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Differential Diagnosis of Fibroadenoma and Phyllodes Tumor
- Additional Histopathologic Feature besides Common Diagnostic Criteria

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Abstract

Background: Fibroadenoma is common mammary disease and dosen't recur after surgical treatment. But some phyllodes tumor has similar morphologic feature, its clinical course may be different. So differential diagnosis between two entity is important. However, widely accepted, helpful ancillary test is not identified by now. The aim of this study is the evaluation of additional histologic feature besides commonly used diagnostic criteria.
Methods: We had reviewed medical records, pathologic records and corresponding slides for variable histopathologic features of fibroadenoma group (FAs) during 1 year and phyllodes tumor group (PTs) during 3 years. We had determined significance of histologic features between two groups; first group set with FAs and PTs (both benign and borderline), and second group set with FAs and benign PTs.
Results: All 90 fibroepithelial tumors (62 FAs and 28 PTs) were histologically assessed. Besides commonly used diagnostic criteria, periductal stromal hypercellularity, heterogeneity of stromal cellularity, heterogeneity of glandular distribution, stromal expansion, dilated gland and beaded gland were significant for differential diagnosis between FAs and PTs ($p<0.01$). For the differential diagnosis between FAs and benign PTs, stromal cellularity, stromal nuclear atypia, stromal expansion, heterogeneity of glandular distribution and beaded gland are significant ($p<0.01$), but heterogeneity of stromal cellularity ($p=0.034$), dilated gland ($p=0.743$) or tumor margin ($p=0.053$) is insignificant.
Conclusion: Besides common diagnostic criteria, some histologic features such as periductal stromal hypercellularity, heterogeneity of stromal cellularity, heterogeneity of glandular distribution, stromal expansion, dilated gland and beaded gland are useful for differential diagnosis between FAs and PTs. However, the useful histologic features for differential diagnosis between FAs and benign PTs are limited to stromal cellularity, stromal nuclear atypia, stromal expansion, heterogeneity of glandular distribution and beaded gland.

Key words : fibroadenoma, phyllodes tumor, differential diagnosis, heterogeneity of glandular distribution, stromal expansion, beaded gland

INTRODUCTION

Fibroadenoma is one of the most common mammary disease, and it has typical clinical presentation and pathologic feature. Its diagnosis and treatment is relatively simple and easy. But sometimes, differential diagnosis with phyllodes tumor is considered and different clinical approach is needed due to potential of recurrence. Although it is arguable what is predictive feature for recurrence of phyllodes tumor, and the suggested histologic features are surgical margin status, tumor grade, stromal overgrowth, tumor necrosis, and heterologous stromal elements.[1,2] Even though these features are helpful for differential diagnosis between fibroadenoma and phyllodes tumor, troublesome cases still are present. The current study aimed to find the additional histologic features of fibroadenoma and phyllodes tumor.

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MATERIAL AND METHOD

Case collection

Cases were collected from surgical pathology list of the Department of Pathology at Gospel Hospital, Kosin University, Busan, Korea. They were composed of fibroadenoma groups(FAs) including fibroadenoma, fibroadenomatosis, fibroadenomatoid hyperplasia from 2003

January to 2003 December and phyllodes tumor groups(PTs) including benign, borderline, malignant phyllodes tumor from 2001 January to 2003 December.

Histology and grading

All of the original H&E slides were reviewed to confirm the diagnosis. Pathologic data obtained from the macroscopic report and histopathological review and they included: tumor size, tumor number, tumor margin, stromal mitotic count, stromal nuclear atypia, stromal cellularity, stromal overgrowth at 40 magnification, stromal expansion at 100 magnification, heterogeneity of stromal cellularity, heterogeneity of glandular distribution, periductal stromal hypercellularity, intratumoral non-specialized stroma, heterologous elements, collagenous change, necrosis, intratumoral glandular arrangement, large leaf-like architecture, and surgical margin. The inadequate cases for evaluation of some histologic feature were excluded in corresponding item. The requirements of each histologic feature were summarized in Table 1-3 and representative features were presented in Fig. 1-6.

Phyllodes tumor was basically graded by WHO classification[3]. Malignant phyllodes tumor was diagnosed when they had marked stromal cellularity in more than 80% of the tumor, marked cytologic atypia in more than 80% of the tumor, infiltrative margin in any proportion of

Table 1. Definition and grading of overall histologic feature

Histologic feature	Grade	Definition
Tumor margin	pushing	expansile growth without infiltrative foci
	indefinite	blurred but indistinct border
	infiltrative	fibroblast infiltrating into adjacent mammary epithelial component or fat
Surgical margin	exposed	exposed by tumor
	abutted	free (safety margin: less than 0.5mm)
	free	free (safety margin: more than 0.5mm)
Leaf-like architecture	present/absent	papillary stromal projection into slit-like, different shaped, epithelial lined spaces
	indefinite	papillary stromal projection into narrow and parallel epithelial lined space

Table 2. Definition and grading of stromal histologic features

Histologic feature	Grade	Definition
Mitotic count		sum of mitosis in continuous 10 high power field(hpf) at 400 magnification
Nuclear atypia	little	nuclei resembling normal periductal cells
	moderate	mildly irregular and enlarged nuclei (less than double size) with occasional nucleoli
	marked	markedly irregular or enlarged nuclei (more than double size) with common nucleoli at 100 magnification field
Cellularity	scanty	few stromal cell
	mild	intercellular space more than one stromal cell diameter
	moderate	intercellular space as one stromal cell diameter
	marked	little intercellular space, resulting in touched stromal nuclei
Periductal stromal hypercellularity	present/absent	more increased cellularity along gland
Stromal overgrowth(x40)	present/absent	only stroma without epithelium at least one 40 magnification field
Stromal expansion(x100)	present/absent	only stroma without epithelium at least one 100 magnification field
Heterogeneity of cellularity	present/absent	different stromal cellularity in continuous 3 representative field at 40 magnification
Heterologous elements	present/absent	differentiation into fat, smooth muscle, bone, cartilage
Necrosis	present/absent	coagulative necrosis
Intratumoral non-specialized stroma	present/absent	intersecting non-specialized stroma between mammary lobule
Collagenous change	present/absent	change into acellular fibrotic change

Table 3. Definition and grading of epithelial histologic features

Histologic feature	Grade	Definition
Arrangement	intracanalicular	elongated gland
	pericanalicular	round gland
	mixed	both intracanalicular and pericanalicular
Heterogeneity of glandular distribution	present/absent	irregular and asymmetric distribution in continuous 3 representative field at 40 magnification
Beaded gland	present/absent	discontinuously fused gland like chain
Dilated gland	present/absent	glands with dilated lumen

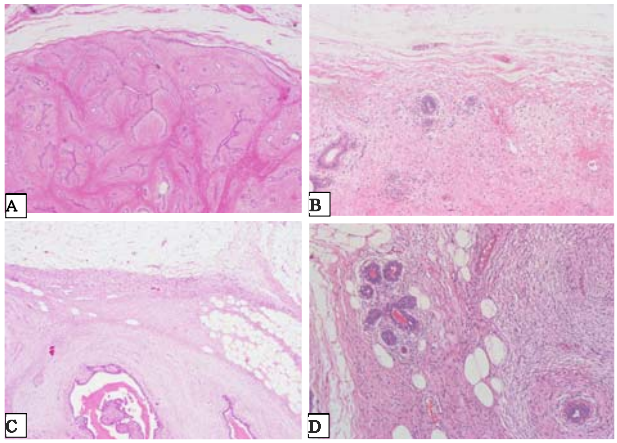

Fig. 1. Tumor margin. (A) Well-defined pushing margin with surrounding fibrous capsule, (B) Blurred indefinite margin without definite infiltration, (C,D) Infiltrative margin with invasive stromal cells into adjacent adipose tissue and terminal duct-lobular unit

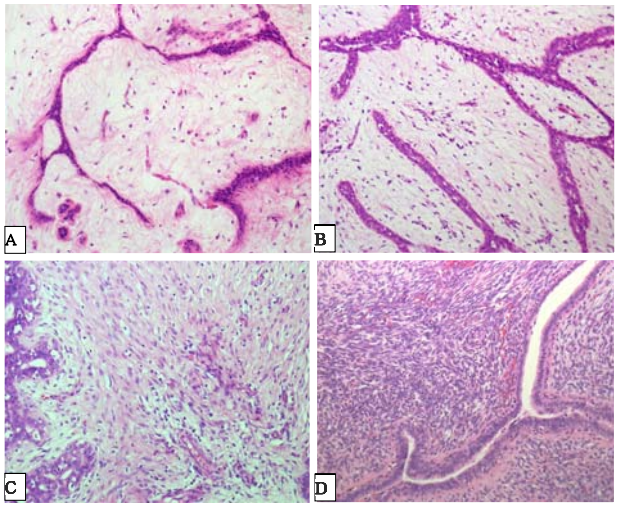

Fig. 2. Stromal cellularity. (A) Scanty cellularity with few stromal cells, (B) Mild cellularity with intercellular space more than one stromal cell diameter, (C) Moderate cellularity with intercellular space as one stromal cell diameter, (D) Marked cellularity with little intercellular space, resulting in touched stromal nuclei

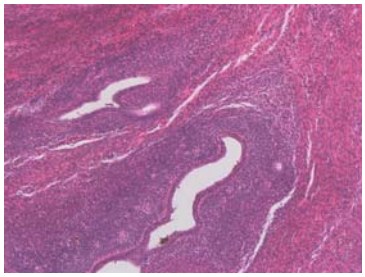

Fig. 3. Periductal hypercellularity defined as more increased stromal cellularity in periglandular area than distant area from gland

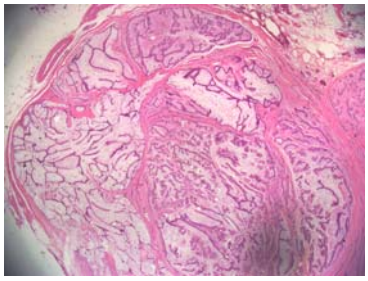

Fig. 4. Intratumoral non-specialized stroma intersecting the mammary lobule

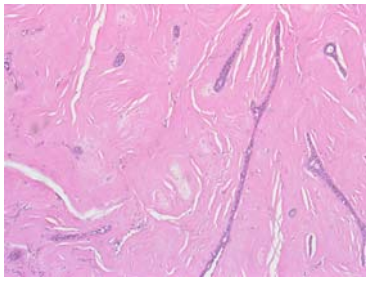

Fig. 5. Collagenous stromal change into acellular fibrosis

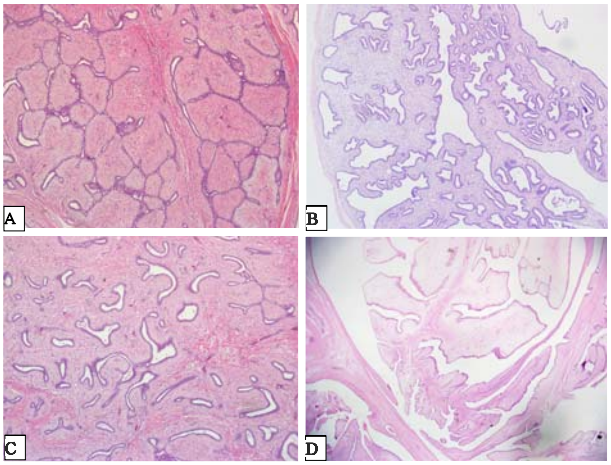

Fig. 6. Glandular arrangement. (A) Intracanalicular pattern with beaded gland, (B) Intracanalicular pattern with dilated gland, (C) Pericanalicular pattern, (D) Leaf-like architecture distinguished from dilated and wide lumen of intracanalicular pattern

circumference, stromal overgrowth and a mitotic count ≥ 10/10 high power fields (hpfs). If two former histologic feature did not fulfill the required proportion, it was adjusted into one down grade. If the spindle cell lesion with overt malignant heterologous element had no epithelial element and previous history, it was excluded from this

Table 4. Result of the histologic findings in FAs and PTs

Histologic feature	FA (n=62)	PT (n=28)	
Tumor margin			p<0.001
NA	7 (11.2%)	2 (7.1%)	
Pushing	53 (85.4%)	12 (42.9%)	
Indefinite	2 (3.2%)	4 (14.3%)	
Infiltrative	0 (0%)	10 (35.7%)	
Leaf-like architecture			p<0.001
Absent	49 (74.4%)	18 (64.3%)	
Indefinite	13 (21.0%)	2 (7.1%)	
Present	0 (0%)	8 (28.6%)	
Stromal mitosis (mean count/10hpfs & distribution)	14 (0.2, 0-1)	22 (4, 0-20)	p<0.001
Stromal nuclear atypia			p<0.001
Little	61 (98.4%)	14 (50.0%)	
Moderate	1 (1.6%)	10 (35.7%)	
Marked	0 (0%)	4 (14.3%)	
Stromal cellularity			p<0.001
Scanty	6 (9.7%)	0 (0%)	
Mild	27 (43.5%)	2 (7.1%)	
Moderate	29 (46.8%)	12 (42.9%)	
Marked	0 (0%)	14 (50.0%)	
Periductal stromal hypercellularity			p<0.001
NA	0 (0%)	3 (10.7%)	
Absent	62 (100%)	22 (78.6%)	
Present	0 (0%)	3 (10.7%)	
Stromal overgrowth			p<0.001
Absent	62 (100%)	19 (67.9%)	
Present	0 (0%)	9 (32.1%)	
Stromal expansion			p<0.001
Absent	59 (95.2%)	11 (39.3%)	
Present	3 (4.89%)	17 (60.7%)	
Heterogeneity of stomal cellularity			p=0.006
Absent	42 (67.7%)	10 (35.7%)	
Present	20 (32.3%)	18 (64.3%)	
Heterologous elements			p=0.528
Absent	61 (98.4%)	28 (100%)	
Present	1 (1.6%)	0 (0%)	
Necrosis			p=0.028
Absent	62 (100%)	25 (89.3%)	
Present	0 (0%)	3 (10.7%)	
Intratumoral non-specialized stroma			p=0.023
Absent	49 (79.0%)	15 (53.6%)	
Presnet	13 (21.0%)	13 (46.4%)	
Collagenous change			p=0.700
Absent	5 (8.1%)	3 (10.7%)	
Present	57 (91.9%)	25 (89.3%)	
Glandular Arrangement			p=0.017
NA	0 (0%)	4 (14.3%)	
Intracanalicular	41 (66.1%)	15 (53.6%)	
Pericanalicular	3 (4.8%)	3 (10.7%)	
Mixed	18 (29.0%)	6 (21.4%)	
Heterogeneity of glandular distribution			p<0.001
NA	0 (0%)	2 (7.1%)	
Absent	50 (80.6%)	4 (14.3%)	
Present	12 (19.4%)	22 (78.6%)	
Beaded gland			p<0.001
NA	0 (0%)	2 (7.1%)	
Absent	7 (11.3%)	15 (53.6%)	
Present	55 (88.7%)	11 (39.3%)	
Dilated gland			p<0.001
NA	0 (0%)	2 (7.1%)	
Absent	27 (43.5%)	16 (57.1%)	
Present	35 (56.5%)	10 (35.7%)	

study. Borderline phyllodes tumor was diagnosed when they had some but all the characteristics observed in malignant phyllodes tumor. Benign phyllodes tumor was diagnosed when the evident leaf-like architecture or stromal mitotic count >2/10hpfs is seen in the fibroepithelial tumor. Fibroadenoma was diagnosed when they were fibroepithelial tumor without evidence of phyllodes tumor.

Table 5. Result of the histologic findings in FAs and benign PTs

Histologic feature	FA (n=62)	benign PT (n=10)	
Tumor margin			p=0.053
NA	7 (11.2%)	2 (20.0%)	
Pushing	53 (85.4%)	6 (60.0%)	
Indefinite	2 (3.2%)	2 (20.0%)	
Infiltrative	-	-	
Leaf-like architecture			p<0.001
Absent	49 (79.0%)	4 (40.0%)	
Indefinite	13 (21.0%)	1 (10.0%)	
Present	0 (0%)	5 (50.0%)	
Stromal mitosis (mean count/10hpfs & distribution)	14 (0.2, 0-1)	6 (2.3, 0-4)	p<0.001
Stromal nuclear atypia			p=0.001
Little	61 (98.4%)	6 (60.0%)	
Moderate	1 (1.6%)	4 (40.0%)	
Marked	-	-	
Stromal cellularity			p=0.004
Scanty	6 (9.7%)	0 (0%)	
Mild	27 (43.5%)	2 (20.0%)	
Moderate	29 (46.8%)	5 (50.0%)	
Marked	0 (0%)	3 (30.0%)	
Periductal stromal hypercellularity			NA
Absent	62 (100%)	10 (0%)	
Present	-	-	
Stromal overgrowth			NA
Absent	62 (100%)	10 (0%)	
Present	-	-	
Stromal expansion			p=0.001
Absent	59 (95.2%)	5 (50.0%)	
Present	3 (4.8%)	5 (50.0%)	
Heterogeneity of stromal cellularity			p=0.034
Absent	42 (67.7%)	3 (30.0%)	
Present	20 (32.3%)	7 (70.0%)	
Heterologous elements			p=1.000
Absent	61 (98.4%)	10 (100%)	
Present	1 (1.6%)	0 (0%)	
Necrosis			NA
Absent	62 (100%)	10 (100%)	
Present	-	-	
Intratumoral non-specialized stroma			p=0.232
Absent	49 (79.0%)	6 (60.0%)	
Present	13 (21.0%)	4 (40.0%)	
Collagenous change			p=1.000
Absent	5 (8.1%)	1 (10.0%)	
Present	57 (90%)	9 (90%)	
Glandular arangement			p=0.209
Intracanalicular	41 (66.1%)	6 (60.0%)	
Pericanalicular	3 (4.8%)	2 (20.0%)	
Mixed	18 (29.0%)	2 (20.0%)	
Heterogeneity of glandular distribution			p=0.002
Absent	50 (80.6%)	3 (30.0%)	
Present	12 (19.4%)	7 (70.0%)	
Beaded gland			p=0.002
Absent	7 (11.3%)	6 (60%)	
Present	55 (88.7%)	4 (40%)	
Dilated gland			p=0.743
Absent	27 (43.5%)	5 (50%)	
Present	35 (56.5%)	5 (50%)	

Clinical and follow-up data

Clinical data was obtained from the medical records. Each individual case history was reviewed to obtain demographic and clinical data which included: age, sex, operation type, length of follow-up, recurrence, and previous breast disease history.

Statistics

The Fisher exact test was used to determine significance of histologic feature between two groups; first group set with FAs and PTs (both benign and borderline), and second group set with FAs and benign PTs. Analysis for mitosis was done by mitotic count not number of presenting cases, and others were done by number of presenting cases. Significance was established at $p<0.01$.

RESULTS

The 62 FAs and 30 PTs were collected. Among them, two cases diagnosed as phyllodes tumor were excluded due to need of differential diagnosis of sarcoma and phyllodes tumor having only stromal element including malignant heterologous element at first presentation.

Of the 90 fibroepithelial tumors assessed histologically, there were 62 FAs (68.8%) and 28 PTs (31.1%). PTs were graded into 10 benign PTs (35.7% among PTs) and 18 borderline PTs (64.2%). Malignant PT was not identified in this study.

The median age was 43.5 years (range, 19-54 years), 48 years (range, 21-60 years) and 43 years (range, 18-45 years) in patient with FAs, benign PTs and borderline PTs, respectively. The number and mean size of tumor were 1.1, 1.3 and 1.14, and 2.03cm, 4.64cm and 5.23cm in FAs, benign PTs and borderline PTs, respectively. Due to operation type such as enucleation or fragmented excision, and paucity of epithelial component, some case had limitation for evaluation of resection margin and several features relating with epithelial component.

The significant histologic features for differential diagnosis between FAs and PTs were periductal stromal hypercellularity, stromal expansion, heterogeneity of stromal cellularity, heterogeneity of glandular distribution, beaded gland, dilated gland as well as common diagnostic criteria such as stromal cellularity, stromal nuclear atypia, tumor margin, stromal overgrowth, stromal mitotic count or leaf-like architecture (Table 4).

The significant histologic features for differential diagnosis between FAs and benign PTs were stromal expansion, heterogeneity of glandular distribution, beaded gland as well as common diagnostic criteria such as stromal cellularity, stromal nuclear atypia, leaf-like architecture or stromal mitotic count. In contrast to differential diagnosis between FAs and PTs (including both benign and borderline PTs), neither tumor margin ($p=0.053$), heterogeneity of stromal cellularity ($p=0.034$) nor dilated gland ($p=0.743$) was significant (Table 5).

Either necrosis, intratumoral non-specialized stroma, collagenous change or glandular arrangement was insignificant for two groups of differential diagnosis. Heterologous element was insignificant, but this results had limited value due to exclusion of the spindle cell lesion with overt malignant heterologous element, no epithelial element and no previous history of phyllodes tumor, possible malignant phyllodes tumor with extensive heterologous element.

Heterogeneity of glandular distribution reflected the heterogeneity of stromal area without entrapped glands and it was significant for two groups of differential diagnosis. But heterogeneous stromal cellularity itself without consideration of stromal area was not significant for differential diagnosis between FAs and benign PTs (Table 6).

Table 6. Histologic feature relating stromal heterogeneity

Histologic feature	FA (n=62)	Benign PT (n=10)	p-value
Hetergeneous stromal cellularity only	20/62 (32.3%)	7/10 (70%)	0.034
Heterogeneous glandular distribution only	12/62 (19.4%)	7/10 (70%)	0.002
Both hetergeneous stromal cellularity and heterogeneous glandular distribution	5/62 (8.1%)	5/10 (50%)	0.003
Either hetergeneous stromal cellularity or heterogeneous glandular distribution	27/62 (43.5%)	9/10 (90%)	0.014

DISCUSSION

Fibroadenoma is most common benign neoplasm in breast. It is typically presented as well-defined, non-tender, movable mass in adolescents and young adults. Grossly it is encapsulated, firm and solid mass. So it is treated by enucleation, mammotome excision, or only observed in situ in the patient, and it do not recur after surgical removal. Furthermore, if wide resection with surrounding normal breast tissue is taken, it may be excess. In contrast, any phyllodes tumor, regardless tumor grade, have potential of recurrence, although variable and different frequency was reported depending on tumor grade and study groups(recurrence: 10-25% in benign phyllodes tumor, up to 32% in borderline phyllodes tumor, up to 25-40% in malignant phyllodes tumor; metastasis: less than 5% in borderline phyllodes tumor, 25% in malignant phyllodes tumor.[4,5,6] So it usually requires the surgical excision with prompt safety margin for prevention of recurrence and metastasis.[7,8] Therefore it is important to distinguish fibroadenoma from phyllodes tumor as well as grading of the phyllodes tumor.

The pathologic diagnosis for fibroadenoma is a part of daily practice, and not usually difficult. However it sometimes need to be differentiated from other mimicking diseases, particularly phyllodes tumor.[9] Although more cellularity and leaf like papillary projection into cystic space in phyllodes tumor is suggested as helpful finding for differential diagnosis, it may be still problematic in practice due to their overlapping histologic findings, such as cellular fibroadenoma, hypocellular region in phyllodes tumor and artificial papillary projection in fibroadenoma resulting from violent specimen handling.[2,10,11]

In 2003, WHO made the grading system for phyllodes tumor into benign, borderline, malignant , and it was based on stromal cellularity, cellular pleomorphism, mitotic count, tumor margin appearance and stromal heterogeneity. But it didn't present clear cut-off value of individual criteria and detailed combination condition into each grade. In addition, many another grading systems are still used and their variable terminology and cut-off of individual criteria can make pathologist and clinician to be confusing.[2,4,12]

Disappointingly, there is no widely accepted ancillary test for differential diagnosis and grading of fibroadenoma and phyllodes tumor, although many investigations have been taken with immunohistochemistry such as CD10, p53, c-kit, EGFR, ER, and PR, and molecular study by DNA sequencing, DNA flow cytometry, comparative genomic hybridization(CGH) and array CHG.[1,10,13-18] In this situation, the knowledge about additional histologic feature in addition to common histologic feature will be helpful.

In phyllodes tumor, the leaf-like architecture may be so distinctive that its name "cystosarcoma phyllodes" was suggested at first. But it is not always seen in phyllodes tumor. In this study, it is identified in 8/28 (28%) overall PTs, 5/10 (50%) benign PTs and 3/18 (16%) borderline PTs. Although there is no leaf-like architecture in FAs, there is indefinite leaf-like architecture in 13/62 (20%) cases. These mimicking foci are small-sized stromal projection, epithelial papillary projection, or wide glandular cleft made by violent specimen handling. For prevention of confusion, the leaf-like architecture should be diagnosed strictly, based on large papillary stromal projection into slit-like, epithelial lined spaces with different shape.[11]

Traditionally, fibroepithelial tumor is considered as neoplasm of specialized intralobular stroma with entrapped and distorted non-neoplastic glandular element. Neoplastic specialized intralobular stroma in phyllodes tumor can infiltrate into fat, adjacent terminal duct-lobular units and ducts, and stimulate the growth of the entrapped glands. So phyllodes tumor have haphazardly incorporated adipose tissue and non-altered mammary lobule as well as disorderly proliferating gland.[10,19] In some other way, "fibroproliferation" defined as presence of fibroadenomatous satellite nodules and/or periductal stromal proliferation adjacent to the main lesion may be identified in phyllodes tumors.[20] By right, these infiltrative fibroproliferative foci can lead to increased probability of local recurrence. In contrast to phyllodes tumor, fibroadenoma is characterized by expansile growth pattern and vested with outmost capsule formed by compression of nonspecialized stroma. But early fibroadenoma have no capsule, and so called "fibroadenomatoid mastopathy" or "fibroadenomatosis" shows dispersed and less compact

fibroblastic proliferation without distinct delineation.[11] In this study, two FAs and two benign PTs have indefinite tumor margin, though majority of them have pushing margin (96% in FAs and 75% benign PTs, except non-available case).

With progression, non-specialized stroma in interlobular region are incorporated into tumor, it is orderly arranged in fibroadenoma but it may be disrupted in phyllodes tumor.[11] But in this study, intratumoral non-specialized stroma is more frequently seen in benign and borderline PTs rather than FAs, and it is insignificant for differential diagnosis between two groups (p=0.023, p=0.232)

In phyllodes tumor, expansion of specialized stroma become to be more marked, glandular element is subsequently reduced. Progressing this course, marked stromal proliferation without glandular element, so called stromal overgrowth is made. In this point and by definition, stromal overgrowth (x40) is seen in not fibroadenoma or benign phyllodes tumor but borderline or malignant phyllodes tumor. In this study, stromal overgrowth (x40) is identified in 9/18 (50%) borderline PTs, and it is important feature for borderline and malignant (albeit not seen in this study) phyllodes tumor. But it is not helpful to differential diagnosis of benign phyllodes tumor and fibroadenoma. Stromal expansion (x100) is identified in 12/18 (66%) borderline PTs, 5/10 (50%) benign PTs and 3/62 (4%) FAs. Even though stromal expansion itself is not specific for phyllodes tumor, it is helpful for differential diagnosis between FAs and PTs ($p<0.001$), and between FAs and benign PTs (p=0.001). This result is similar with previous study for breast core biopsy in 82 fibroepithelial tumor, which show stromal overgrowth and stromal expansion (defined with same standard) in 2% FAs and 36% in PTs.[21] These stromal overgrowth or expansion results from advanced stromal heterogeneity, important histologic feature of phyllodes tumor. But accurate definition for stromal heterogeneity is not suggested by WHO. The stromal heterogeneity may be along the both heterogeneity of stromal cellularity or heterogeneity of stromal area reflected by glandular distribution. In this study, heterogeneity of glandular distribution is significant feature in two groups of differential diagnosis. But heterogeneity of stromal cellularity has limited value for differential diagnosis between FAs and benign PTs, if heterogeneous area is not considered together.

Nevertheless, the heterogeneity of stromal cellularity may result in misdiagnosis, especially with limited specimen, such as needle core biopsy and fine needle aspiration. The suggested helpful findings by a few study are stromal mitosis, Ki67 labelling index (6% phyllodes tumor vs 1.6% in fibroadenoma), fragmentation of stroma with epithelial lining on opposing edges, stromal overgrowth or expansion, infiltrative margin and presence of entrapped fat.[20,22-24] But suggested findings and their frequency are variable. If tumor have one or more previous findings, large size (>3cm) or rapid growth, excision is recommended.[10]

Stromal mitosis is one of the criteria for grading of phyllodes tumor, and increase in proportion to tumor grade. As expected, the borderline PTs have higher mitotic count (6/10hpfs) than benign PTs (2.3/10hpfs) and FAs (0.2/10hpfs) in this study. But 22% FAs show few mitosis (1/10hpfs in 13 FAs and 2/10hpfs in 1 FAs), particularly in FAs with moderate cellularity (8/29, 27%) rather than FAs with little to mild cellularity (6/33, 18%). These FAs have no otherwise features favoring phyllodes tumor and don't recur except for one case with recurrence as combined fibroadenoma and benign phyllodes tumor after four years. These results conflict with previous reports that mitosis is rarely seen in fibroadenoma.[3,4] Although the opinion by Fechner is that a mitotic count up to 2/10hpfs is acceptable for diagnosis of fibroadenoma, it is not generally accepted now.[25] Fibroadenoma with mitosis seem to be not rare as expected, and few mitosis itself may not be diagnostic criteria for phyllodes tumor. However, one of them have subsequent phyllodes tumor, and significance of mitosis in that case is uncertain for malignant potential. The stromal mitotic activity is frequent in area close to the epithelium.[26] In addition, the cellularity in area close to the epithelium may be higher than distant stroma from the epithelium. These, so called periductal hypercellularity may be seen in PTs, but not FAs. In this study, periductal hypercellularity is identified in only 3 cases of PTs, all of which are borderline PTs. Although its frequency is not high, if present, it may be helpful in differential diagnosis

($p<0.001$).

Recently, a new concept for phyllodes tumor is suggested, contrasting with the traditional one that regards epithelial component as nonfunctional, entrapped component within the neoplastic stromal component. According that, epithelial component have monoclonality and function, even though it is a part of the whole. Some study suggests the mechanism about initiation and progression of phyllodes tumor, which epithelium is considered as functional component through epithelial stromal interaction, which loss results in increased stromal mitotic activity, increased stromal cellularity, stromal overgrowth, and increasing progression to malignancy.[18,27,28] But these are still under the investigation, and further evaluation is needed for the wide agreement.

The epithelial component of fibroadenoma is arranged in intracanalicular, pericanalicular and mixed pattern. These glandular arrangement is subsequent presentation according to stromal growth pattern. The epithelial component of phyllodes tumor is most commonly arranged in intracanalicular pattern, but pericanalicular pattern is also seen. In this study, PTs with pure pericanalicular pattern is one in borderline PT and two in benign PTs.

The glandular lumen of intracanalicular pattern in fibroadenoma is generally narrow and its epithelium is closed to opposed side with beaded appearance. But some glands may be dilated or mixed.

In this study, the size of PTs and FAs are 1cm to 23cm and 1cm to 6.5cm, respectively. Its median size is 4cm, 3cm and 2cm in borderline, benign PTs and FAs, respectively and tumors tends to be enlarged corresponding to malignant potential. But 3/16 borderline PTs and 3/10 benign PTs are smaller than 2cm, median size of FAs, and 7/62 FAs are larger than 3cm, median size of PTs. So tumor size can't be a suggesting feature for tumor entity. This finding is similar with previous results that the tumor size is not considered as reliable criteria for differential diagnosis and grading due to wide range of tumor size in phyllodes tumor and fibroadenoma, although phyllodes tumor tends to be larger than fibroadenoma.[2,29]

Phyllodes tumor is most commonly presented in middle aged adult (median age: about 45 years), although it may occur adolescent or older adult. In this study, the age range of PTs is wide and the median ages of benign and borderline PTs are 40.6 and 43.4 years, respectively. These are similar with previous study that higher age corresponds to higher tumor grade. Tse et. al concluded that progression of phyllodes tumor evoke increased grade during aging.[30] But the older median age of FAs (35.5 years) is contrast with previous well-established reports that fibroadenoma is most commonly presented in young adult, 15-20 years younger than phyllodes tumor.[29] Fibroadenoma in the older woman may be regarded as problem related with hormonal imbalance, such as hormone therapy, variable drugs.[11] But there are no enough evidence to prove the relation with older age and hormonal status in this study.

Conclusion

Besides common diagnostic criteria such as leaf-like architecture, stromal mitotic count, stromal cellularity, stromal nuclear atypia, tumor margin or stromal overgrowth, some histologic features such as periductal stromal hypercellularity, heterogeneity of stromal cellularity, heterogeneity of glandular distribution, stromal expansion, dilated gland and beaded gland are useful for differential diagnosis between FAs and PTs. However, the useful histologic features for differential diagnosis between FAs and benign PTs are limited to stromal cellularity, stromal nuclear atypia, stromal expansion, heterogeneity of glandular distribution and beaded gland.

Some features in this study have limitation to analyze due to small number of case, so additional study with more cases will be helpful.

References

1) Tan PH : 2005 Galloway Memorial Lecture : Breast phyllodes tumours: morphology and beyond. Ann Acad Med Singapore 34:671-677, 2005
2) Karim RZ, Gerega SK, Yang YH, Spillane A, Carmalt H, Scolyer RA, Lee CS : Phyllodes tumours of the breast: a

clinicopathological analysis of 65 cases from a single institution. Breast 18:165-170, 2009
3) Tavassoli F : World health organization classification of tumors: Tumors of the breast and female genital organs, 1st ed, Lyon, France, IARC Press, 2003, 99-103
4) Rosen PP : Rosen's breast pathology, 3rd ed, Philadelphia, Lippincott Williams & Wilkins, 2009, 187-226
5) Moffat CJ, Pinders SE, Dixon AR, Elston CW, Blamey RW, Ellis IO : Phyllodes tumors of the breast: a clinicopathological review of thirty-two cases. Histopathology 27:205-18, 1995
6) Cohn-Cedermark G, Rutqvist LE, Rosendahl I, Silfversward C : Prognostic factors in cystosarcoma phyllodes. A clinicopathologic study of 77 patients. Cancer 68:2017-2022, 1991
7) Taira N, Takabatake D, Aogi K, Ohsumi S, Takashima S, Nishimura R, Teramoto N : Phyllodes tumor of the breast: stromal overgrowth and histological classification are useful prognosis-predictive factors for local recurrence in patients with a positive surgical margin. Jpn J Clin Oncol 37:730-736, 2007
8) Kraemer B, Hoffmann J, Roehm C, Gall C, Wallwiener D, Krainick-Strobel U : Cystosarcoma phyllodes of the breast: a rare diagnosis: case studies and review of literature. Arch Gynecol Obstet 276:649-653, 2007
9) Putti TC, Pinder SE, Elston CW, Lee AH, Ellis IO : Breast pathology practice: most common problems in a consultation service. Histopathology 47:445-457, 2005
10) Giri D : Recurrent challenges in the evaluation of fibroepithelial lesions. Arch Pathol Lab Med 133:713-721, 2009
11) Koerner FC : Diagnostic problems in breast pathology, 1st ed, Philadelphia, Saunders, 2009, 301-342
12) Lae M, Vincent-salomon A, Savignoni A, Huon I, Freneaux P, Sigal-Zafrani B, Aurias A, Sastre-Garau X, Couturier J : Phyllodes tumors of the breast segregate in two groups according to genetic criteria. Mod Pathol 20:435-444, 2007
13) Zamecnik M, Kinkor Z, Chlumska A : CD10+ stromal cells in fibroadenomas and phyllodes tumors of the breast. Virchows Arch 448:871-872, 2006
14) Tsai WC, Jin JS, Yu JC, Sheu LF : CD10, actin, and vimentin expression in breast phyllodes tumors correlates with tumor grades of the WHO. Int J Surg Pathol 14:127-131, 2006
15) Tse GMK, Niu Y, Shi HJ : Phyllodes tumor of the breast: an update. Breast Pathol Epub ahead of print, 2009
16) Djordjevic B, Hanna WM : Expression of c-kit in fibroepithelial lesions of the breast is a mast cell phenomenon. Mod Pathol 21:1238-45, 2008
17) Sapino A, Bosco M, Cassoni P, Castellano I, Arisio R, Cserni G, Dei Tos AP, Fortunati N, Catalano MG, Bussolati G : Estrogen receptor-beta is expressed in stromal cells of fibroadenoma and phyllodes tumors of the breast. Mod Pathol 19:599-606, 2006
18) Karim RZ, Scolyer RA, Tse GM, Tan PH, Putti TC, Lee CS : Pathogenic mechanisms in the initiation and progression of mammary phyllodes tumours. Pathology 41:105-117, 2009
19) Jacobs TW, Chen YY, Guinee DG Jr, Holden JA, Cha I, Bauermeister DE, Hashimoto B, Wolverton D, Hartzog G : Fibroepithelial lesions with cellular stroma on breast core needle biopsy: are there predictors of outcome on surgical excision?. Am J Clin Pathol 124:342-354, 2005
20) Barrio AV, Clark BD, Glodberg JI, Hoque LW, Bernik SF, Flynn LW, Susnik B, Giri D, Polo K, Patil S, Van ZEE KJ : Clinicopathologic features and long-term outcomes of 293 phyllodes tumors of the breast. Ann Surg Oncol 14:2961-2970, 2007
21) Lee AHS, Hodi Z, Ellis IO, Elston CW : Histological features useful in the distinction of phyllodes tumor and fibroadenoma on needle core biopsy of the breast. Histopathology 51:336-344, 2007
22) Dillon MF, Quinn CM, McDermott EW, O'Doherty A, O'Higgins N, Hill ADK : Needle core biopsy in the diagnosis of phyllodes neoplasm. Surgery 140:779-784, 2006
23) Komenaka IK, EL-Tamer M, Pile-Spellman E, Hibshoosh H : Core needle biopsy as a diagnostic tool to differentiate phyllodes tumor from fibroadenoma. Arch Surg 138:987-990, 2003
24) Yohe YS, Yeh IT : "Missed" diagnoses of phyllodes tumor on breast biopsy: Pathologic clues to its recognition. Int J Surg Pathol 16:137-142, 2008
25) Fechner RE : Diagnostic histopathology of the breast. Edinburgh, Scotland, Churchill Livingstone, 1987, 72-85
26) Sawhney N, Garrahan N, Douglas-Jones AG and Williams ED : Epithelial-stromal interactions in tumors. A morphologic study of fibroepithelial tumors of the breast. Cancer 70:2115-2120, 1992
27) Matrisian LM, Cunha GR, Mohla S : Epithelial stromal interactions and tumor progression: meeting summary and future directions. Cancer Res 61:3844-3846, 2001
28) Sawhney N, Garrahan N, Douglas-Jones AG, Williams ED : Epithelial-stromal interactions in tumors. A morphologic study of fibroepithelial tumors of the breast. Cancer 70:2115-2120, 1992
29) Jacklin RK, Ridgway PF, Ziprin P, Healy V, Hadjiminas D, Darzi A : Optimising preoperative diagnosis in phyllodes tumor of the breast. J Clin Pathol 59:454-459, 2006
30) Tse GM, LEE CS, Kung FY, Scolyer RA, Law BK, Lau TS, Putti TC : Hormonal receptors expression in epithelial cells of mammary phyllodes tumors correlates with pathologic grade of the tumor: a multicenter study of 143 cases. Am J Clin Pathol 118:522-526, 2002