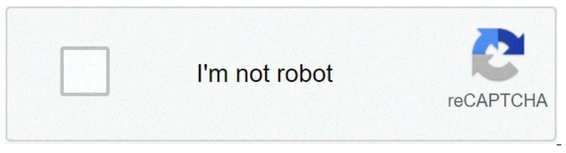

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Difference between fibroadenoma and phyllodes tumor

The histologic border between these two is not always sharp Juvenile Fibroadenoma High Grade Phyllodes Tumor No stromal atypia Atypical stroma Stromal mitotic rate < 3/10 hpf Elevated stromal mitotic rate No stromal overgrowth Stromal overgrowth Does not infiltrate May infiltrate surrounding breast Stromal overgrowth defined as at least one low power field (40x total magnification) composed entirely of stroma Fibroadenoma Low Grade Phyllodes Tumor Lacks significant stromal hypercellularity Hypercellular stroma is prominent No stromal overgrowth May have stromal overgrowth No leaf-like architecture Prominent leaf-like architecture No condensation around ducts Stromal condensation around ducts Does not infiltrate May infiltrate surrounding breast The histologic border between these two is not always sharp Metaplastic Carcinoma Phyllodes Tumor Spindled component may be positive for high molecular weight keratin or p63 Stromal component negative for high molecular weight keratin and p63 Epithelial component is malignant Epithelial component is benign Squamous differentiation may be present No squamous differentiation Pure Sarcoma of the Breast Very rare The presence of an epithelial component defines phyllodes tumor Fibromatosis Bland spindle cells Stellate configuration Absence of intrinsic epithelial component May entrap normal breast lobules Myofibroblastoma Resembles solitary fibrous tumor Lacks intrinsic epithelial component Skip Nav Destination PDF Split View Article contents Figures & tables Video Audio Supplementary Data Cellular fibroepithelial lesions (CFELs) are a heterogeneous group of tumors encompassing cellular fibroadenoma (CFA) and phyllodes tumor (PT). Distinction between the two is challenging on core needle biopsy (CNB) specimens. The objective of this study was to evaluate histologic features that can help distinguish PT from CFA on CNB specimens.Records of all patients diagnosed with CFELs on CNB specimens with follow-up excision between January 2002 and December 2012 were retrieved. Histopathologic stromal features were evaluated on CNB specimens, including mitoses per 10 high-power fields (hpf), overgrowth, increased cellularity, fragmentation, adipose tissue infiltration, heterogeneity, subepithelial condensation, and nuclear pleomorphism.Twenty-seven (42.2%) of 64 were diagnosed as PT (24 benign PTs and three borderline PTs) and 37 (57.8%) as CFA on excision. All features except for increased stromal cellularity were statistically significant. The average number of histologic features seen in PT and CFA was 3.9 and 1.4, respectively (odds ratio [OR], 7.27; 95% confidence interval [CI], 2.44–21.69; P = .0004). The average number of mitoses per 10 hpf was 3.0 for PT compared with 0.8 for CFA (OR, 2.14; 95% CI, 1.18–3.86; P = .01).The presence of mitoses (three or more) and/or total histologic features of three or more on CNB specimens were the most helpful features in predicting PT on excision. Cellular fibroepithelial lesions (CFELs) of the breast are commonly encountered in clinical daily practice. They comprise a heterogeneous group of neoplasms composed of cellular fibroadenoma (CFA) and phyllodes tumor (PT). The core needle biopsy (CNB) is used as a part of triple approach, along with radiology and clinical examination, to make the primary diagnosis on breast lesions. The distinction between CFA and benign phyllodes tumor (BPT) is challenging on CNB specimens due to morphologic overlap in most of those cases. However, it carries a significant impact on clinical management decisions. CFA behaves in an indolent fashion without significant risk of local recurrence1–3 and may be either clinically monitored or treated by simple surgical removal (enucleation). On the other hand, BPT has an unpredictable biologic behavior and carries a risk of local recurrence without distant metastatic potential.4 The reported rate of local recurrence for BPT is 20% in old literature series.4–6 Therefore, the current standard treatment is surgical excision.The extent of surgery remains controversial. Most authors believe that BPT should be widely excised to reduce the risk of local recurrence.7–9 These management decisions are mainly based on the reported observations that surgical margins are the single most important predictor of local recurrence, and BPT should be completely excised with adequate margins.5,10–12 However, data from other studies showed that BPT may be followed up if incompletely removed at the first excision, with wide excision only after recurrence.13 Hence, improvement in preoperative diagnostic accuracy is crucial in the treatment of patients with CFELs on CNB specimens. Furthermore, a substantial proportion of CFEL cases were identified as PT on excision, and consequently, surgical excision has been recommended for complete evaluation of all these lesions.14,15Several studies involving CFELs on CNB specimens have been performed to identify histologic features that can predict BPT on subsequent excision16–19; however, the results are somewhat controversial. Therefore, the purpose of this study is to evaluate several histologic features of CFELs on CNB specimens that can help differentiate the two entities and predict BPT on subsequent excision. Materials and Methods All patients diagnosed with CFELs on CNB specimens at the Mayo Clinic in Rochester, Minnesota, were retrieved from the Mayo Clinic anatomic pathology database from January 2002 through December 2012. Since our study focused on evaluating histologic features of indeterminate CFELs on CNB specimens, all patients with clear-cut diagnoses of CFA and BPT on CNB specimens were excluded. All patients without subsequent surgical excision after the initial core biopsies were also excluded from the study. The study was approved by the Mayo Clinic Institutional Review Board (IRB 12-006492; August 13, 2012). Pathology Review Histologic slides of initial core biopsy specimens and surgical excisions were retrieved on all selected cases and reviewed by two breast pathologists (A.N. and S.Y.) blinded to the original diagnoses on core biopsy and surgical excision specimens. The following histologic features were evaluated on both core biopsy and excisional specimens:Stromal mitoses were counted in 10 high-power fields (hpf) at ×40 Image 1A.Stromal overgrowth was defined as the presence of a merely stromal component/absence of an epithelial component. Stromal overgrowth was evaluated at ×10 for core biopsy specimens Image 1B and at ×4 for excision specimens Image 1C.Increased stromal cellularity was categorized as absent or present. Assessment of stromal cellularity was made on the most cellular areas of the specimen (0, when the stromal cellularity was not increased; 1, when there was a definitive increase in the density of the stromal cells, in the form of stromal nuclear crowding or overlapping) Image 1D.Stromal fragmentation was defined as detached stromal fragments completely covered by the ductal epithelium Image 1E. Stromal fragmentation corresponded to an exaggerated intracanalicular growth pattern and leaf-like architecture.Adipose tissue infiltration or fat entrapment Image 1F was defined as an extension of the stromal cells into the surrounding adipose tissue in an infiltrative pattern. It was considered a feature of a noncircumscribed lesion.Stromal heterogeneity was defined as the overall heterogeneous appearance of a stromal component. This was demonstrated as a difference in stromal cellularity or atypia in different areas of the same tumor Image 1G and Image 1H. Similarly, the stromal component of an individual case showed a hypocellular fibrotic/myxoid appearance (Image 1G) in one area and a hypercellular appearance in another area (Image 1H).Subepithelial stromal condensation was defined as an enhancement of stromal density adjacent to or underneath the ductal epithelium Image 1I.Stromal nuclear pleomorphism or cellular atypia was defined as absent when the stromal cells had small uniform nuclei with evenly distributed chromatin and inconspicuous nucleoli or present when the stromal cells had variability in nuclear size and shape with nuclear membrane irregularity and conspicuous nucleoli Image 1J. Open in new tabDownload slideOpen in new tabDownload slideA, Stromal mitotic activity (H&E, ×40). B, Stromal overgrowth (absence of epithelial component) identified in a core needle biopsy specimen (H&E, ×10). C, Stromal overgrowth (absence of epithelial component) on an excision specimen (H&E, ×4). D, Increased stromal cellularity (H&E, ×20). E, Stromal fragmentation. Stromal fragments completely lined by epithelial cells (H&E, ×4). F, Adipose tissue infiltration (H&E, ×4). G and H, Stromal heterogeneity. Two different areas of the same tumor demonstrate heterogeneity in terms of difference in stromal cellularity and stromal atypia. The stroma is fibrotic (G) in one area and hypercellular in another area (H) (H&E, ×20). I, Subepithelial stromal condensation (H&E, ×10). J, Stromal cells demonstrate moderate to severe nuclear pleomorphism and hyperchromasia (H&E ×40).Final diagnoses of CFA or BPT/borderline PT were made on the excisional specimens based on the previously established histologic criteria, including stromal mitoses, stromal overgrowth, stromal cellularity, infiltration into the surrounding adipose tissue, and stromal atypia.18 The evaluation of excision specimens was performed blinded to the histopathologic features evaluated on a respective CNB specimen. All histologic features evaluated on CNB specimens were then correlated in a retrospective manner with the diagnoses on excision specimens to determine which features on CNB specimens would be helpful in predicting the diagnosis of BPT on a subsequent excision. Clinical Characteristics The patients' clinical records were reviewed to collect demographic and clinical information in a blinded manner, including age of the patient, site and size of the lesion, and other information. Statistical Analysis Patient characteristics and tumor features were summarized with median and range (or mean and standard deviation, as appropriate) for continuous data and with frequencies and percentages for categorical data. As a way to incorporate each of seven features into a single summary measure, the total number of features present (among seven) was calculated for each tumor specimen. In calculating the total number of features, each was given equal weight regardless of univariate significance, so as not to bias this measure based on the limited data available. Data were compared by diagnosis (BPT vs CFA) using two-sample t tests (age, mitoses, and total features) and with $\chi 2$ tests (or Fisher exact tests, as appropriate) for categorical features. Logistic regression modeling was used for further univariate and multivariable analysis. The C statistic was reported for each logistic regression model as a measure of predictive accuracy (equivalent to area under the receiver operating characteristic curve). Values of 0.5 indicate that the model does no better than chance, and values of 1 indicate perfect predictive accuracy. All analyses were performed using SAS version 9 (SAS Institute, Cary, NC). P values less than .05 were considered statistically significant. Results Our initial search identified 73 patients (76 cases) with a diagnosis of CFELs on CNB specimens. Twelve patients were excluded from the study cohort (five patients without subsequent excision, two patients with hamartoma on excision, and five patients with no residual CFELs on excision). Finally, a total of 61 patients met our study criteria. There were 64 CNB and excision specimens, since three patients had bilateral disease and underwent two CNBs and subsequent excision of those lesions. The mean age of the entire study cohort was 41 years (range, 15–83 years). Of the 64 specimens, 27 (42.2%) were diagnosed as PT, including 24 BPTs and three borderline PTs. Thirty-seven (57.8%) of 64 cases were diagnosed as CFA. The final diagnoses of PT and CFA were based on histologic features on excisional specimens.Patients' demographic information and histologic characteristics on CNB specimens were tabulated across the excisional diagnoses Table 1. The mean age of patients diagnosed with PT and CFA was 40.7 and 40.6 years, respectively (P = .98). The mean tumor size in the PT and CFA groups was 2.9 and 1.8 cm, respectively (P = .03). The increase in stromal cellularity was seen in 26 (96.3%) of 27 PTs and 32 (86.5%) of 37 CFAs (P = .39). The stromal cells demonstrated cytologic/nuclear atypia in 20 (74.1%) of 27 PTs and 12 (32.4%) of 37 CFAs (P = .001). Stromal overgrowth was seen in 11 (42.3%) of 27 PTs and only two (5.4%) of 37 CFAs (P = .0004). Twenty-four (88.9%) women with PT and 18 (48.6%) women with CFA showed stromal fragmentation (P = .001). Stromal heterogeneity was observed in 19 (70.4%) of 27 PTs and nine (24.3%) of 37 CFAs (P = .0002). Prominent adipose tissue infiltration was seen in 13 (48.1%) of 27 PTs and six (16.2%) of 37 CFAs (P = .006). Subepithelial condensation was prominent in 17 (63%) of 27 PTs and six (16.2%) of 37 CFAs (P = .0001). The average mitotic figures per 10 hpf were 3 and 0.8 in the PT and CFA groups, respectively (P < .0001). In 27 PTs, 20 (74.1%) cases had three or more mitoses per 10 hpf, three (11.1%) had one to two mitoses per 10 hpf, and four (14.8%) had no mitotic activity. In contrast, among 37 CFA cases, most (22 [59.5%]) had no mitotic activity, 11 (29.7%) had one to two mitoses per 10 hpf, and only four (10.8%) cases had three or more mitoses per 10 hpf. The data on mitotic activity were also analyzed based on two categories (zero to two and three or more), which showed that 20 (74.1%) of 27 PTs had three or more mitoses per 10 hpf, and 33 (89.2%) of 37 CFAs had zero to two mitoses per 10 hpf (P < .0001). Table 1Univariate Analysis of Clinicopathologic Features With Final Excisional Diagnosis (CFA and BPT)a On univariate analysis, except for increased stromal cellularity, all histologic features, including stromal mitotic activity of three or more per 10 hpf, stromal overgrowth, stromal fragmentation, adipose tissue infiltration, stromal heterogeneity, subepithelial condensation, and stromal atypia/pleomorphism, were seen in a significantly higher proportion of women in the PT group than in the CFA group.When the total numbers of evaluated histologic features were calculated for each individual case, it was found that PT cases had more features on average compared with CFA cases. The average number of features seen in PT was 3.9 compared with 1.4 in CFA (P < .0001; data shown in Table 1). Among 27 PT cases, 23 (85.2%) had three to seven features and four (14.8%) had zero to two features. In contrast, of 37 CFA cases, only four (10.8%) had three to seven features, and 33 (89.2%) had zero to two features (P < .0001). In general, the likelihood of PT increases as the total number of features increases. Among those with zero to one feature, none were PT. The percentage with PT increased from 23.5% to 70.0% to 87.5% to 100% for two, three, four, and five to six features, respectively (no case had seven total features). Furthermore, the estimated odds ratio of PT for each additional increase in features was 7.8 (95% confidence interval [CI], 2.8–21.4; P < .0001).With respect to the predictive accuracy of each measure or feature, the total number of evaluated histologic features performed the best (C statistic for continuous version, 0.94), followed by mitoses (C statistic, 0.83). Most of the remaining features performed similarly (C statistic range, 0.66–0.73), with the exception of increased stromal cellularity (C statistic, 0.55) and age (C statistic, 0.51), which had essentially no predictive accuracy. Stromal heterogeneity and subepithelial condensation appear to be the best predictors for PT (C statistic, 0.73 each), followed by stromal pleomorphism (C statistic, 0.71) (see Table 1).A multivariable logistic regression model was estimated, including mitoses and total number of other histologic features (stromal overgrowth, increased stromal cellularity, stromal fragmentation, infiltration into fat, stromal heterogeneity, subepithelial stromal condensation, and stromal nuclear pleomorphism) Figure 1A and Figure 1B. Each variable was statistically significant (mitoses, P = .01; total histologic features, P = .0004). The C statistic for this model was 0.95, and this indicates excellent discrimination between these two groups based on this model. The odds ratio for PT (compared with CFA) for mitoses was 2.14 (adjusted for total features; 95% CI, 1.18–3.86); the odds ratio for total number of histologic features was 7.27 (adjusted for mitoses; 95% CI, 2.44–21.69). The odds ratio can be interpreted as the multiplicative increase in odds of PT for each one-unit increase in the predictor. In a separate model that included tumor size, similar results were found, and tumor size was not statistically significant (data not shown). Open in new tabDownload slideThe boxplots show the difference in mitoses (A) and total number of histologic features (B) between the groups. Note how little they overlap. To interpret the boxplots, the outlined boxes show the middle 50% of the data (between the 25th and 75th percentiles), along with the median shown as the horizontal line in the middle of the box—note that the median and 25th percentile are equal among those with cellular fibroadenoma (CFA) for each of these two measures. The mean is shown by the diamond. BPT, benign phyllodes tumor.The sensitivity and specificity values for mitotic activity and total number of histologic features were calculated. The sensitivity for detecting PT with mitoses of three or more was 74.1%. Similarly, the sensitivity for detecting PT with total histologic features of three or more was 85.2%. Among those who had CFA, the specificity of mitoses of two or less was 89.2%, and the specificity of total histologic features of two or less was also 89.2%. Discussion CFELs on CNB specimens are commonly encountered entities in everyday practice, and differential diagnosis includes CFA or PT. Distinction between the two is often challenging due to significant morphologic overlap and lack of consensus on objective criteria and clear cutoff values. In other words, there are no uniform or standardized distinguishing features that discriminate between CFA and PT on CNB specimens.Most of the previous studies focused on identifying individual histologic features for differentiation between the two entities. Similarly, our data highlight important histologic features on CNB specimens that can help predict PT on subsequent excision. On univariate analysis, except for increased stromal cellularity, all other histologic features evaluated, including stromal mitoses of three of more per 10 hpf, stromal overgrowth, stromal fragmentation, adipose tissue infiltration, stromal heterogeneity, subepithelial condensation, and stromal nuclear pleomorphism, were statistically significant features that discriminated PT from CFA.Jara-Lazaro et al20 showed that moderate to severe stromal cellularity, stromal overgrowth, moderate nuclear atypia, stromal mitoses of two or more per 10 hpf, and ill-defined lesional borders on CNB specimens were exclusive to the diagnosis of PT on excision. Lee et al21 reported that an increase in stromal cellularity of at least 50% greater than typical fibroadenoma, stromal overgrowth, fragmentation, and adipose tissue infiltration were significantly more common in the CNB specimens of PT. Similar results were reported in another study as well.15 Gould et al22 found additional interesting features that are more associated with PT on excision after a diagnosis of fibroepithelial neoplasm in CNB specimens: larger tumor diameter (mean, 4.0 cm; P < .002) and increased hyperechoic mass density (P < .001) on preoperative imaging, in addition to Hispanic ethnicity.In agreement with other studies,15,20 we found that the presence of stromal overgrowth evaluated at ×10 was a useful feature. In comparison with other studies,15,20 we found that increased stromal cellularity was not a helpful feature (seen in 96.3% and 86.5% of PT and CFA cases, respectively). This difference could be related to our lower threshold for increased stromal cellularity.Most of the individual histologic features assessed in this study were seen in both PT and CFA groups. Therefore, the use of a combination of histologic features would be desirable and more helpful. Our data highlight an important aspect of our review that the total number of histologic features seen in an individual case of PT was significantly more than in those with CFA, regardless of which particular features were seen. Most PT cases (85.2%) demonstrated a combination of more than three histologic features. In contrast, most CFA cases (89.2%) showed fewer than three histologic features. In our cohort, the mean (SD) number of histologic features seen in PT was 3.9 (1.2), whereas it was 1.4 (1.0) in CFA. In other words, there was very little overlap in the number of features seen in PT and CFA groups. This is statistically significant (P < .0001) and helpful in real practice, since it provides a clear- cut number of histologic features that are in favor of PT.Our data support that the presence of any three or more evaluated histologic features (stromal overgrowth, increased stromal cellularity, stromal fragmentation, infiltration into fat, stromal heterogeneity, subepithelial stromal condensation, and stromal nuclear pleomorphism) on CNB specimens favors PT over CFA on multivariate analysis. The likelihood or probability of BPT increases with every one-unit increase in the number of histologic features assessed on CNB specimens. In particular, the constellation of stromal heterogeneity, subepithelial condensation, and stromal pleomorphism appears to be the best predictors for PT (Table 1).Furthermore, our data showed that the stromal mitotic activity of three or more by itself was very helpful in discriminating PT based on a multivariable logistic regression model. Both mitotic activity (P = .01) and the total number of histologic features (P = .0004) were statistically significant. The patients' age was not helpful in distinguishing PT from CFA on univariate (data shown in Table 1) and multivariate analysis, respectively (data not shown). Although tumor size was significantly different between the groups on univariate analysis (Table 1), this was no longer helpful in distinguishing PT from CFA on multivariate analysis (after adjusting for mitoses and number of features). In contrast to previous studies, we showed that patients' age as well as tumor size is not a useful clinical parameter in the distinction of PT.7,22–24In conclusion, two important significant findings in the current study are in favor of the diagnosis of PT on follow-up excision. The finding of prominent mitotic activity (≥3/10 hpf) is by itself adequate to favor PT over CFA based on multivariate analysis. On the other hand, if there is no stromal mitotic activity, the constellation of other (at least three) histologic features (stromal overgrowth, increased stromal cellularity, stromal fragmentation, infiltration into fat, stromal heterogeneity, subepithelial stromal condensation, and stromal nuclear pleomorphism) in a CNB specimen are more predictive of PT than CFA.We thank Victoria L. Jackson, MLIS (Academic and Research Support, Mayo Clinic, Jacksonville, FL), for editorial assistance. References 15. et al. . Fibroepithelial lesions with cellular stroma on breast core needle biopsy: are there predictors of outcome on surgical excision?. ;:–.16. . Analysis of histological features in needle core biopsy of breast useful in preoperative distinction between fibroadenoma and phyllodes tumour. . ;:–.21. et al. . Histological features useful in the distinction of phyllodes tumour and fibroadenoma on needle core biopsy of the breast. . ;:–.22. et al. . Factors associated with phyllodes tumor of the breast after core needle biopsy identifies fibroepithelial neoplasm. . ;:–.23. et al. . The sensitivity of needle core biopsy in combination with other investigations for the diagnosis of phyllodes tumor of the breast. . ;:–.24. Original Articles