrosopically the breast tissue may not display the typical appearances of the active phase but this does not nullify the active changes present in the sections taken. Half of all cases exhibit this type. Small sized, subareolar tissue fragments with outwardly attenuated surrounding fibrous tissue can compromise the diagnosis in such instances [67].

4. Conclusion

Gynecomastia is a common benign condition characterized by the enlargement of male breast tissue due to an imbalance between estrogen and androgen levels. This comprehensive study highlights the clinical features, underlying pathophysiology, and morphological and microscopic characteristics of gynecomastia. Clinically, the condition presents as unilateral or bilateral breast enlargement, often associated with tenderness. The pathophysiology involves hormonal imbalances caused by various factors, including puberty, aging, medication use, and systemic diseases. Morphological examination reveals fibroglandular proliferation, while microscopic analysis shows ductal hyperplasia, stromal fibrosis, and periductal inflammation. Understanding these aspects is essential for accurate diagnosis and differentiation from malignant breast conditions. Early recognition and appropriate management, whether through observation, medical therapy, or surgical intervention, can significantly improve patient outcomes. Further research is needed to explore novel therapeutic strategies and the long-term impact of gynecomastia on patients' quality of life.

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