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ORIGINAL ARTICLE

A Comparative Histopathological Evaluation of Simple Versus Complex Fibroadenomas: Implications for Breast Cancer Risk Stratification

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ABSTRACT

Background: Fibroadenomas represent the most common benign breast lesions, yet their histopathological diversity—particularly between simple (SFAs) and complex fibroadenomas (CFAs)—may influence subsequent breast cancer risk. While CFAs exhibit proliferative and architectural complexities, their precise association with malignancy remains to be fully elucidated.

Objectives: To compare the histopathological features of SFAs and CFAs and determine their respective associations with breast cancer risk.

Methodology: In this retrospective comparative study, 200 patients were selected, with 100 cases each of SFAs and CFAs. Clinical parameters, including age, presenting symptoms, tumor size, and family history of breast cancer, were documented. Histopathological analysis was conducted on H&E-stained slides to evaluate proliferative changes, complex features (sclerosing adenosis, apocrine metaplasia, calcifications), and stromal alterations, following standardized diagnostic criteria. Statistical analyses employed Chi-square tests for categorical variables, t-tests for continuous variables, and Kaplan-Meier survival analysis to assess time to malignancy, with significance set at $p < 0.05$.

Results: Patients with CFAs were significantly older (mean 47 years) compared to those with SFAs (mean 29 years, $p < 0.05$) and had smaller tumor sizes (mean 1.3 cm vs 2.5 cm, $p < 0.05$). Histopathologically, CFAs demonstrated a markedly higher incidence of sclerosing adenosis (56% vs 12%, $p < 0.001$), apocrine metaplasia (22% vs 8%, $p = 0.02$), and calcifications (18% vs 5%, $p = 0.04$). CFAs conferred a 2.27-fold increased risk of malignancy (95% CI: 1.84–2.68), with Kaplan-Meier analysis revealing a significantly shorter time to malignancy diagnosis ($p < 0.0001$).

Conclusion: CFAs exhibit distinct histopathological features and a significantly higher breast cancer risk compared to SFAs. These findings emphasize the need for rigorous histopathological evaluation and tailored clinical surveillance of complex fibroadenomas. Future investigations should integrate molecular markers to further refine risk stratification and optimize patient management.

Keywords: fibro adenomas, Sclerosing adenosis, calcifications, malignancy, histopathological, stratification.

INTRODUCTION

The abnormal growth of living cells usually forms a mass-referred tumor or tumor. Fibroadenomas (FAs) are benign fibro-epithelial tumors of the breast, characterized by being biphasic and having stromal and epithelial components[1]. Estrogen, progesterone, pregnancy, and breastfeeding all increase FAs, which atrophy during menopause. FAs often have atypical presentations such as juvenile, gigantic, extramammary, and complicated forms, in addition to their typical form, and are often small lumps of 4–5 cm or less that manifest as breast lumps. Fibroadenomas are generally considered benign, however, their histological diversity, especially in complex variants, has been the topic of increasing interest concerning the possibility of malignancy. Painful fibroadenomas and complex fibroadenomas (CFAs) are reported to have a higher relative risk of developing breast cancer than simple fibroadenomas (SFAs) [2].

Most fibroadenomas have been managed conservatively, with most cases followed by imaging and clinical observation. However, there is recent evidence that suggests that CFAs may need more aggressive follow-up given their increased risk of malignancy. Previous studies show that women with CFAs have a 2-3 times higher risk of developing breast cancer than the general population. [3, 4]. The increased risk for malignancy persists for decades and calls for further characterization of histopathological fibroadenoma variations and their clinical meaning. The distinguishing histopathological examination is critical in defining SFAs from CFAs. Features of complexity include ductal or lobular hyperplasia, calcifications, and stromal changes, which are also potential markers of malignant transformation. With the development of techniques such as core needle biopsy and imaging-guided pathology, more accurate fibroadenoma classification and directed clinical intervention can be achieved[5, 6].

However, there is disagreement in the literature as to whether CFAs make an independent contribution to breast cancer risk or whether proliferative changes in surrounding tissue are more important.[7]. The objective of this study was to compare the histopathological features and breast cancer risk association with SFAs and CFAs. The unique combination of a well-characterized cohort with powerful statistical models allows us to learn about the biological behavior of fibroadenomas and to inform clinical decision-making. Knowledge of these distinctions is important to optimize patient management, particularly in high-risk populations, and to tune diagnostic and therapeutic strategies in breast pathology.

MATERIALS AND METHODS

A retrospective comparative study was conducted from January 2021 to October 2022 in Pathology Department of Nawaz Sharif Medical College Gujrat and Sughra Shafi Medical Complex-Narowal, Pakistan, to evaluate the histopathological difference between simple fibroadenomas (SFAs) and complex fibroadenomas (CFAs) and their relation to the risk of breast cancer. From a pathology database over 1 year, we included n=100 patients with fibroadenomas. SFAs (50 cases) and CFAs (50 cases) were used to ensure histopathological criteria for representation. Patients were aged 18 to 85 years with histopathologically proven fibroadenomas. Medical records and histopathology reports were reviewed, and clinical and histological data were extracted. For this study, women aged 18–85 years with histopathologically confirmed fibroadenomas and complete clinical records (including presenting symptoms, tumor size, and family history of breast cancer) were included. Inclusion cases had

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sufficient tissue for detailed histopathological analysis. Concurrent invasive or in situ breast carcinoma at diagnosis, history of previous breast malignancy or hereditary cancer syndromes, or specimens with insufficient tissue for complete evaluation were excluded.

Clinical data were meticulously extracted from medical records, including patient age, presenting symptoms like a palpable lump, pain, tumor laterality, size, and family history of breast cancer. Histopathological analysis was conducted on Hematoxylin and Eosin (H&E)-stained slides by two independent pathologists, focusing on identifying proliferative epithelial changes, complex features such as sclerosing adenosis, apocrine metaplasia, calcifications, cysts ≥3 mm, and stromal alterations as hyalinization, pseudoangiomatous stromal hyperplasia (PASH) were considered respectively. Classification into simple or complex fibroadenomas followed Dupont et al.. criteria. Cases with discordant evaluations underwent a consensus review to ensure diagnostic precision, adhering to stringent standards for reproducibility and diagnostic accuracy.

Statistical analysis was performed using SPSS (v26.0), with significance set at $p<0.05$. Descriptive statistics were used to summarize demographic, clinical, and histopathological data, presenting means and standard deviations for continuous variables and frequencies and percentages for categorical data. Group comparisons between simple fibroadenomas (SFAs) and complex fibroadenomas (CFAs) were conducted using the Chi-square test for categorical variables, such as the presence of complex features, and the student's t-test for continuous variables, including patient age and tumor size. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated to assess the association between fibroadenoma type and breast cancer risk. Time to malignancy diagnosis between SFAs and CFAs was compared using Kaplan-Meier survival analysis, and log-rank tests were used to determine statistical significance. A comprehensive approach was taken that led to robust, clinically meaningful insights into the comparative analysis of SFAs and CFAs.

The study was ethically approved by the Institutional Review Board (IRB). Anonymized patient data were used together with archived histopathological samples obtained with appropriate permissions, so as to comply with the Declaration of Helsinki and national ethical guidelines.

RESULTS

This retrospective study comprised of 100 cases of fibroadenomas divided equally into simple fibroadenomas (SFAs) and complex fibroadenomas (CFAs). The results underscore differences between the two groups with regard to clinical, histopathological, and survival outcomes, including that of higher malignancy risk in CFAs.

Results of the study show significant differences between simple and complex fibroadenomas on several clinical and histopathological parameters. Patients with CFAs were older, with a mean of 47 years (range: 30–65 years), than those with SFAs, with a mean of 29 years (range: 18–45 years), suggesting an age-related predisposition for complex features. Tumor size was smaller in CFA's mean size of 1.3 cm (range: 0.8–2.0 cm) compared to 2.5 cm (range: 1.5–3.5 cm) in SFAs ($p < 0.05$). Histopathological features were significantly more complex in CFAs compared to SFAs, as shown in Table 1. In 56% of CFAs versus 12% of SFAs ($p < 0.001$), sclerosing adenosis was observed. CFAs contained apocrine metaplasia in 22% versus 8% of SFAs ($p = 0.02$), and calcifications were more common in CFAs (18%) than in SFAs (5%) ($p = 0.04$). Also more common in CFAs (35%) than in SFAs (10%) ($p < 0.01$) were cystic changes (≥3 mm). In 25% of CFAs, compared to 15% of SFAs ($p = 0.03$), hyalinization was noted. These findings highlight the greater architectural complexity of CFAs and their correlation with features associated with malignancy risk.

Table 1: Comparative Analysis of Clinical and Histopathological Features between Simple Fibroadenomas (SFAs) and Complex Fibroadenomas (CFAs)

Parameter	SFAs	CFAs	p-value
Number of patients	50	50	-
Mean age (years)	29	47	<0.05
Tumor size (mean, cm)	2.5	1.3	<0.05
Sclerosing adenosis (%)	12%	56%	<0.001
Apocrine metaplasia (%)	8%	22%	0.02
Calcifications (%)	5%	18%	0.04
Cysts ≥3 mm (%)	10%	35%	<0.01
Hyalinization (%)	15%	25%	0.03
Relative risk (RR) of malignancy	1.49	2.27	-

Simple fibroadenomas (SFAs) vs complex fibroadenomas (CFAs) time to malignancy diagnosis is compared using Kaplan Meier survival analysis as shown in fig-1. CFAs have a shorter time to malignancy diagnosis as survival probability of CFAs declines more rapidly than SFAs. This yields a p-value (<0.0001) for a statistically significant difference between the groups, with CFAs having a higher malignancy risk. 95% confidence intervals are shaded, and the risk table indicates several patients at risk at different time points, with CFAs tending to reduce faster. Therefore, this figure emphasizes the necessity to monitor more closely and manage more carefully the CFAs, as they have a higher and earlier malignancy risk.

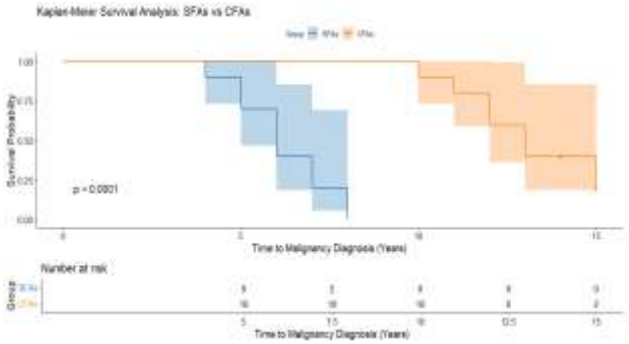

Fig 1: Kaplan-Meier Survival Analysis of Time to Malignancy in Simple Fibroadenomas (SFAs) and Complex Fibroadenomas (CFAs).

Fig-2 represents a high-power histological view of tissue, likely from a fibroadenoma or a similar fibroepithelial lesion, stained with Hematoxylin and Eosin (H&E). This fig-2 is consistent with a benign fibroadenomatous lesion, specifically the stromal component. The increased stromal cellularity could suggest a complex fibroadenoma if associated with features such as sclerosing adenosis, apocrine metaplasia, or calcifications in other sections. It is essential to evaluate the epithelial and stromal components together to make a definitive diagnosis.

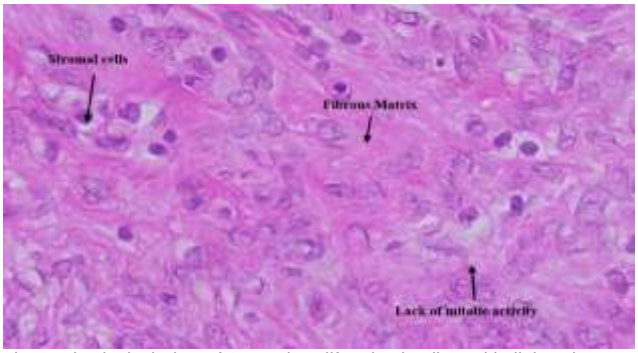

Fig. 2: Histological View of Stromal Proliferation in Fibroepithelial Lesion

Fig-3 illustrates a histological section of a fibroepithelial lesion, stained with Hematoxylin and Eosin (H&E). The section reveals a prominent stromal component with dense collagenous tissue and spindle-shaped stromal cells, interspersed with scattered glandular and ductal structures. The ducts are lined by benign epithelium without atypia. The stromal proliferation is uniform, with scant mitotic figures with areas of increased cellularity but without significant pleomorphism. The features are consistent with a fibroadenoma, and there are no overt features of malignant transformation. Fig-3 demonstrates with clarity the structural organization typical of fibroadenomas, with benign interaction between epithelial and stromal components.

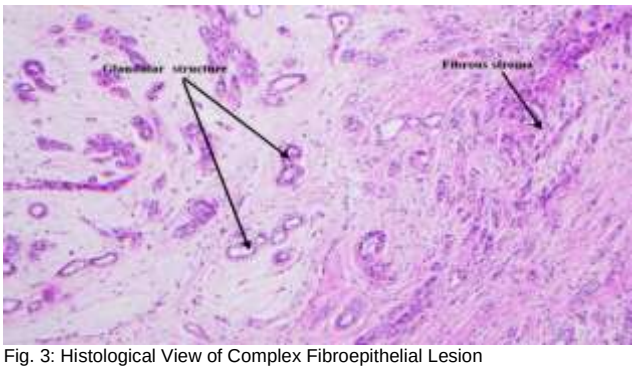

Fig. 3: Histological View of Complex Fibroepithelial Lesion

Histopathological characteristics (fig-1, fig-2) of Simple and complex fibroadenomas differ and affect their clinical significance. Fibroadenoma, simple, with uniform fibrous stroma, scant and regular glandular structures, and absence of atypia or mitotic activity is a benign process not likely to undergo malignant transformation. Whereas complex fibroadenomas show a more heterogeneous composition with irregular stroma, increased cellularity, and marked glandular elements, Sclerosing adenosis, apocrine metaplasia, epithelial calcifications, and cystic changes (≥3 mm) are complex features of these lesions and are not observed in the simple fibroadenoma. Histological differences between complex and simple fibroadenomas correlate with a higher risk of malignancy in complex fibroadenomas and support the need for closer clinical monitoring and specific management than are warranted in simpler fibroadenomas.

DISCUSSION

The present study compared simple fibroadenomas (SFAs) and complex fibroadenomas (CFAs) concerning their distinctive histopathologic features and their association with malignancy[8]. Important differences in types and emphasis that CFAs should be regarded as a higher risk in clinical practice were highlighted by the results. This replication of previous literature finds that CFAs occur at a mean age of 47 years compared to 29 years for SFAs, presumably from cumulative hormonal or microenvironmental influences over time. The complexity was inversely related to the tumor size: CFAs had a mean size of 1.3 cm and SFA 2.5 cm, perhaps indicating that the stroma stabilized earlier in CFAs, limiting growth potential. This is consistent with previous work suggesting that complex lesions are smaller but more histologically complex[9].

The results showed the heterogeneity of CFAs and suggest that CFAs may be precursors to malignancy, since the incidence of histopathological complexities, including sclerosing adenosis (56% in CFAs vs. 12% in SFAs), apocrine metaplasia (22% vs. 8%), calcifications (18% vs. 5%), and cystic changes (35% vs. 10%), is greater in CFAs. The findings are in agreement with Dupont et al., who noted that CFA harbors proliferative changes that increase the relative risk (RR) of malignancy[10]. This elevated risk is likely due, in part, to the increased stromal cellularity and the presence of atypical features in CFAs. The stromal proliferation in CFAs, however, is histologically denser and more cellular, with scattered glandular and ductal structures showing complex architectural features[11]. While SFAs present a uniform fibrous stroma with sparse regular glandular structures, the irregular changes seen in CFAs are not present. The benign behavior of SFAs is corroborated by the absence of atypia and mitotic activity, and the complex histological features in CFAs indicate that a more cautious approach in clinical management is indicated[12].

Consistent with earlier studies, the elevated relative risk of malignancy apparent for CFAs (RR = 2.27) relative to SFAs (RR = 1.49) suggests they should be closely surveilled. Nevertheless, the risk is still small, however, and calls for individualized management strategies, particularly in older patients or those with a family history of breast cancer. These results also bear implications for clinical practice[13]. In patients with histopathologically proven CFAs, the risk of progression may suggest a more intensive regimen of follow-up, including regular imaging and possible surgical excision. However, the minimal risk of SFAs lends itself well to a conservative approach, where observation is generally sufficient.[9, 14].

Due to the retrospective design and the limited sample size of 100 patients, the study has limitations in generalizing the findings to fibroadenoma across the entire spectrum of the disease. These findings must be validated in future prospective studies with larger patient cohorts, longer follow-up, and additional molecular markers to further stratify malignancy risk in fibroadenomas.[15, 16]. Finally, this study shows that there are key histopathological and clinical differences between CFAs and SFAs, with the latter at increased risk of malignancy. Differences in these characteristics must be recognized to achieve optimal diagnostic and management strategies and early intervention for high-risk patients and avoidance of overtreatment of low-risk patients. Together, these findings support the increasing body of evidence that histopathological evaluation should guide clinical decision-making for fibroadenomas[17, 18].

CONCLUSION

This study illustrates large histopathologic differences between simple fibroadenomas (SFAs) and complex fibroadenomas (CFAs), with CFAs revealing features, including sclerosing adenosis, apocrine metaplasia, and calcifications, which are associated with a higher malignancy risk. Older age, smaller size, and increased relative risk of breast cancer were associated with CFAs compared with SFAs. These findings stress the need to perform a precise histopathological evaluation to guide management. While SFAs can often be managed conservatively, CFAs require closer follow-up and possible surgery. Future research will focus on molecular markers to improve risk stratification and develop more personalized diagnostic and therapeutic strategies for fibroadenomas.

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