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Evaluation of Incidental Proliferative Non-Proliferative Lesions Detected in Mammoplasty Specimens Performed for Aesthetic Purposes

Estetik Amacı ile Yapılan Mammoplasti Spesmenlerinde Saptanan İnsidental Proliferatif Non-Proliferatif Lezyonların Değerlendirilmesi

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ABSTRACT

Aim: Reduction mammoplasty (RM) operations are frequently performed for breast reduction and asymmetry correction. Evaluation of these materials is important in patients at high risk of developing invasive breast carcinoma (IBC) to detect precancerous lesions or lesions that may accompany cancer. This study aimed to evaluate the histopathologic and clinical features of proliferative and non-proliferative lesions in RM materials.
Material and Methods: In this study, 214 cases (402 specimens) of RM operated for aesthetic purposes (except gynecomastia) at Eskişehir Osmangazi University Hospital between the years 2020 and 2023 were included. The age of cases, location and bilaterality of the lesions, and proliferative and non-proliferative lesions were evaluated.
Results: The mean age of RM cases was 38.5±10.9 years. The most common lesion was apocrine metaplasia in RM materials. Proliferative and non-proliferative lesions were found bilaterally in 24.8% (n=53) of all RM cases. The most common bilaterality was intraductal papilloma and the most common unilateral lesion was ductal ectasia. 0.2% (n=1) case of ductal carcinoma in situ and 0.9% (n=4) cases of lobular carcinoma in situ was found.
Conclusion: Detection of high-risk lesions is important for appropriate clinical follow-up. In this study, high-risk proliferative lesions were found considerably in RM cases. Patients with high-risk proliferative lesions should be followed up more closely in terms of cancer risk in the future. In addition, it is crucial to perform a careful macroscopic examination in mammoplasty operations performed for aesthetic purposes to avoid missing these lesions.
Keywords: Breast carcinoma in situ; breast neoplasms; mammoplasty.

ÖZ

Amaç: Redüksiyon mammoplasti (RM) operasyonları sıklıkla meme küçültme ve asimetri düzeltilmesi için yapılmaktadır. İnvaziv meme karsinomu (İMK) gelişme riski yüksek hastalarda bu materyallerin değerlendirmesi prekanseröz lezyonların ya da kansere eşlik edebilecek lezyonların saptanması açısından önemlidir. Bu çalışmada RM materyallerinde görülen proliferatif ve non-proliferatif lezyonların histopatolojik ve klinik özelliklerinin değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntemler: Bu çalışmaya 2020 ve 2023 yılları arasında Eskişehir Osmangazi Üniversitesi hastanesinde estetik amaçlı (jinekomasti hariç) olarak opere edilmiş olan, 214 RM olgusu (402 örnek) dahil edildi. Olguların yaşları, lezyonların lokalizasyonu ve bilateralitesi ve proliferatif ve non-proliferatif lezyonlar değerlendirildi.
Bulgular: RM olgularının yaş ortalaması 38,5±10,9 yıl idi. RM materyallerinde en sık rastlanan lezyon apokrin metaplazi idi. Tüm RM olgularının %24,8 (n=53)'inde proliferatif ve non-proliferatif lezyonlar bilateral olarak saptandı. En çok bilateralite gösteren lezyon intraduktal papillom, çoğunlukla unilateral olan lezyon ise duktal ektazi idi. %0,2 (n=1) duktal karsinoma in situ olgusu ve %0,9 (n=4) lobüler karsinoma in situ olgusu saptandı.
Sonuç: Yüksek riskli lezyonların tespiti uygun klinik takip için önemlidir. Bu çalışmada RM olgularında önemli oranda yüksek riskli proliferatif lezyonlar saptanmıştır. Yüksek riskli proliferatif lezyon saptanan hastaların gelecekte kanser riski açısından daha sıkı takip edilmesi gerekmektedir. Ayrıca estetik amaçlı yapılan mamoplasti operasyonlarında bu lezyonların gözden kaçırılmaması amacı ile makroskopik incelemenin dikkatli yapılması büyük önem taşımaktadır.
Anahtar kelimeler: Duktal karsinoma in situ; meme neoplazileri; mammoplasti.

INTRODUCTION

Reduction mammoplasty (RM) operations are frequently performed for breast reduction and asymmetry correction. Evaluating these materials is important in patients at high risk of developing invasive breast carcinoma (IBC) to detect precancerous lesions or lesions associated with cancer (1). RM, the seventh most common reconstructive surgical procedure in the United States, is one of the most common procedures performed by plastic surgeons. Performed more than 100,000 times per year, RM accounts for more than 40% of plastic surgery breast procedures (2). Previous studies have compared the incidence of occult malignancy (3,4) or atypical lesions (5) in resection specimens between groups undergoing breast reduction for symptomatic macromastia and breast asymmetry after breast cancer surgery. It is known in the literature that the risk of IBC is seen in patients with proliferative lesions. Previous studies have found that the relative risk of proliferative lesions with atypia increases compared to proliferative lesions without atypia (6).

This study aimed to analyze the interrelationships and clinical follow-up of proliferative and non-proliferative lesions seen in RM materials.

MATERIAL AND METHODS

This study has 214 RM cases (402 specimens) operated on at Eskişehir Osmangazi University Hospital between 2020 and 2023. Age distribution of the cases and bilaterality of the lesions were evaluated. For the clinical and molecular follow-up of the operated patients, help was received from the relevant clinician and hospital database. All cases who underwent mammoplasty for aesthetic purposes in the study center were included in the study, and male mammoplasty cases operated due to gynecomastia were not included in the study.

After the materials were received in formalin from the clinic, they were cut into 1-2 cm thick sections and left to formalin fixation for 20-22 hours. When any lesion was noticed after fixation, lesion-directed sampling was performed. Otherwise, a random tissue sampling was performed. At least three samples per breast were taken from each resected breast specimen. Additional samples are routinely taken when precancerous lesions are detected incidentally. After the tissue processing steps, tissue was embedded in paraffin, and 4-5 micrometer-thick sections were taken and stained with hematoxylin and eosin. Paraffin-embedded, hematoxylin-eosin-stained slides were prospectively reviewed by one breast pathologist, and detailed findings were recorded on a data form.

Age, weight of breast tissue, location (right/left), and bilaterality of lesions were recorded. Proliferative and non-proliferative lesions detected in all breasts were recorded. Cystic changes, ductal ectasia, apocrine metaplasia, columnar cell change, and usual ductal epithelial hyperplasia were recorded as non-proliferative lesions. Florid epithelial hyperplasia, fibroadenoma, sclerosing adenosis, intraductal papilloma, radial scar, atypical lobular hyperplasia, atypical ductal hyperplasia, lobular carcinoma in situ (LCIS), and ductal carcinoma in situ (DCIS) were recorded as proliferative lesions. The cases were divided into two groups: over 30 years old and over 40 years old. Then, it was evaluated whether proliferative and non-proliferative lesions showed a significant increase over the age of 30 or 40. Among all lesions, lesions that were more frequently seen together with other lesions were evaluated. Also, since DCIS and LCIS cases are the highest-risk preneoplastic lesions, their relationship with other lesions and age groups was evaluated. Reoperations of patients at high risk of developing cancer (LCIS, DCIS) were recorded.

Statistical Analysis

The normal distribution assumption was evaluated with the Shapiro-Wilk test. Continuous data were reported as mean±standard deviation, and categorical data were as a percentage (%). The Pearson chi-square or Fisher's exact test evaluated the differences between groups regarding these parameters and clinical and pathological variables. The data analysis was done with SPSS v.16.0, and $p<0.05$ was accepted as a statistical significance level.

RESULTS

Of the 214 operations performed, 191 (89.3%) were symptomatic mammoplasty, 3 (1.4%) were implant revision, 5 (2.3%) were for correction of breast asymmetry, and 15 (7%) were contralateral breast reduction after IBC. There were 402 breast specimens evaluated in total.

The distribution of non-proliferative lesions was as follows; cystic changes were detected in 40 (9.9%), ductal ectasia in 20 (4.9%), apocrine metaplasia (Figure 1) in 89 (22.1%), columnar cell changes in 26 (6.4%), and usual epithelial hyperplasia in 25 (6.2%) materials. As proliferative lesions; florid epithelial hyperplasia (Figure 2) was detected in 6 (1.4%), fibroadenoma in 27 (6.7%), sclerosing adenosis (Figure 3) in 25 (6.2%), and intraductal papilloma (Figure 4) in 7 (1.7%) materials. Radial scar, atypia ductal hyperplasia, atypia lobular hyperplasia, and IBC were not detected. 1 (0.2%) case of DCIS (Figure 5) and 4 (0.9%) cases of LCIS (Figure 6) were found in RM specimens. The mean weight of the materials was 867.9 (range, 6-6356) grams. This was not found related to detecting any other lesion.

The mean age of the patients was 38.5±10.9 years. The mean age of patients with lesions was 42.2±2.5 years, and 35.9±12.0 years without lesions. While the patients with columnar cell changes in the lesions were the oldest, fibroadenoma patients were the youngest (Table 1).

Table 1. Mean ages of the patients by lesions

Lesions	**Age** (years)
Non-Proliferative Lesions	
Cystic changes	40.3±7.9
Ductal ectasia	41.9±11.5
Apocrine metaplasia	41.9±8.3
Columnar cell change	45.9±6.9
Usual epithelial hyperplasia	43.0±9.3
Proliferative Lesions	
Florid epithelial hyperplasia	41.0±8.8
Fibroadenoma	37.7±9.5
Sclerosing adenosis	42.1±6.8
Intraductal papilloma	44.6±5.6
DCIS	40
LCIS	45.0±4.2

DCIS: ductal carcinoma in situ, LCIS: lobular carcinoma in situ

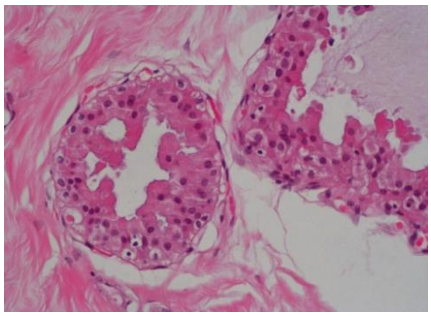

Figure 1.
Apocrine metaplasia (H&E x400)

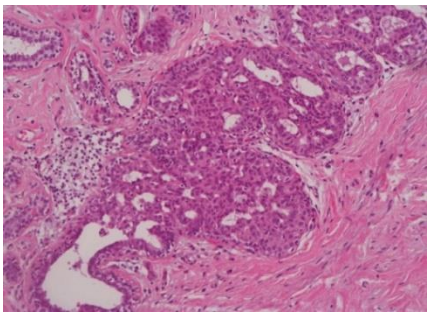

Figure 2.
Florid epithelial hyperplasia (H&E x100)

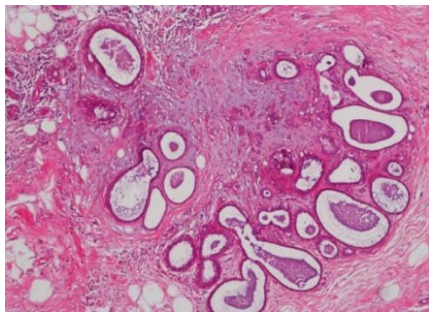

Figure 3.
Sclerosing adenosis (H&E x40)

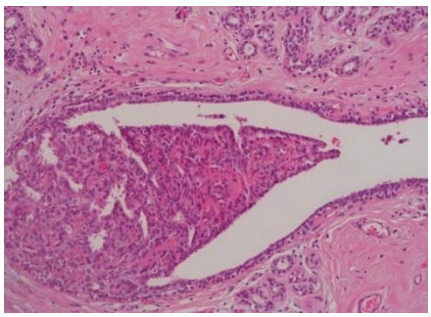

Figure 4.
Intraductal papilloma (H&E x100)

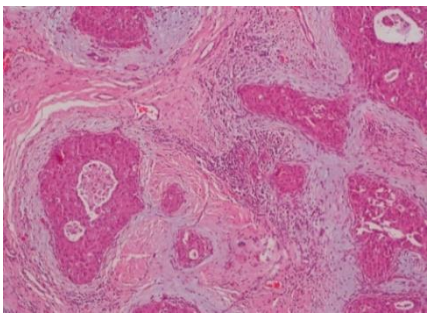

Figure 5.
Ductal carcinoma in situ (H&E x40)

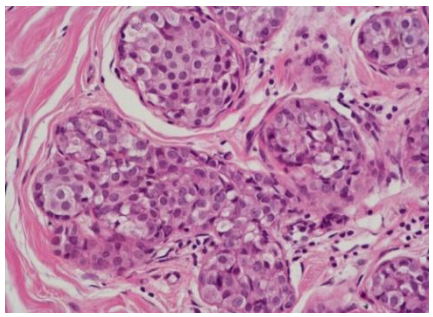

Figure 6.
Lobular carcinoma in situ (H&E x400)

In breast cancer screening studies, imaging screening is recommended due to the increased incidence of cancer in women over the age of 40. Based on this, we investigated whether there was a statistically significant increase in proliferative lesions that increase the risk of cancer in cases over 40 years of age, compared to the cases under 40 years of age (7). Additionally, in cases with a family history or known BRCA mutation, breast cancer screening should be started earlier due to the high risk. For this reason, we also investigated whether the frequency of proliferative lesions increased in patients over 30 years of age compared to the cases under 30 years of age (8,9). In patients aged 30 years and older, a significantly higher frequency of both proliferative ($p=0.016$) and non-proliferative ($p<0.001$) lesions was found. In patients aged 40 years and older, no association was found with proliferative lesions (Table 2). In these patients, the frequency of detection of non-proliferative lesions was found to be statistically significant.

Proliferative and non-proliferative lesions were found to coexist statistically significantly more frequently with columnar cell change (Table 3).

Some lesions were mainly observed bilaterally. Among the proliferative lesions, intraductal papilloma was the most common bilateral lesion, while among the non-proliferative lesions, apocrine metaplasia was the most common bilateral lesion. The most common unilateral lesion was ductal ectasia. Whether the lesions were on the right or left side did not show a significant result.

Additionally, the prevalence of DCIS and LCIS in cases over 30 and 40 years of age was evaluated (Table 4). It was also evaluated whether the co-occurrence of DCIS and LCIS with non-proliferative and proliferative lesions was statistically significant. Accordingly, the co-occurrence of LCIS cases in proliferative and non-proliferative lesions was found to be statistically significant ($p=0.003$, and $p=0.027$, respectively). 2 of these cases had subcutaneous mastectomy. Diffuse LCIS was reported in these two specimens. These patients are followed up with magnetic resonance imaging (MRI) every six months. No metastasis, recurrence, or IBC development has been observed so far. Three patients refused subcutaneous mastectomy. They are followed up with MRI every six months.

Table 2. Relationship of age groups with PL and NPL

	Age (years)		**p**
	<30 (n=47)	**≥30 (n=167)**	
PL, n (%)	5 (10.6)	46 (27.5)	**0.016**
NPL, n (%)	7 (14.9)	81 (48.5)	**<0.001**

	Age (years)		**p**
	<40 (n=112)	**≥40 (n=102)**	
PL, n (%)	23 (20.5)	28 (27.5)	0.236
NPL, n (%)	36 (32.1)	52 (51.0)	**0.005**

PL: proliferative lesion, NPL: non-proliferative lesion

Table 3. Relationship of columnar cell change with PL and NPL

	Columnar Cell Change		**p**
	Negative (n=195)	**Positive (n=19)**	
PL, n (%)	42 (21.5)	9 (47.4)	**0.021**
NPL, n (%)	71 (36.4)	17 (89.5)	**<0.001**

PL: proliferative lesion, NPL: non-proliferative lesion

Table 4. Relationship of age groups, PL, and NPL with DCIS and LCIS

	Age (years)		p
	<30 (n=47)	≥30 (n=167)	
DCIS, n (%)	0 (0.0)	1 (0.6)	>0.999
LCIS, n (%)	0 (0.0)	4 (2.4)	0.578

	Age (years)		p
	<40 (n=112)	≥40 (n=102)	
DCIS, n (%)	0 (0.0)	1 (1.0)	0.477
LCIS, n (%)	0 (0.0)	4 (3.9)	**0.050**

	Proliferative Lesion		p
	Negative (n=163)	Positive (n=51)	
DCIS, n (%)	0 (0.0)	1 (2.0)	0.238
LCIS, n (%)	0 (0.0)	4 (7.8)	**0.003**

	Non-Proliferative Lesion		p
	Negative (n=126)	Positive (n=88)	
DCIS, n (%)	0 (0.0)	1 (1.1)	0.411
LCIS, n (%)	0 (0.0)	4 (4.5)	**0.027**

PL: proliferative lesion, NPL: non-proliferative lesion, DCIS: ductal carcinoma in situ, LCIS: lobular carcinoma in situ

DISCUSSION

Detection of precancerous and high-risk lesions is essential for appropriate clinical follow-up. RM materials usually contain lesions with benign proliferation (10). According to the data in this study, the associations of proliferative and non-proliferative lesions have increased significantly in patients aged 30 years and over who underwent RM surgery. Atypical lesions are known to carry a higher risk of developing IBC. The literature reports that high-risk proliferative lesions are detected more frequently in cases of IBC (10). In our cases, the lesions that increased the relative risk of developing IBC were relatively numerous. We think that early diagnosis and treatment of these incidental lesions is important. In a study by Nergiz et al. (11), patients with lesions at high risk of IBC were followed clinically, and IBC developed in 2 of them. In the same study, the age group of 40 years was used, and proliferative lesions over 40 years of age were found to be significant in contrast to the present study. Non-proliferative lesions in patients over 40 years of age were significant. In a study conducted by Kakagai et al. (12) on current specimens without follow-up, 3 (1%) cases of occult breast cancer were found in 314 RM cases. We found 1 (0.2%) case of DCIS and 4 (0.9%) cases of LCIS in RM specimens. This rate is similar to the literature (13). A more recent study found 0.7% (n=1) of DCIS in 288 patients (14). Especially when DCIS and LCIS, which are precursor lesions of IBC, are detected, reoperation is recommended. Three of five carcinoma in situ cases in this study were reoperated. In 1 reoperated case, a unilateral lesion was seen on the RM specimen, but bilateral LCIS was detected on subcutaneous mastectomy. All our carcinoma in situ cases are followed up with an MRI every six months. BRCA testing and breast MRI are sometimes indicated for patients perceived to be at higher risk, including patients with a strong family history of breast cancer (15). We wonder whether these incidental precursor lesions are associated with BRCA mutation. We think that the relationship between BRCA status and carcinoma in situ may be important in the future. None of our patients received genetic counseling. We also believe that specimen sampling may vary depending on BRCA1 or BRCA2 status. We agree with the literature on this issue (16). Recent publications on this subject show a correlation between increased proliferative lesions and atypical hyperplasia in patients with familial history (17). In our study, there was no increase in proliferative lesions and atypical hyperplasia with age. Columnar cell changes are believed to represent the same genetic alterations as low-grade breast neoplasia. But so far, it has been found that it does not increase the risk of developing IBC more than proliferative lesions (18). In cases in this study, its association with proliferative and non-proliferative lesions was found to be significant. It is particularly noteworthy that it is seen together with DCIS and LCIS. Additionally, it was observed that the significance level of columnar cell change increased with increasing age. In this respect, we think that the relative risk assessment of columnar cell changes can be updated in light of other studies in the literature. We think that the English literature does not sufficiently cover columnar cell change. However, many studies have documented lesions with significant association with columnar cell change in this research.

The limitation of this study is that the cases were evaluated retrospectively. We think prospective studies are needed, especially in correlation with preoperative radiology.

CONCLUSION

Patients over the age of 30 years should be approached more carefully histopathologically, macroscopically, and intraoperatively. RM specimens are important materials for early diagnosis and treatment of patients. In light of the parameters found significant in this study, macroscopic sampling should be performed more carefully. It should be known that patients over 40 years of age with RM may be at risk for proliferative and non-proliferative lesions. When lesions such as fibroadenoma, sclerosing adenosis, and intraductal papilloma are encountered, additional sampling can be performed in terms of accompanying lesions that increase the risk of IBC. Sensitivity to these issues in macroscopy guidelines will significantly affect the prognosis of patients with a possible IBC case.

Ethics Committee Approval: The study was approved by the Non-Invasive Clinical Research Ethics Committee of Eskişehir Osmangazi University (16.05.2023, 21).

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