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Review Article

Phyllodes Tumor of the Breast

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Abstract...

A phyllodes tumors (PT) of the breast is type of fibroepithelial lesions that accounts for 1% of all breast tumors. Based on histological grading, PTs are classified into three groups by histological grading: benign, borderline and malignant, with grade considered to be associated with prognosis. In immunohistochemistry findings, Ki-67, p53, Rb, and survivin are useful markers for grading of PTs, and it may be prognostic factors, especially when there is difficulty with differentiating benign from malignant. Although presently there is no known definitive molecular feature for diagnosis of PT, molecular analysis could be helpful as well for grading. Method of a diagnosis of PT including grading of PT. The present study reviewed use of morphology, immunohistochemistry, and molecular analysis in PT cases for diagnosis including grading.

Keywords: Phyllodes tumor; Grade; Immunohistochemistry; Molecular analysis.

Abbreviations: PT: Phyllodes tumor; HPF: High-power field.

Introduction

A phyllodes tumor (PT) of the breast is a rare type of fibroepithelial lesion accounting for 1% of all breast tumors [1]. Although PTs have a morphological resemblance to the intracanalicular fibroadenoma at the benign end of the spectrum, that are classified based on histological results, as benign, borderline, or malignant, with prognosis differing among those. We occasionally encounter cases for which a diagnosis of PT or histological grade cannot be established. The present study presents pathological features of PTs and also provides a review of immunohistochemical and molecular markers for classification of these tumors. In addition, autopsy findings of a case of malignant PT with a history of benign PT 15 years prior are presented.

General presentation

PTs accounts for less than 1% of all primary tumors of the breast [2]. PT occur predominantly in older women (average age: 40-50 years), approximately 15-20 years later than fibro-

adenoma occurrence [2]. A malignant PT develops on average 2-5 years later than a benign tumor. That study also noted that this type of tumor is essentially a circumscribed fibroepithelial neoplasm that show a prominent intracanalicular architectural pattern with leaf-like stroma fronds, capped by luminal epithelial and myoepithelial cell layers, and accompanied by stromal hypercellularity [2].

Pathology

According to the World Health Organization classification, a PT is diagnosed when the fibroepithelial architecture shows an exaggerated intracanalicular pattern with leaf-like frons protruding into cystically dilated spaces accompanied by stromal hypercellularity. PTs are classified into three groups on histological grading, benign, borderline and malignant PT [2]. As compared with a fibroadenoma, a benign PT shows mildly increased stromal cellularity along with minimal nuclear atypia and pushing borders, with number of mitoses of ≤4/10 high-power fields (HPFs). Stromal overgrowth, defined as the presence of stroma without epithelium in at least one low-power field when observed with a 4x objective microscope object is not present. In the absence of well-developed stromal fronds, the presence of elongated, branching and cleft-like ducts meandering through the cellular stroma, presenting a staghorn appearance, suggest a diagnosis of PT [2].

Borderline PTs show no obvious malignant features, as they may have a circumscribed or a focally invasive border, and frequent mitoses atypia. Stromal overgrowth is usually absent. Histologically, moderate stromal cellularity, nuclear atypia, and a focal infiltrative border are features that can be seen in both benign and borderline PTs [2,3]. The mitotic activity of those tumors classified as borderline is 5-9/10 HPFs.

A malignant PT shows marked stromal cellularity and atypia, and permeative margins, along with mitotic activity of at least 10/10 HPFs. Stromal overgrowth is usually easily identified. Commonly known histological parameters include the nature of the tumor edge, stromal overgrowth, mitotic activity, and cellular atypia [2,4]. While the tumor edge, stromal overgrowth, and cellular atypia are obscure findings, mitotic number is definitive.

Grading of phyllodes tumor

Immunohistochemistry

PTs histological grade is associated with prognosis [5]. The markers described following may be useful as prognostic factors, when difficulties between benign PT and malignant are encountered.

Control of cell cycling and proliferation is critical for the development of neoplasia, and those play roles in the pathogenesis of a PT. Immunohistochemical expression is associated with the histological grade. Expressions of stromal nuclear and cytoplasmic p16, stromal and epithelial pRb, stromal and epithelial Ki-67 markers, as well as stromal survivin show significant increases in association with increased tumor grade [6-8].

p16 is a cyclin-dependent kinase inhibitor that has an inhibitory effects on progression through the G1 transition checkpoint and on cell cycling. The stroma in high-grade PTs may have gained other alternations in the G1/S transition checkpoint markers to bypass the inhibition generally caused by the action of apparently elevated p16 levels. Alternatively, elevated stromal p16 in a higher grade PT may reflect compensatory attempts by cells in response to other abnormalities, thus appropriately driving the cell cycle inappropriately [7].

Increased levels of pRb in a malignant tumor may could reflect increased hyperphosphorylated and inactive pRb, and/or mutant/inactive pRb. Alternatively, similar to p16, the elevated pRb in a higher-grade PT could be the result of compensatory attempts by the cell respond to other abnormalities and inappropriate alter the cell cycle [7].

An increasing tumor grade of a PT is associated with increased Ki-67 expression including both stromal and epithelial Ki67 counts [6,7]. An increase in epithelial proliferation in higher-grade tumors could be interpreted as evidence showing that the epithelial component of a PT is not a passive bystander or simply entrapped elements, and may indicate a role for the epithelium in the characteristic stromal proliferation seen in these tumors. Proliferating epithelium might be an attempt to keep the proliferation of stroma in check. Alternatively, the epithelium could be responding to the paracrine signals derived from or the result of stromal proliferation [6,7].

P53 expression has been noted in 66.6% of malignant, 50% of borderline and 8.3% of benign PTs. As seen with Ki-67, the level of expression differs between the malignant/borderline and benign groups [6].

Survivin is expressed in the nucleus and/or cytoplasm of cells in a variety of malignant tumors. In the nucleus, it interacts with aurora kinase B and the inner centromere protein to complete mitosis. Stromal cells in a malignant a PTs show more extensive expression of nuclear surviving than stromal cells in a benign PT [8].

Molecular analysis

Some reports of molecular analysis performed for diagnosis of PT, including grading and differentiation from a fibroadenoma or other type of spindle cell tumor, as well as selection of target therapy have been presented [9-14]. Although no definitive diagnostic molecular feature has been demonstrated, the molecular analysis can be helpful for diagnosis of PT including grading.

MED12 is an X-linked gene encoding for the mediator complex subunit 12, which is associated with transcription factors that recruit the mediator complex and influence target gene expression. MED12 mutations have also subsequently been found in PTs, and shown to occur at a higher frequency in fibro adenomas as well as PTs with a lower as compared to a higher grade [9].

TERT encodes the catalytic domain of the human telomerase reverse transcriptase gene, and plays a role in cellular senescence and immortality due to its effects on telomere length. Telomere lengthening avoids cellular senescence and telomerase expression is a hallmark finding indicating cancer. TERT promoter mutation in PTs is associated with MED12 mutation, suggesting that these interact in the pathogenesis of development of these tumors [9,14]. Anne et al reported that benign PTs showed none or a few chromosome changes, while malig-

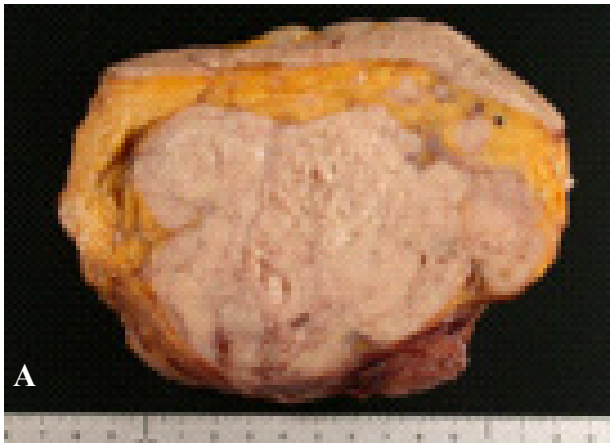
nant PTs showed none or a few chromosomal changes, while malignant PTs had numerous recurrent chromosomal changes, in particular 1q gain and 13q loss[11] .

Prognosis

The rate of recurrence rates of a benign PT ranges from 10-17%, while that for borderline and malignant cases is 14-25% and 23-30% for benign, respectively [2]. As for PT metastasis, the report by Chaney is the only one presented, which described that distant metastasis were reported to occur in 1.7%, 0%, and 26.7% of benign, borderline and malignant tumor cases, respectively [15]. Although no pathological details of these unusual cases of metastatic benign PT were provided, it is very interesting to note that metastasis of a benign PT occurred in some patients. Roa [5] reported that presence of pain, postmenopausal status, heavy cellular pleomorphism, high mitotic activity, tumor grade and metastasis were prognostic factors related to poor survival [5], while as the prognostic factors, marked cytological atypia and heterogenous differentiation were significantly correlated with PT-related relapse-free survival [4].

Case presentation

A 70-year-old female underwent the tumor excision under diagnosis of benign PT about 15 years ago. The patient was readmitted 15 years later because of the recurrence, and she underwent a mastectomy, with the resected specimen shown as a white-grayish, solid mass, sized 13 X 10 cm (Figure 1A). Histo-



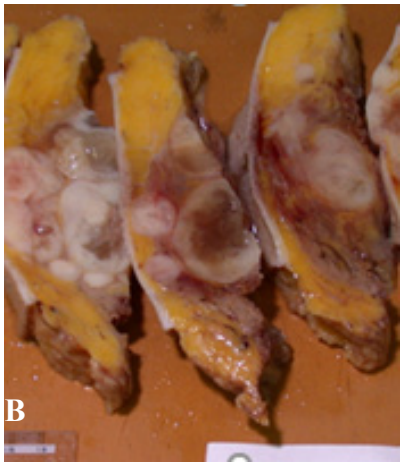


Figure 1: Macroscopic appearance
(A) Resected specimen from initial surgery, a white-grayish, solid mass, sized 13 X 10 cm.
(B) Resected specimen following recurrence tumor, a solid bulging mass with hemorrhage and necrosis, sized 15 X 10 cm.

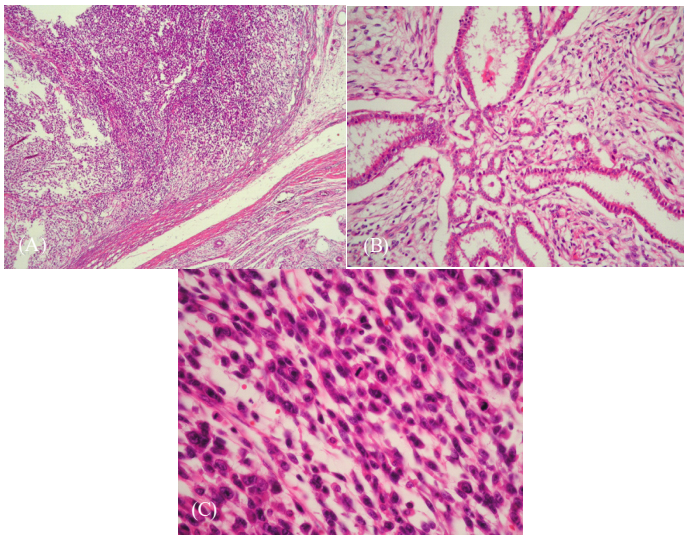


Figure 2: Histological features.
(A) The tumor was composed of a benign epithelial component and cellular spindle cell stroma.
(B) Benign epithelial components were seen lining the luminal aspect, with myoepithelial cells beneath them
(C) Stromal cells showing marked nuclear pleomorphism.

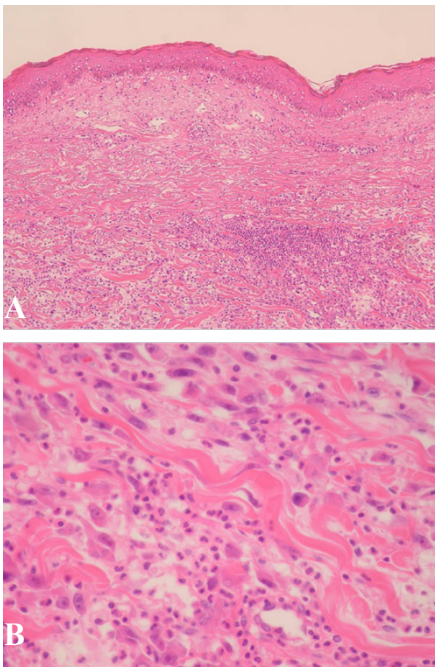


Figure 3: Histological features of recurrent tumor.
Proliferation of neoplastic oval cells with nuclear pleomorphism in the dermis, without epithelia an l component. **(A)** Low power field. **(B)** High power field.

logical results showed the mass to be composed of a benign epithelial component and a cellular, spindle cell stroma containing slit-like spaces (Figure 2A). Benign epithelial components were found lining luminal aspect, with myoepithelial cells beneath them (Figure 2B). Stromal cells had marked nuclear pleomorphism, and the mitotic count was 12/10 High power field (HPF) (Figure 2C). These findings led to a diagnosis of malignant PT.

One month later, the tumor recurred, and the patient underwent a tumorectomy with chest wall resection. The resected specimen was a solid, bulging mass with hemorrhage and necrosis, and sized 15 X 10 cm (Figure 1B). Histological features included proliferation of neoplastic oval cells with nuclear pleomorphism in the dermis, without an epithelial component. The mitotic count was 12/HPF (Figure 3A,3B). Therefore, metastases were found in vertebrae portions by computed tomography scanning. Although radiation therapy was added, the patient died. Autopsy findings revealed metastases in both lungs, as well as uterine body and a mediastinal lymphnode.

Conclusion

This review provide details regarding histological morphology, immunohistochemistry and molecular analysis for diagnosis of PT, as well as grading, which may be associated with prognosis. In addition, findings of an autopsy case of malignant PT in a patient who was initially presented with a benign PT 15 years prior are provide.

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