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Incidence of Atypical Change and Risk of Breast Cancer in Patients with Gynecomastia

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Abstract

Background: Although it is generally accepted that gynecomastia poses no risk of male breast cancer (MBC), the incidence of atypical changes observed in gynecomastia and their effects on the risk of MBC has been investigated recently.

Objectives: Therefore, with follow-ups in our series, the present research was conducted to determine the incidence of atypia and its effect on breast cancer in gynecomastia cases.

Methods: A total of 151 breast tissues were surgically removed from 108 patients between the ages of 12-90. Atypia was investigated based on gynecomastia in the preparations sampled from these tissues.

Results: Around 22 simple hyperplasia, eight atypical ductal hyperplasia (ADH), and one ductal carcinoma in situ were found in 151 breast tissues. Breast cancer was not observed in any patients during the follow-up period. Atypical ductal hyperplasia was seen in younger patients compared to simple hyperplasia (P=0.021). No relationship was observed between lesion size and the incidence of atypia (P=0.538).

Conclusion: According to the findings of this study, ADH determined in cases with gynecomastia pose no risk of breast cancer in parallel with the current data in the literature. However, it is accepted that the presence of atypia based on gynecomastia needs to be investigated in series with a large number of cases.

Keywords: Atypical ductal hyperplasia, Gynecomastia, Male breast

1. Background

The adult male breast consists of a fibrous stroma and large channels embedded in adipose tissue. These channels are located under the areola-nipple complex. The channels contain a layer of myoepithelial cells and an overlying flat cubic epithelial layer. Lobule can be rarely encountered, and it is hardly seen. Moreover, male breast tissue is sensitive to hormonal influence like the female breast (1). Gynecomastia is originally defined as breast enlargement in men. The term gynecomastia (Greek; gyne-woman, mastos-breast) was first used by Galen to denote the increase in the amount of adipose tissue under the breast. It was later described as a diffuse or focal proliferation of glandular tissue in the male breast. Today, the histological definition is mostly the enlargement of the mammary glands, which can be accompanied by connective tissue increase, inflammatory cell infiltration, and proliferation, elongation, or branching of varying degrees. Histologically, the expansion is due to both glandular and stromal proliferation. It is known that there are active, inactive, and transition phases that correspond to different stages of gynecomastia (2). Gynecomastia is the most common type of male breast lesion, and its rate is in a wide prevalence range of 32-65%, varying according to series (3). Gynecomastia is generally seen as a part of normal physiological development in newborns (60-90%), adolescents (48-65%), and adults over 50. Physiological proliferation can be seen in the breast in male neonates due to the effect of maternal estrogen passing from the mother. Physiological gynecomastia can reach as high as 90% of all male neonates and disappear spontaneously within weeks. If gynecomastia continues after age 1, it creates a risk for puberty. Gynecomastia is common in adolescence and affects most boys. It can also occur in apparently normal adult males and those with diseases that directly or indirectly lead to high estrogen exposure (4). The clinical manifestations of gynecomastia are believed to result from hormonal imbalance. It is often identified as a painful, retroareolar mass. It should be differentiated from false gynecomastia (pseudo-gynecomastia). Pseudo-gynecomastia is a condition in which the male breast grows due to the accumulation of adipose tissue and is often associated with obesity. Physical examination is required to distinguish the two types. True gynecomastia is the increase of mammary gland tissue, often manifested as a tightened, elastic tissue mass in the subareolar region (5). The pathogenesis of gynecomastia is not fully understood. It is assumed to be caused by several mechanisms,

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such as an imbalance in the testosterone-estrogen ratio, increased human chorionic gonadotropin receptors, and luteinizing hormone receptors in male breast tissue (6). There are many factors or diseases that can cause gynecomastia. Although gynecomastia occurs due to many pathological causes such as endocrine disorders, especially testicular or adrenal malignancies, and various drugs, the most common reason is physiological or idiopathic (7). Testicular examination of the patients, careful anamnesis, additional diseases and used medications should be questioned. The lesion is determined around the nipple, and the diagnosis is made with ultrasonography and mammography (3). Treatment in gynecomastia is related to surgery because there is no place for medical treatment. Most cases are asymptomatic, self-limiting, and rarely require treatment.

2.1. Pathology of Gynecomastia

The macroscopic appearance of gynecomastia may be variable; it can be seen as a separate hard nodular well-circumscribed mass or as a soft rubber consistency, unclear, gray-white mass. The spectrum of histological changes seen in gynecomastia is a combination of two main patterns defined as type 1 (floride) and type 2 (fibrous). The floride type is characterized by periductal encircling and ductal epithelial hyperplasia (Figure 1). Sometimes myoepithelial hyperplasia may accompany. Atypical proliferation can be seen in the floride type, cribriform and papillary patterns. The fibrous type has minimal epithelial proliferation; the stroma is denser and collagenized. Rarely, it may include apocrine and squamous metaplasia. Variations in the stroma may show the same stromal changes as pseudoangiomatous stromal hyperplasia in the female breast (1, 8).

2.2.Pathological Definition of Atypical Changes in Gynecomastia

While distinguishing the usual ductal hyperplasia of floride from atypical ductal hyperplasia (ADH) in the histopathology of gynecomastia, the criteria must be fully established. Tavassoli and Norris defined hyperplasia as ADH in ducts smaller than 2 mm, whereas Page et al. included atypical data such as cellular monotony affecting two or fewer ducts, nuclear enlargement, nucleolar prominence, and presence of sharp fenestrations. They recommended a lesion larger than 2 mm or involvement of three or more ducts as ductal carcinoma in situ (DCIS). These data are still used as an evaluation standard for pathological definitions (9, 10).

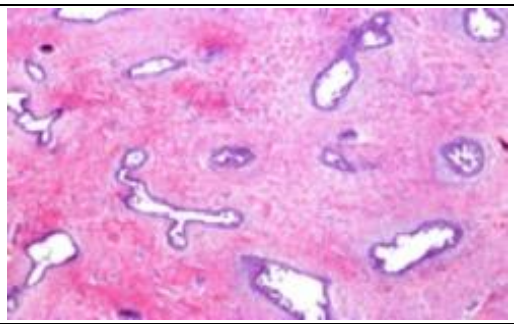

Figure 1. Classical gynecomastia histomorphology, hematoxylin-eosin , X 40

2.3. Atypical Ductal Hyperplasia and Male Breast Cancer Risk at Gynecomastia

Since the incidence of male breast cancer (MBC) is less than 1% of all breast cancers, its etiology and risk factors are less understood than in female breast cancers (11). Although ADH is a known risk factor for female breast cancer, little is known about its effects in men, and it is a rare event in patients with gynecomastia (12). The relationship between gynecomastia and atypical changes in the male breast (especially ADH) and the high risk of cancer is also being studied. The number of studies addressing the issue of breast cancer risk following ADH in the male population is limited. Since the number of cases is often limited and retrospective in single-center studies, the obtained data are viewed with suspicion. Some studies show that gynecomastia in men is a risk factor for the development of breast cancer, with uncertain increase values between 1% and 12.5%, suggesting that the risk increase is questionable. In some publications gynecomastia is associated with 10 times increased risk of breast cancer among men (13). However, up-to-date data indicate that gynecomastia and rarely determined ADH do not increase the risk of MBC.

2. Objectives

Therefore, with follow-ups in our series, the present research was conducted to determine the incidence of atypia and its effect on breast cancer in gynecomastia cases.

3. Methods

Cases diagnosed in our center between 2010 and 2020 were included in the study. The study was conducted under the institutional review board approval in Sisli Hamidiye Etfal Research and Training Hospital, Istanbul, Turkey (Approval no:1808/ Date:30.03.2021). Cases with insufficient specimen quality, follow-up problems, and an indefinite pathological diagnosis were excluded. A total of 108 cases between the ages of 12-90 were included in the study. All clinical records, medical history, diseases, postoperative neoplastic breast lesion development, and follow-up periods were determined. The samples on which tissue follow-up procedures were applied in automatic devices were prepared in serial sections by staining with routine hematoxylin-eosin (HE). An

experienced breast pathologist evaluated the preparations. In controversial cases, preparations were examined with estrogen receptor (ER) (Leica ER Clone 6F11) and CK5/6 (Dako Clone D5/16B4) immunohistochemically.

Additionally, the ductal structures subjected to hyperplasia in the background of gynecomastia were examined. Structural and cytological atypia affecting the ducts were observed in the lesions. Structurally, solid, cribriform, papillary, micropapillary, and less visible forms, sharp fenestrations, cytologically, the monotony of epithelial cells, increased intercellular distance, nuclear enlargement, large nucleolus, and atypical mitosis were accepted as criteria. Cytological and structural atypia are not seen in simple hyperplasia. Lesions with cytological and structural atypia less than 2 mm or less than 2 ducts affected are atypical hyperplasia. Lesions larger than 2 mm or affected by more than 2 ducts with cytological and structural atypia are described as dcis (9). In contradictory cases, strong immunoreactivity with ER and loss of expression with CK5/6 were evaluated in favor of atypia, and a definitive definition was made (14).

3.1. Statistical Analysis

Statistical analysis was performed using SPSS (version 26.0) for the Windows program. Descriptive statistics, numbers, and percentages for categorical variables, and the mean and standard deviation for numerical variables were used. The distribution condition of numerical variables in groups was evaluated by the Shapiro-Wilk test. Age and excised mass size were evaluated with Chi-squared tests, and comorbid factors were evaluated with the Mann-Whitney U test. A *P*-value of less than 0.05 was considered statistically significant.

4. Results

A total of 151 materials belonging to 108 cases of gynecomastia (43 bilateral) were examined. Some of these patients (n=38, 35.1%) had additional diseases such as diabetes and other organ malignancies, including testicular cancer (n=1). The lesion size ranged from 1 cm to 22 cm (Table 1). Simple mastectomy and stereotactic biopsy were the most common surgeries; few patients underwent a subcutaneous mastectomy, and one underwent a modified radical mastectomy. Fluoride type gynecomastia was detected in 31 materials and fibrous type gynecomastia in 120 materials. In 22 of the materials, usual forms of hyperplasia (15.2%), consisting of 8 (5.3%) ADH and 1 (0.7%) DCIS, were found. None of these patients developed breast cancer during their follow-up period (minimum 9 months, maximum 110 months, and average 74 months). Various accompanying diseases (e.g., diabetes mellitus (DM) and Malignancy) were found in 8 and 2 patients with usual hyperplasia and ADH, respectively (Table 2).

Table 1. Demographics and clinical features of the patients

	Patients (n=108)
Age	38.44 ± 20.21 (12-90)
Size	7.57 ± 3.85 (1-22 cm)
Localization	
Right	26 (24%)
Left	39 (36.1%)
Bilateral	43 (39.8%)
Comorbidity	38 (35.1%)
Hypertansion	5 (4.6 %)
Chronic Obstructive Pulmonary Disease	2 (1.85%)
Diabetes Mellitus	5 (4.6%)
Hypothyroidism	2 (1.85%)
Obesity	4 (3.7%)
Cancer*	5 (4.6%)
Obsessive-compulsive disorder	3 (2.77%)
Cerebrovascular accident	1 (0.9%)
Congestive heart failure	3 (2.77%)
Benign prostatic hypertrophy	4 (3.7%)
Cirrhosis	1 (0.9%)
Hepatit B	2 (1.85)
Ancilosan Spondilitis	1 (0.9%)

Abbreviations: 2 cases lung carcinoma, 1 case testicular carcinoma, 1 case tongue root carcinoma, 1 case rectal carcinoma.

Table 2. Data according to pathological groups

	Usual Hyperplasia (n=22)	Atypical Hyperplasia (n=8)	*P*-value*
Age	47.27 ± 2.85	38.5 ± 16.11	0.021
Size (cm)	5.63 ± 2.85	5.64 ± 2.79	0.538
Comorbidity			
Diabetes Mellitus	2	1	
Cancer	2	1	
Obesity	1		
Hepatit B	1		

* Kruskal Wallis test

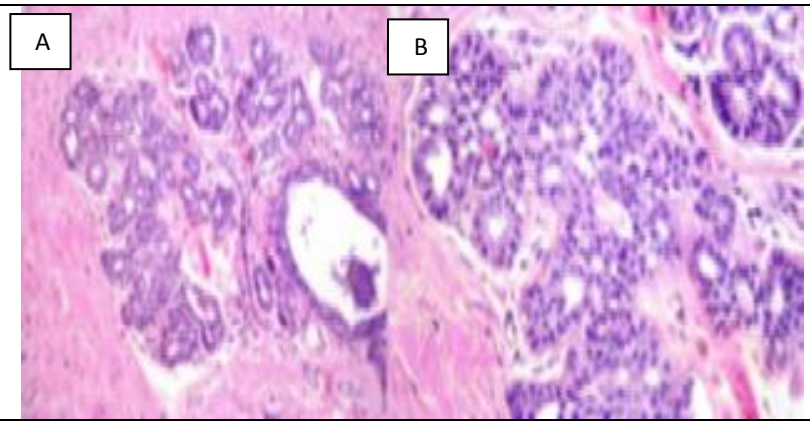

Figure 2A-B. Gynecomastia case, the presence of a rare terminal ductal lobular unit in the male breast, atypical ductal hyperplasia developing in this area, hematoxylin-eosin , X 100, 200

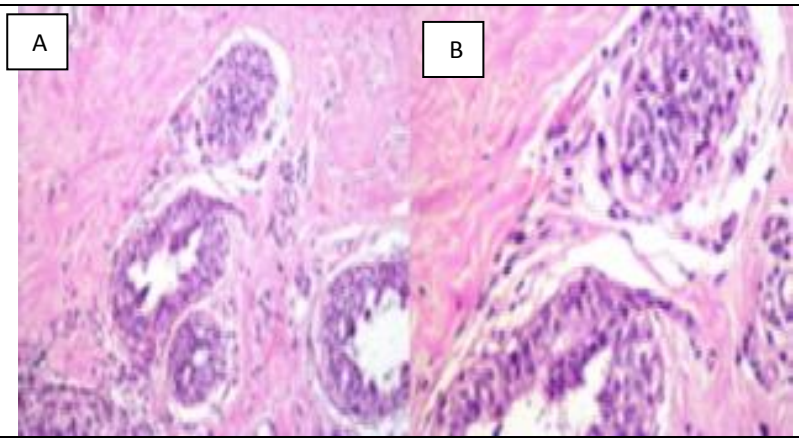

Figure 3A-B. Atypical ductal hyperplasia in gynecomastia, hematoxylin-eosin, X 40, 100, 200, 400

Compared to the age group in usual hyperplasia, the incidence of ADH at younger ages was higher, and the difference was statistically significant (P=0.021). There was no relationship between the size of the lesion and the presence of ADH (Figure 2 A-B, Figure 3 A-B, Figure 4 A-B-C-D).

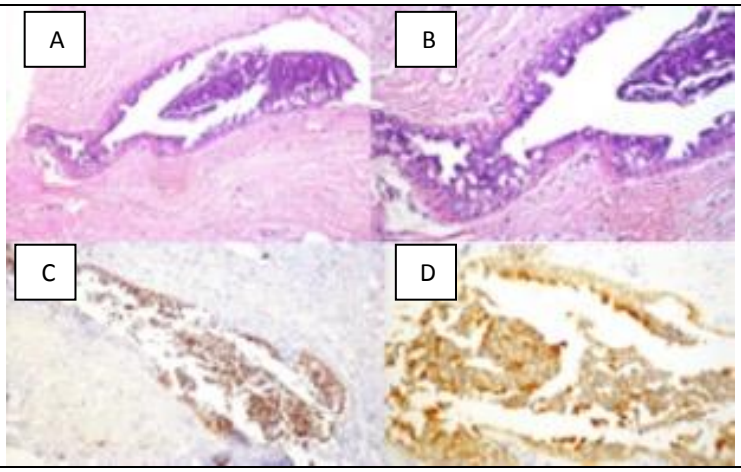

Figure 4A-B-C-D. Staining on strong with estrogen receptor, mosaic pattern with CK5/6 in the focus of ductal carcinoma in situ in gynecomastia,, hematoxylin-eosin X 40, 100 (A-B) , Immunohistochemistry, X 40, 100 (C-D)

5. Discussion

The clinical significance of ADH in men with gynecomastia is unclear. Gynecomastia was thought to be a premalignant condition in some cases due to the observation that the incidence of MBC was higher in regions with high gynecomastia, and breast cancer increased significantly in patients with Klinefelter

syndrome (14). The incidence of ADH in gynecomastia samples ranges from 0.4% to 5.4%. The estimated 5-year and 10-year breast cancer risk in women with ADH was 4.5% and 17.3%, respectively (12). Bannayan et al., in 351 histologically proven gynecomastia cases, found ADH in 15 cases, atypical lobular hyperplasia and DCIS in three and four cases, respectively (15).

In contrast, Senger et al. analyzed tissue samples of 452 gynecomastia patients and found no premalignant or malignant lesions in any of the cases (16). Gynecomastia was detected in 55 (55%) cases in the series in which 100 random male autopsies were examined by Andersen and Gram (17). About 7 (7%) cases had severe epithelial hyperplasia, defined as "ADH or DCIS," five of which were gynecomastia cases. Cole and Quizilbash were unable to detect any evidence of neoplasia in 233 cases of gynecomastia. They also examined 32 MBC samples, of which only one demonstrated gynecomastia-like histopathological changes (18). In the study conducted by Wells et al., it was reported that 2 (8%) of 25 ADH cases in gynecomastia patients had DCIS, corresponding to a higher value than those stated in the literature (14). The prospective analysis by Coopey et al., which included 19 gynecomastia cases with ADH in a 6-year follow-up period, determined that none of the cases developed carcinoma.

According to the authors, that data showed that ADH in men poses no risk as in women or that surgical removal of symptomatic gynecomastia in men effectively reduces the risk of breast cancer (12). In a large series in which 5,113 gynecomastia patients were analyzed, the overall prevalence of ADH was 0.4% (0.23% in patients under 20 years old, the youngest patient was 16 years old). The overall prevalence of invasive carcinomas and in situ carcinomas were 0.11% and 0.18%, respectively (19). The youngest patient with invasive carcinoma was 65 years old, and the youngest patient with in-situ carcinoma was 24 years old.

Consequently, these authors concluded that the incidence of ADH and malignancy was very low in men with gynecomastia, and there were no risk factors as in women (18). On the other hand, some authors acknowledged that there may be a risk in gynecomastia cases with ADH, although they suggested a weak relationship between gynecomastia and breast cancer and that the risk is low (20). Of the 151 surgical materials extracted from our 108 patients, only 8 (5.3%) and 1 (0.7%) had ADH and DCIS, respectively.

The ADH cases were significantly younger than gynecomastia with usual hyperplasia. Supporting this data, Wells et al. evaluated ADH cases caused by gynecomastia, and it was suggested that young patients (under 25 years of age) with extensive and bilateral ADH were determined, and further studies were required (14). Most studies reported no statistical correlation between ADH and the age group. However, it is known that DCIS and invasive carcinoma in the male breast is mostly seen in the advanced age group. However, we also know the existence of a series with an average age of 22 years, in which DCIS was determined in five cases with gynecomastia. However, all these cases had a familial history of breast cancer (21). In situ ductal carcinoma of the male breast is rare and occurs in 5-10% of all MBC cases (22). The factors that increase the risk of MBC are high estrogen status, Klinefelter syndrome, family history, *BRCA2* gene, hyperprolactinemia, and radiation exposure. Moreover, it was also found that there is no increased risk of breast cancer associated with gynecomastia (13, 23). Furthermore, DCIS usually occurs in women. Although the exact cause of DCIS in men (since they lack terminal canal lobular units) is unknown, it is assumed to arise from the canal epithelium (24). Although the relationship between gynecomastia and MBC has been extensively studied, there is no convincing evidence that gynecomastia is associated with a higher risk of developing MBC. In the prospective cohort study of Olsson et al., 446 patients with gynecomastia were followed over 30 years. Although men who have had gynecomastia surgery have a significantly increased risk of developing testicular cancer and squamous cell skin cancer, there was no increased risk of male breast cancer (25). Shirah et al. declared that histopathological examination of the resected breast tissue with gynecomastia should be performed carefully in all patients by reporting high incidence of in situ ductal carcinoma (6.76%) in gynecomastia patients (21). In contrast to these high rates, very low rates of 0.11% for invasive carcinoma and 0.19% for DCIS were reported in an extensive series of 5,113 breasts with gynecomastia (19). In a study by Kasielska and Antoszewski et al., 113 gynecomastia patients were observed, and no malignancy was found (26). In 81 gynecomastia patients examined by Koshy et al., there was only 1 case with cellular atypia, and no malignancy was detected (27). Although examining 151 surgical materials out of 108 cases with follow-up in our series is a good number in male breast pathology and gynecomastia surgery, it may not be sufficient given the limited data in this field. The incidence rates of ADH and DCIS in our study are similar to the series with larger number of patients in the literature. however, it is noteworthy that the ADH containing gynecomastia group in our series was at a young age. This data has been shown in this way by Wells et al (14). Perhaps due to the prevalence of gynecomastia surgery, this data can be interpreted as the ADH detected in gynecomastia poses no risk to MBC development because it cannot be transferred to advanced ages. It is now accepted that there is no direct relationship between gynecomastia and MBC development. Although a causal relationship between the two has not been

proven, it has also been claimed that gynecomastia is associated with a wide range of carcinomas ranging from 3-40% (28). The reasons for this wide range; is the fact that there are many factors affecting male breast cancer, the retrospective nature of these studies and the low number of cases in the series (5). Some publications define gynecomastia as enlarged breast tissue larger than 0.5 cm (29), while in some series it is defined as glanduler tissue larger than 2 cm (30). This different definements are one of the reasons for the wide gap between the series.

The retrospective nature of the study limits its value. A limited number of studies investigated the relationship between MBC and ADH, and due to its nature, most of it is based on retrospective records, the same as the present study. However, a considerable number of cases with clinical follow-up for gynecomastia, the number of surgical materials belonging to them, the fact that an experienced breast pathologist examined them, and the definitive diagnosis confirmation with immunohistochemical evidence in addition to routine preparations when defining atypia are Strengths of our study.

6. Conclusion

The answer to the question of whether gynecomastia is a risk factor or it is a precursor lesion of breast carcinoma is not valid today. In the related literature, no data showed a direct or significant relationship between gynecomastia and breast carcinoma. However, speculation about the clinical significance of ADH-based findings on gynecomastia seems to continue. Series and prospective studies with large numbers of clinical follow-up cases evaluating the incidence of gynecomastia and ADH in MBC samples may help to clarify the relationship between them. As with many issues, ongoing advances and innovations in molecular pathology are likely to answer this question.

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Footnotes

Conflicts of Interest: The authors declare no conflict of interest and have no financial issues to disclose.
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Ethical statements: Hereby, all authors consciously assure that the manuscript is fulfilled the following:
1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis truthfully and completely.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of the research.
6) All sources used are properly disclosed (correct citation). Literal copying of text should be indicated using quotation marks and proper references.
7) All authors have been personally and actively involved in substantial work leading to the paper and will take public responsibility for its content.

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