

Phyllodes Tumor of the Breast

Histopathologic Features, Differential Diagnosis, and Molecular/Genetic Updates

Yanhong Zhang, MD; Celina G. Kleer, MD

• **Context.**—Phyllodes tumor (PT) of the breast is a rare fibroepithelial neoplasm with risks of local recurrence and uncommon metastases. The classification proposed by the World Health Organization for PTs into benign, borderline, and malignant is based on a combination of several histologic features. The differential diagnosis between PT and fibroadenoma and the histologic grading of PT remain challenging. In addition, the molecular pathogenesis of PT is largely unknown.

Objective.—To provide an updated overview of pathologic features, diagnostic terminology, and molecular alterations of PT.

Phyllodes tumor (PT) of the breast is a rare fibroepithelial neoplasm, accounting for 0.3% to 1% of all breast tumors.¹ Phyllodes tumor presents a morphologic continuum from benign to malignant. The classification of PT proposed by the World Health Organization (WHO) into benign, borderline, and malignant is based on a combination of several histologic features, including stromal cellularity, nuclear atypia, mitotic activity, stromal overgrowth, and tumor margin appearance.² However, there are no defined criteria or clear cutoffs for individual histologic parameters. Thus, the diagnosis of PTs based on the integration of morphology remains challenging, particularly in the distinction of PTs from fibroadenoma. The majority of PTs behave in a benign fashion, with the risk of local recurrence ranging from 17% in benign PT to 27% in malignant PT. Distant metastasis occurs in up to 22% of malignant PTs.² The histologic grading of PT generally correlates with prognosis; however, histologic features have not always been found to be predictive of clinical behavior in individual patients.^{3–5} Several biomarkers have been reported to be associated with histologic grades and show some

Data Sources.—Current English literature related to PT of the breast.

Conclusions.—Phyllodes tumor shows a wide spectrum of morphology. There are no clearly distinct boundaries between PT and fibroadenoma. Strict histologic assessment of a combination of histologic features with classification can help to achieve the correct diagnosis and provide useful clinical information. The genomic landscapes of PT generated from genomic sequencing provide insights into the molecular pathogenesis of PT and help to improve diagnostic accuracy and identify potential drug targets in malignant PT.

(*Arch Pathol Lab Med.* 2016;140:665–671; doi: 10.5858/arpa.2016-0042-RA)

prognostic value. However, at present, none of them have been proven to be of clinical value in daily practice. The pathogenesis and molecular biologic features of PT are largely unknown. The most favored theory on the pathogenesis of PT is epithelial-stromal interactions. The most recent genome sequencing studies have identified frequent MDM12 somatic mutations in fibroadenoma and PT, suggesting these 2 entities may share a common origin.^{6–10} This review will address some of the diagnostic problems that are encountered in routine practice and provide molecular/genetic updates on PTs of the breast.

HISTOPATHOLOGIC CHARACTERISTICS, GRADING, AND DIFFERENTIAL DIAGNOSIS

Phyllodes tumors are biphasic tumors, histologically characterized by a leaflike architecture resulting from an enhanced intracanalicular growth pattern, cleftlike spaces lined by epithelium, and hypercellular stroma. A variety of terms have been used to describe these tumors, the most common being cystosarcoma phyllodes, cellular fibroadenoma, and juvenile fibroadenoma. The term *cystosarcoma phyllodes* was first introduced by Müller in 1838.¹¹ It is derived from the Greek words *sarcoma*, meaning flesh appearance, and *phyllon*, meaning leaflike. This term may be misleading because the majority of PTs are benign. Cellular fibroadenoma and juvenile fibroadenoma are common benign biphasic tumors recognized as distinct entities; the terms have been used interchangeably. Cellular fibroadenoma has the architecture of a fibroadenoma with prominent cellular stroma.² Juvenile fibroadenoma exhibits a pericanalicular growth pattern, gynecomastoid-like epithelial hyperplasia, and an increased stromal cellularity.¹² Juvenile fibroadenomas occur predominantly in adolescents

Accepted for publication March 11, 2016.

From the Department of Pathology and Laboratory Medicine, University of California, Davis Medical Center, Sacramento (Dr Zhang); and the Department of Pathology, University of Michigan, Ann Arbor (Dr Kleer).

The authors have no relevant financial interest in the products or companies described in this article.

Presented in part at the 2nd Princeton Integrated Pathology Symposium; February 9, 2015; Plainsboro, New Jersey.

Reprints: Celina G. Kleer, MD, Department of Pathology, University of Michigan, 4217 Comprehensive Cancer Center, 1500 E Medical Center Dr, Ann Arbor, MI 48109 (email: kleer@umich.edu).

Table 1. Three-Tiered Grading System for Phyllodes Tumors Based on 2012 World Health Organization Classification

Histologic Features	Benign	Borderline	Malignant
Stromal cellularity	Mild	Moderate	Marked
Stromal atypia	Mild	Moderate	Marked
Mitosis (per 10 HPF)	<5	5–9	≥10
Stromal overgrowth	Absent	Absent or focal	Present
Tumor margin	Well-defined	Well-defined or focal infiltrative	Infiltrative

Abbreviation: HPF, high-power field.

and may grow to enormous sizes.¹³ Juvenile fibroadenoma is considered giant when larger than 5 cm.

Phyllodes tumor is classified as benign, borderline, or malignant according to the WHO classification of 2012 (Table 1).² Like all morphologic grading systems, this grading scheme is somewhat subjective, especially at the cut points between grades. Of note, PT may contain foci with benign, borderline, and malignant features intermingled within the same neoplasm, making careful gross examination and histologic sampling particularly important. Therefore, given PT's histologic heterogeneity, excision is required to accurately classify and grade PT. Definitions of the histologic features commonly used for evaluation of PT are summarized in Table 2.

Benign PT

Benign PT comprises 60% to 75% of all PT. The local recurrence rate has been reported to be about 20%. These tumors are characterized by mildly increased stromal cellularity and mild nuclear atypia. Mitoses are rare, usually fewer than 5 per 10 high-power fields (HPF) (Figure, A). It can be difficult to distinguish benign PT from cellular fibroadenoma because increased stromal cellularity is a prominent feature of both. The distinction between the 2 is important, however, because their treatment and prognosis are different. The leaflike pattern that is typical of PT is not seen in cellular fibroadenoma and, if present, is focal and not well developed. One source of difficulty is the fact that

fibroadenoma-like areas can be seen in otherwise typical cases of PT. Histologic heterogeneity in stromal cellularity and structure in PT may further create difficulty in the distinction between PT and cellular fibroadenoma on core biopsy. Numerous studies have attempted to determine which histologic features of PTs are useful in predicting PT on surgical excision and clinical behavior.

Stromal cellularity is categorized as mild, moderate, or marked, and is assessed in the most cellular area. The threshold for mild stromal cellularity has not been well defined. Jacobs et al¹⁴ have considered mildly increased stromal cellularity as being approximately twice the cellularity of that of normal perilobular stroma, with no or rare stromal nuclei appearing to touch each other. With this definition, they found all core biopsy specimens with mildly increased stromal cellularity (n = 4) were fibroadenomas on excision. Among 20 core biopsy specimens with moderate stromal cellularity, 12 (60%) were fibroadenomas on excision. The data suggest that their threshold for stromal cellularity is low. Lee et al¹⁵ defined the stromal cellularity as mild increase in at least 50% of the stroma in PT compared with a typical fibroadenoma. In their study, the concordance rate for diagnosis of PT on core needle biopsy and surgical specimen was higher (36 of 50; 72%), and the reproducibility of assessment of this feature by 4 pathologists was excellent. In another study by Yasir et al,¹⁶ increased stromal cellularity was defined as the presence of stromal nuclear crowding or overlapping. Although this cutoff seems to be

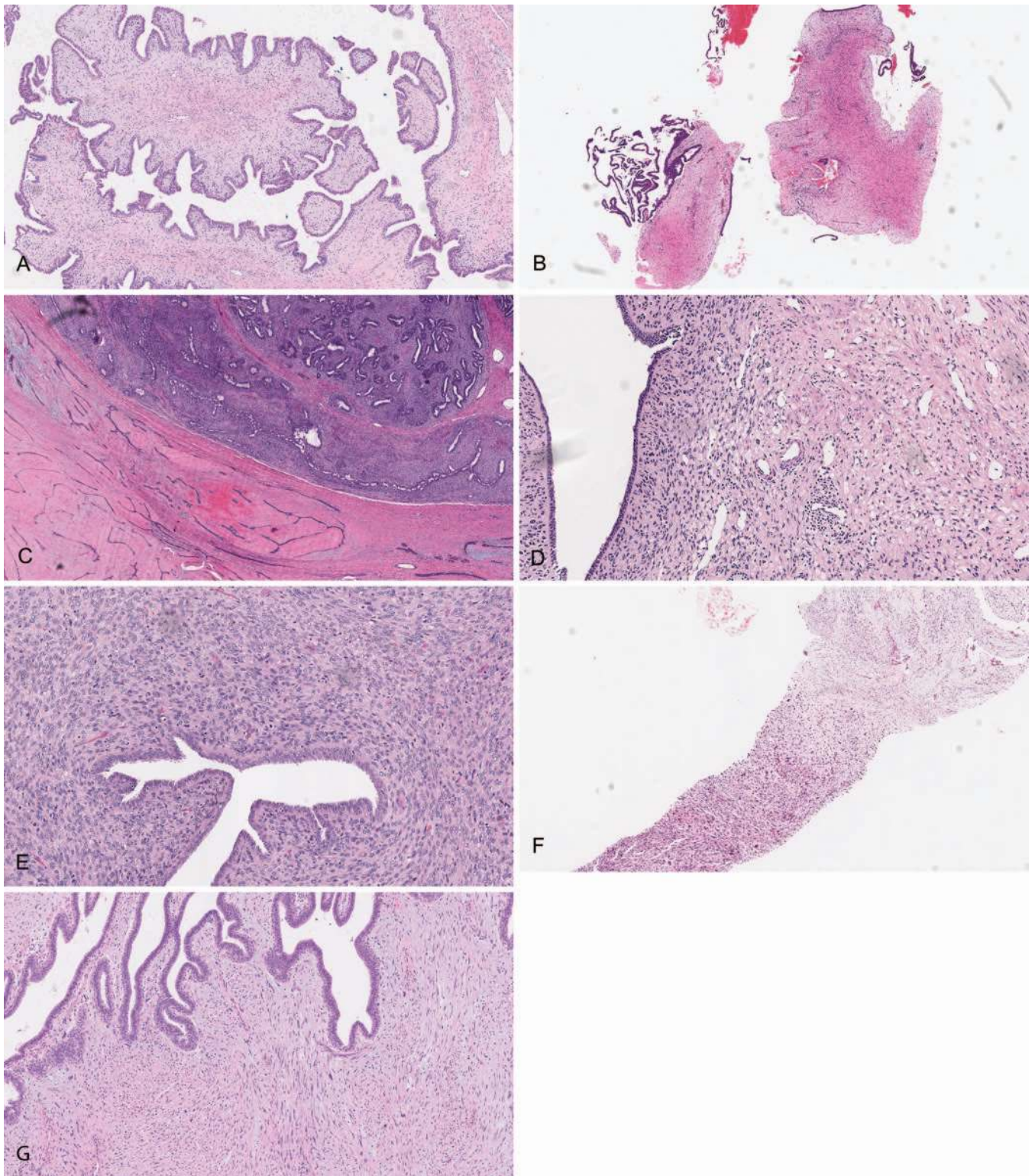
Table 2. Definitions of Histologic Parameters for Evaluation of Phyllodes Tumors in Core Biopsy and Excisional Specimens

Histologic Parameters	Definitions
Mitotic activity	Evaluated in more cellular areas and quantified per 10 HPF (×40)
Stromal overgrowth	Stromal proliferation without accompanying epithelial elements in at least 1 low-power field (×4) ^a
Stromal cellularity	Evaluated in the most cellular areas
Mild	Twice cellularity of normal perilobular stroma with evenly spaced nuclei without overlapping ^{14,18,b}
Moderate	Intermediate in degree between mildly and markedly
Marked	Stromal cells in close contiguity with nuclei appearing to touch and overlapping
Stromal atypia	
Mild	Small, uniform nuclei, with absent or inconspicuous nucleoli
Moderate	Intermediate in degree between mildly and markedly
Marked	Marked variation in nuclear size and shape, irregular nuclear membrane, and prominent nucleoli
Intratumor heterogeneity	Variability in structure and stromal cellularity or atypia in a single tumor
Infiltrative tumor margin	Projections of tumor stroma into the peritumoral stroma or adipose tissue
Leaflike pattern	Enhanced intracanalicular pattern, characterized by projection of cellular stroma into epithelial-lined clefts of cystic spaces
Stromal fragmentation	Stroma with epithelium at one or both ends of the biopsy fragment, result of leaflike pattern in core biopsy specimen
Subepithelial stromal condensation	Enhanced stromal cellularity adjacent to or underneath epithelium

Abbreviation: HPF, high-power field.

^a It is evaluated at a ×10 field for core biopsy specimens.^{15,16}

^b It is also defined as increase in at least 50% of the stroma compared with typical fibroadenoma.¹⁵



A, Benign phyllodes tumor. Leaflike projections of mildly increased stromal cellularity. B, Stromal fragmentation in core biopsy. C, Intratumoral stromal heterogeneity. The stroma is fibrotic in the left lower area and hypercellular in the right upper area in the same tumor. D, Subepithelial stromal condensation. E, Malignant phyllodes tumor. The stroma is markedly cellular and the stromal cells show marked nuclear pleomorphism. There are numerous mitoses. F, Malignant spindle cell proliferation. The presence of a bland epithelial component in the upper right of this core biopsy is typical of malignant phyllodes tumor. G, Borderline phyllodes tumor. The stroma is moderately cellular and the stromal cells show moderate nuclear atypia (hematoxylin-eosin, original magnifications $\times 40$ [A and D], $\times 20$ [B and F], $\times 10$ [C], and $\times 100$ [E and G]).

comparable with that for moderate cellularity in other studies, increased stromal cellularity was not a helpful feature in predicting a diagnosis of PT on excision in their study. Although the data on increased stromal cellularity are inconsistent, many studies have found that subepithelial condensation of stromal cells is a common feature of PT and may be the best predictor of PT in core biopsies.¹⁶

Stromal overgrowth, defined as a stromal proliferation without accompanying epithelial elements in at least 1 low-power field ($\times 4$), is a feature of PT. However, stromal overgrowth is absent in benign PT. Several studies found that stromal overgrowth defined as a $\times 10$ field with no epithelium could be useful to diagnose PT on core biopsy.^{15,16} A leaflike pattern, often seen in PT, can also be present in fibroadenoma and is not useful unless it is diffuse and well developed. Stromal nuclear atypia and infiltrative margin (adipose tissue within stroma) were found to be useful features in the distinction of PT and fibroadenoma on core biopsy,^{15,16} but another study found that they were of little value.¹⁴

The mitotic activity of the stromal cells may also help distinguish PT from cellular fibroadenoma. Stromal mitoses have been evaluated in more cellular areas and quantified per 10 HPF. A minority of fibroadenomas have 1 or 2 mitoses per 10 HPF. Mitoses reported by Jacobs et al¹⁴ ($>2/10$ HPF) and by Jara-Lazaro et al¹⁷ ($\geq 2/10$ HPF) might help determine the probability of PT. Similarly, Yasir et al¹⁶ found the average mitotic figures per 10 HPF were 3 and 0.8 in PT and cellular fibroepithelial lesions, respectively. This suggests that a count of 3 or more mitoses per 10 HPF favors PT over fibroadenoma. However, the mitotic count of up to 5/10 HPF has been reported in rare pediatric breast fibroadenomas.¹³

It is clear that PT and fibroadenoma exhibit overlapping histologic features that should not be used in isolation to make a definitive diagnosis. Thus, taking into account several of these features may be a more sensible approach. In a study of 62 cellular fibroepithelial lesions on core biopsy with follow-up excisions, the histologic features of stromal overgrowth at $\times 10$, increased stromal cellularity, stromal fragmentation (Figure, B), infiltration into fat, stromal heterogeneity (Figure, C), subepithelial stromal condensation (Figure, D), and stromal cell nuclear pleomorphism were evaluated. It was found that PT had more features (3.9) on average compared with cellular fibroadenoma (1.4). The findings suggest that presence of any 3 or more of these histologic features on core biopsy favors PT over fibroadenoma.¹⁶

Despite great efforts toward improving the pathologist's ability to better distinguish fibroepithelial lesions, there is still poor interobserver reproducibility. Studies show that the overall rate of correctly diagnosed fibroadenoma and PT ranges from 40% to 60%.^{18–20} In a study by Lawton et al,²¹ 21 fibroepithelial lesions were evaluated among 10 breast pathologists. There was a uniform agreement on only 2 cases (10%). Of the remaining 19 cases, the diagnoses included fibroadenoma, cellular fibroadenoma, PT, and borderline PT. There was fair agreement on the separation of fibroadenoma/cellular fibroadenoma/benign PT from borderline and malignant PT. A number of studies reported that the recurrence rate of fibroadenoma is up to 17%, which is similar to that for benign PT. In addition, studies have shown that expectant management towards benign PTs excised without clear margins may be an acceptable option, given an overall low local recurrence rate and rare

recurrence as a high-grade tumor from a benign PT.^{22,23} These findings suggest that distinction between these 2 entities may not be significant. In core biopsies with morphologic features of fibroadenoma and benign PT, a diagnosis of benign fibroepithelial neoplasm is advocated by some authors and recommended by the WHO classification system.²

Malignant PT

Malignant PT is characterized by marked stromal cellularity and nuclear pleomorphism, stromal overgrowth, and more than 10 mitoses per 10 HPF (Figure, E). The presence of heterologous sarcomatous elements (liposarcoma, chondrosarcoma, and osteosarcoma) alone qualifies a PT as malignant. The differential diagnosis of malignant PT includes sarcomas and metaplastic (sarcomatoid) carcinoma.

The distinction of malignant PT from metaplastic (sarcomatoid) carcinoma is based on the morphology. Like malignant PT, metaplastic (sarcomatoid) carcinoma may also show spindle cells with nuclear pleomorphism, abundant mitoses, and heterologous elements. The presence of leaflike architecture and bland epithelium lining cleftlike spaces is typical of PT (Figure, F), whereas malignant epithelial elements, if present, are more likely to be metaplastic (sarcomatoid) carcinoma. If there is no epithelial component, particularly on core biopsy, immunohistochemistry may be helpful. A panel of cytokeratins (CKs) (CKAE1/AE3, CK5/6, 34 β E12, cam 5.2) and myoepithelial marker p63²⁴ should be used for the workup because of variable staining patterns in metaplastic (sarcomatoid) carcinomas. The majority of PTs are negative for CKs and p63.²⁵ In a recent study of 32 PTs, it was found that p63, p40, and CKs can be focally positive in 57%, 29% and 21%, respectively, of malignant PT but not in benign or borderline PT.²⁶ These results suggest that these markers alone should not be used to differentiate metaplastic (sarcomatoid) carcinoma from malignant PT on core biopsy. CD34 has been reported to be positive in up to 75% of PT and negative in metaplastic (sarcomatoid) carcinoma.^{27–29} However, CD34 positivity was observed in only 37% to 57% of malignant PTs. Nuclear expression of β -catenin is observed in PT; it is frequently seen in the stromal cells of benign and borderline PT.³⁰ A small proportion of sarcomatoid carcinoma may also show nuclear staining of β -catenin. When there is histologic and immunohistochemical ambiguity, a diagnosis of malignant spindle cell neoplasm with a descriptive comment is necessary and surgical excision is recommended for further classification because the clinical treatments for these 2 entities are different. Malignant PT is typically treated with complete surgical excision. Routine sentinel lymph node biopsy is not recommended because of rare lymph node metastases. The role of adjuvant radiotherapy and chemotherapy for malignant PT remains uncertain, whereas metaplastic carcinoma is managed by neoadjuvant or adjuvant chemotherapy and surgery including sentinel lymph node biopsy.

Primary sarcoma of the breast is extremely rare. The majority of sarcomas of the breast arise as a component of a malignant PT. Some undifferentiated mammary sarcomas are morphologically indistinguishable from malignant PT on core biopsy, particularly when no epithelial component is present. However, the clinical management of these 2 entities diagnosed on core biopsy is similar. Several studies have demonstrated that patients with primary breast sarcoma had identical disease-free survival and overall

survival rates to those of patients with malignant PT.³¹ Reports suggest that approximately 10% to 15% of PTs are malignant. Local recurrence rate ranges from 15% to 40%, and 9% to 27% of malignant PTs metastasize to distal organs. Most patients with metastasis do not respond to standard chemotherapy and die within 3 years of the initial treatment.

Borderline PT

According to the WHO definition, PTs that don't possess all the features for malignancy are classified as borderline; this division is arbitrary. Borderline PT may have a circumscribed or focally invasive border, frequent mitoses (5–9/10 HPF), moderate stromal cellularity, and stromal atypia (Figure, G). Stromal overgrowth is usually absent. Borderline PT has not been extensively investigated compared with benign and malignant PT. The lower limit for diagnosis of borderline PT is not well defined. Moderate stromal cellularity, nuclear atypia, and focal infiltrative border are the features that can be seen in both benign and borderline PTs. It appears that mitotic activity is an important parameter for the diagnosis of borderline PT. The mitosis cutoff for the diagnosis of borderline PT has been clearly defined as 5 to 9/10 HPF in the WHO classification of 2012. In a study by Ang et al,³² the gene expression profiling of 29 PTs showed that 2 histologically classified borderline cases had expression profiles similar to those of the benign and malignant groups. These 2 cases showed moderate stromal cellularity and atypia, focally infiltrative borders. The mitoses were 2/10 HPF in the profiled with benign group and an average of 6/10 HPF in the profiled with malignant group. This observation suggests that mitotic activity may be an important parameter among the histologic features. Further histologic and molecular correlation studies will help in redefining the features for tumor grading. The percentage of borderline PT ranges from 12% to 26% in different large series. Its local recurrence rate has been reported to be 14% to 25%. There are rare reports of borderline PTs metastasizing, although these events have not been well characterized.

MOLECULAR/GENETIC FEATURES

The molecular correlations of histologic grade and malignant behavior and the genetic alterations driving PT development remain unclear.

The most favored theory on the pathogenesis of PT is epithelial-stromal interactions. Morphologic association of leaflike fronds with subepithelial stromal condensation hints at the close relationship between epithelial and stromal elements in PT. This observation is supported by the findings of the stromal expression of β -catenin and insulin-like growth factors (IGF-I and II)^{30,33} and the epithelial overexpression of Wnt5a in benign/borderline PT. Furthermore, activation of the Wnt signaling pathway in the epithelium may promote stromal overgrowth.

Multiple immunohistochemistry markers have been studied in an attempt to improve the classification of PT and to predict its outcomes. Studies have shown that p53, Ki67, CD117,^{34,35} EGFR,³⁶ p16,³⁷ and VEGF³⁸ (being the lowest in benign PT and the highest in malignant PT) are associated with histologic grades of PT, but none has been proven to be clinically useful. Among these markers, p53 expression and Ki67 index were reported in some studies^{39,40} to be significantly associated with disease-free and overall sur-

vivals, but other studies^{41,42} found no association with recurrence or clinical behavior. PAX3 and SIX1 expression by immunohistochemistry⁴³ and gene-expression analysis⁴⁴ has recently been identified in borderline and malignant PTs and correlates with a poor clinical outcome.

Recent studies have focused on defining a molecular classification of PT. Comparative genomic hybridization studies show recurrent chromosome imbalances including +1q, -6q, -13q, -9p, -10p, and +5p. Although currently no chromosomal aberrations were found to be specific to PT, Lae et al⁴⁵ reported that low-grade (benign) and high-grade (borderline/malignant) PTs segregate in 2 genetic groups based on genomic alterations, with high-grade PT consistently showing 1q gain and 13q loss and low-grade PT showing few or no alterations. Similar chromosomal changes were identified by Jones et al⁴⁶ in their array-GCH analysis in 126 PTs. We must note, however, that Lv et al⁴⁷ found the gain of 1q did not correlate with grades, and Lu et al⁴⁸ reported that 1q gain was found mainly in benign PTs (6 of 12; 50%), underscoring the need for more conclusive investigations. Loss of 13q in PT suggests that the RB1 gene localized in these regions could be relevant to PT oncogenesis or progression.⁴⁵ In addition, frequent deletions of 9p21 associated with loss of p16^{INK4A} protein expression were identified in borderline/malignant PT.⁴⁶

Gene expression-based classification of PT has been proposed in recent studies. Vidal et al⁴⁹ analyzed the expression of 105 breast cancer-related genes in 75 fibroepithelial lesions. The overall profile of benign PT was found more similar to fibroadenomas and the majority of benign and borderline PT was identified as normal-like by intrinsic breast cancer subtyping, whereas malignant PT was identified as claudin-low and basal-like. Similar to metaplastic carcinomas, malignant PT showed enrichment for cancer stem cell-related biological processes.⁵⁰ In another study by Ang et al,³² a heat map generated from 29 genes showed 3 distinct groups of benign, borderline, and malignant tumors, consistent with histologic classifications. The discrepancy in these studies is largely due to the smaller size of cohort studies with smaller numbers of borderline and malignant PT, and may also reflect differences in the criteria used for classifying PT. Recent genome sequencing studies provide insights into the molecular pathogenesis of breast PTs and identify the potential opportunities for personalized treatment in malignant PT. Recurrent mediator complex subunit 12 (*MED12*) somatic mutations, frequently (50%–70%) in uterine leiomyomas, has been recently identified in fibroadenomas (59%–67%) and PTs (45%–67%). In addition, *MED12* is frequently mutated in all PTs.^{6,7,9,51,52} These findings suggest both entities may share genetic etiology, and *MDM2* mutation is an early event of fibroadenoma and PT pathogenesis. In a recent study by Tan et al,¹⁰ exome sequencing of 22 PTs and targeted sequencing of 100 fibroepithelial tumors exhibited the genetic landscapes of fibroepithelial tumors, with frequent *MED12* (73%) and *RARA* (32%) mutations in both fibroadenoma and all grades of PT. Of note, mutations in *FLNA* (28%), *SETD2* (21%), and *KMT2* (9%) were observed only in PT, suggesting a role in driving PT development. Genome-wide analysis of DNA copy number variations and genomic sequencing have demonstrated significant numbers of amplifications and deletions. In addition to the loss of function mutation in p53, deleterious mutations in Rb1 and NF1, mutations in

PIK3CA and ERBB4, and high-level copy number variations of EGFR were detected in borderline/malignant tumors.¹⁰ Cani et al⁵² reported that p53, RB1, and NF1 mutations and EGFR^{52,53} and IGF1R gene amplifications were detected in only the malignant tumors. These genetic alterations are likely responsible for acquisition of malignant characteristics and aggressive biologic behavior in PT. EGFR and IGF1R may be promising therapeutic targets.

CONCLUSIONS

In summary, PTs are rare fibroepithelial neoplasms with potential for local recurrence and distant metastasis. Histologic classification of PT into benign, borderline, and malignant is challenging in some cases, and the histologic classification does not correlate well with biological behavior. Distinction between fibroadenoma and PT is important but may be difficult on core biopsy. PTs show intratumoral morphologic and genetic heterogeneity, which may contribute to their unpredictable clinical behavior and the difficulty in classifying them histologically. Expression-based and genomics-based classifications of breast fibroepithelial tumors may help with the diagnosis and grading of PT, when used in combination with histologic criteria, and provide clinically useful prognostic information. The genomic landscapes of PT generated from genomic sequencing provide insights into molecular pathogenesis of PT and help to improve diagnostic accuracy and identify potential drug targets in malignant PT. However, most published studies have a limited number of samples, in particular a smaller number of borderline and malignant tumors. Further studies including a large series of well-characterized PT with follow-up data are needed.

References

- Rosen PP, Oberman HA. *Tumors of the Mammary Gland*. Washington, DC: Armed Forces Institute of Pathology; 1993.
- Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, eds. *World Health Organization Classification of Tumours of the Breast*. Lyon, France: IARC; 2012. *World Health Organization Classification of Tumours*; vol 4.
- Lenhard MS, Kahlert S, Himsel I, Ditsch N, Untch M, Bauerfeind I. Phyllodes tumour of the breast: clinical follow-up of 33 cases of this rare disease. *Eur J Obstet Gynecol Reprod Biol*. 2008;138(2):217–221.
- Karim RZ, Gerega SK, Yang YH, et al. Phyllodes tumours of the breast: a clinicopathological analysis of 65 cases from a single institution. *Breast*. 2009;18(3):165–170.
- Tan PH, Thike AA, Tan WJ, et al. Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. *J Clin Pathol*. 2012;65(1):69–76.
- Yoshida M, Sekine S, Ogawa R, et al. Frequent MED12 mutations in phyllodes tumours of the breast. *Br J Cancer*. 2015;112(10):1703–1708.
- Piscuoglio S, Murray M, Fusco N, et al. MED12 somatic mutations in fibroadenomas and phyllodes tumours of the breast. *Histopathology*. 2015;67(5):719–729.
- Pfarr N, Kriegsmann M, Sinn P, et al. Distribution of MED12 mutations in fibroadenomas and phyllodes tumours of the breast—implications for tumor biology and pathological diagnosis. *Genes Chromosomes Cancer*. 2015;54(7):444–452.
- Nagasawa S, Maeda I, Fukuda T, et al. MED12 exon 2 mutations in phyllodes tumors of the breast. *Cancer Med*. 2015;4(7):1117–1121.
- Tan J, Ong CK, Lim WK, et al. Genomic landscapes of breast fibroepithelial tumors. *Nat Genet*. 2015;47(11):1341–1345.
- Fiks A. Cystosarcoma phyllodes of the mammary gland—müller's tumor. *Virchows Arch A Pathol Anat Histol*. 1981(1);392:1–6.
- Pike AM, Oberman HA. Juvenile (cellular) adenofibromas: a clinicopathologic study. *Am J Surg Pathol*. 1985;9(10):730–736.
- Tay TK, Chang KT, Thike AA, Tan PH. Paediatric fibroepithelial lesions revisited: pathological insights. *J Clin Pathol*. 2015;68(8):633–641.
- Jacobs TW, Chen YY, Guinee DG Jr, et al. Fibroepithelial lesions with cellular stroma on breast core needle biopsy: are there predictors of outcome on surgical excision? *Am J Clin Pathol*. 2005;124(3):342–354.
- Lee AH, Hodi Z, Ellis IO, Elston CW. Histological features useful in the distinction of phyllodes tumour and fibroadenoma on needle core biopsy of the breast. *Histopathology*. 2007;51(3):336–344.

- Yasir S, Gamez R, Jenkins S, Visscher DW, Nassar A. Significant histologic features differentiating cellular fibroadenoma from phyllodes tumor on core needle biopsy specimens. *Am J Clin Pathol*. 2014;142(3):362–369.
- Jara-Lazaro AR, Akhilesh M, Thike AA, Lui PC, Tse GM, Tan PH. Predictors of phyllodes tumours on core biopsy specimens of fibroepithelial neoplasms. *Histopathology*. 2010;57(2):220–232.
- Choi J, Koo JS. Comparative study of histological features between core needle biopsy and surgical excision in phyllodes tumor. *Pathol Int*. 2012;62(2):120–126.
- Foxcroft LM, Evans EB, Porter AJ. Difficulties in the pre-operative diagnosis of phyllodes tumours of the breast: a study of 84 cases. *Breast*. 2007;16(1):27–37.
- Khazai L, Middleton LP, Goktepe N, Liu BT, Sahin AA. Breast pathology second review identifies clinically significant discrepancies in over 10% of patients. *J Surg Oncol*. 2015;111(2):192–197.
- Lawton TJ, Acs G, Argani P, et al. Interobserver variability by pathologists in the distinction between cellular fibroadenomas and phyllodes tumors. *Int J Surg Pathol*. 2014;22(8):695–698.
- Ouyang Q, Li S, Tan C, et al. Benign phyllodes tumor of the breast diagnosed after ultrasound-guided vacuum-assisted biopsy: surgical excision or wait-and-watch? *Ann Surg Oncol*. 2016;23(4):1129–1134.
- Cowan ML, Argani P, Cimino-Mathews A. Benign and low-grade fibroepithelial neoplasms of the breast have low recurrence rate after positive surgical margins. *Mod Pathol*. 2016;29(3):259–265.
- Koker MM, Kleer CG. p63 expression in breast cancer: a highly sensitive and specific marker of metaplastic carcinoma. *Am J Surg Pathol*. 2004;28(11):1506–1512.
- Chia Y, Thike AA, Cheok PY, Yong-Zheng Chong L, Man-Kit Tse G, Tan PH. Stromal keratin expression in phyllodes tumours of the breast: a comparison with other spindle cell breast lesions. *J Clin Pathol*. 2012;65(4):339–347.
- Cimino-Mathews A, Sharma R, Illei PB, Vang R, Argani P. A subset of malignant phyllodes tumors express p63 and p40: a diagnostic pitfall in breast core needle biopsies. *Am J Surg Pathol*. 2014;38(12):1689–1696.
- Moore T, Lee AH. Expression of CD34 and bcl-2 in phyllodes tumours, fibroadenomas and spindle cell lesions of the breast. *Histopathology*. 2001;38(1):62–67.
- Dunne B, Lee AH, Pinder SE, Bell JA, Ellis IO. An immunohistochemical study of metaplastic spindle cell carcinoma, phyllodes tumor and fibromatosis of the breast. *Hum Pathol*. 2003;34(10):1009–1015.
- Lee AH. Recent developments in the histological diagnosis of spindle cell carcinoma, fibromatosis and phyllodes tumour of the breast. *Histopathology*. 2008;52(1):45–57.
- Sawyer EJ, Hanby AM, Rowan AJ, et al. The Wnt pathway, epithelial-stromal interactions, and malignant progression in phyllodes tumours. *J Pathol*. 2002;196(4):437–444.
- Wang F, Jia Y, Tong Z. Comparison of the clinical and prognostic features of primary breast sarcomas and malignant phyllodes tumor. *Jpn J Clin Oncol*. 2015;45(2):146–152.
- Ang MK, Ooi AS, Thike AA, et al. Molecular classification of breast phyllodes tumors: validation of the histologic grading scheme and insights into malignant progression. *Breast Cancer Res Treat*. 2011;129(2):319–329.
- Sawyer EJ, Hanby AM, Poulson R, et al. Beta-catenin abnormalities and associated insulin-like growth factor overexpression are important in phyllodes tumours and fibroadenomas of the breast. *J Pathol*. 2003;200(5):627–632.
- Noronha Y, Raza A, Hutchins B, et al. CD34, CD117, and Ki-67 expression in phyllodes tumor of the breast: an immunohistochemical study of 33 cases. *Int J Surg Pathol*. 2011;19(2):152–158.
- Tan PH, Jayabaskar T, Yip G, et al. p53 and c-kit (CD117) protein expression as prognostic indicators in breast phyllodes tumors: a tissue microarray study. *Mod Pathol*. 2005;18(12):1527–1534.
- Tse GM, Lui PC, Vong JS, et al. Increased epidermal growth factor receptor (EGFR) expression in malignant mammary phyllodes tumors. *Breast Cancer Res Treat*. 2009;114(3):441–448.
- Karim RZ, Gerega SK, Yang YH, et al. p16 and pRb immunohistochemical expression increases with increasing tumour grade in mammary phyllodes tumours. *Histopathology*. 2010;56(7):868–875.
- Tse GM, Lui PC, Lee CS, et al. Stromal expression of vascular endothelial growth factor correlates with tumour grade and microvessel density in mammary phyllodes tumors: a multicenter study of 185 cases. *Hum Pathol*. 2004;35(9):1053–1057.
- Yonemori K, Hasegawa T, Shimizu C, et al. Correlation of p53 and MIB-1 expression with both the systemic recurrence and survival in cases of phyllodes tumors of the breast. *Pathol Res Pract*. 2006;202(10):705–712.
- Niezabitowski A, Lackowska B, Rys J, et al. Prognostic evaluation of proliferative activity and DNA content in the phyllodes tumor of the breast: immunohistochemical and flow cytometric study of 118 cases. *Breast Cancer Res Treat*. 2001;65(1):77–85.
- Kleer CG, Giordano TJ, Braun T, Oberman HA. Pathologic, immunohistochemical, and molecular features of benign and malignant phyllodes tumors of the breast. *Mod Pathol*. 2001;14(3):185–190.
- Shpitz B, Bomstein Y, Sternberg A, et al. Immunoreactivity of p53, Ki-67, and c-erbB-2 in phyllodes tumors of the breast in correlation with clinical and morphologic features. *J Surg Oncol*. 2002;79(2):86–92.
- Tan WJ, Thike AA, Bay BH, Tan PH. Immunohistochemical expression of homeoproteins Six1 and Pax3 in breast phyllodes tumours correlates with histological grade and clinical outcome. *Histopathology*. 2014;64(6):807–817.

44. Jones AM, Mitter R, Poulson R, et al. mRNA expression profiling of phyllodes tumours of the breast: identification of genes important in the development of borderline and malignant phyllodes tumours. *J Pathol.* 2008; 216(4):408–417.
45. Lae M, Vincent-Salomon A, Savignoni A, et al. Phyllodes tumors of the breast segregate in two groups according to genetic criteria. *Mod Pathol.* 2007; 20(4):435–444.
46. Jones AM, Mitter R, Springall R, et al. A comprehensive genetic profile of phyllodes tumours of the breast detects important mutations, intra-tumoral genetic heterogeneity and new genetic changes on recurrence. *J Pathol.* 2008; 214(5):533–544.
47. Lv S, Niu Y, Wei L, Liu Q, Wang X, Chen Y. Chromosomal aberrations and genetic relations in benign, borderline and malignant phyllodes tumors of the breast: a comparative genomic hybridization study. *Breast Cancer Res Treat.* 2008;112(3):411–418.
48. Lu YJ, Birdsall S, Osin P, Gusterson B, Shipley J. Phyllodes tumors of the breast analyzed by comparative genomic hybridization and association of increased 1q copy number with stromal overgrowth and recurrence. *Genes Chromosomes Cancer.* 1997;20(3):275–281.
49. Vidal M, Peg V, Galvan P, et al. Gene expression-based classifications of fibroadenomas and phyllodes tumours of the breast. *Mol Oncol.* 2015;9(6):1081–1090.
50. Lin JJ, Huang CS, Yu J, et al. Malignant phyllodes tumors display mesenchymal stem cell features and aldehyde dehydrogenase/disialoganglioside identify their tumor stem cells. *Breast Cancer Res.* 2014;16(2):R29.
51. Ng CC, Tan J, Ong CK, et al. MED12 is frequently mutated in breast phyllodes tumours: a study of 112 cases. *J Clin Pathol.* 2015;68(9):685–691.
52. Cani AK, Hovelson DH, McDaniel AS, et al. Next-gen sequencing exposes frequent MED12 mutations and actionable therapeutic targets in phyllodes tumors. *Mol Cancer Res.* 2015;13(4):613–619.
53. Kersting C, Kuijper A, Schmidt H, et al. Amplifications of the epidermal growth factor receptor gene (*egfr*) are common in phyllodes tumors of the breast and are associated with tumor progression. *Lab Invest.* 2006;86(1):54–61.