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CASE REPORT

Malignant transformation of phyllodes tumor: a case report and review of literature

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Key Clinical Message

Malignant phyllodes may transform from benign phyllodes; low-aggressive malignant phyllodes tumor is manageable by locally wide excision.

Keywords

Fibroepithelial lesions, fibroepithelial tumors, giant fibroadenoma, juvenile fibroadenoma, malignant transformation, phyllodes tumor, recurrent tumors.

Introduction

The transformation of a benign phyllodes tumor into a malignant phyllodes tumor is very uncommon and unpredictable. We report a case of a 54-year-old woman with postlocal excision proven benign phyllodes tumor that transformed into a malignant phyllodes tumor after 36 months of surgery. We present the ultrasound and mammography images and the pathology slides of the surgical wide excision specimen. It has been suggested that mutation of residual tumor cells caused the malignant transformation. Complete surgical excision with adequate margin is essential to decrease the risk of recurrence and the malignant transformation of phyllodes tumors.

Phyllodes tumors are rare fibroepithelial breast tumors and are found in approximately 1% of primary breast tumors [1, 2]. Phyllodes tumors are initially described as "cystosarcoma phyllodes" by Johannes Müller in 1838 [3], and these tumors have as many as 62 different synonyms [3]. Phyllodes tumor's structural pathology is similar to fibroadenoma; however, phyllodes tumors have an increased stromal hypercellularity with typical leaflike projection from histopathology [2].

The size of the tumor that has been reported ranged from 1 to 40 cm [4]. Approximately 20% of patients had a mass larger than 10 cm [5]. Triple assessment, that is, clinical, radiological, and histological examination, forms the fundamental basic evaluation for such lesions. The diagnosis of phyllodes tumor is based on the criteria defined by the World Health Organization in 2003, and this includes the degree of stromal hypercellularity, mitoses, cytologic atypia, stromal overgrowth, and the nature of the tumor border. The WHO classification distinguished phyllodes tumor into three histological subtypes: benign, borderline, and malignant [2], which account for 58.4–74.6%, 15.0–16.1%, and 9.3–31% of all phyllodes tumors, respectively [6–8].The behavior is unpredictable, and the distinction between benign, borderline, and malignant tumors is often difficult and does not always reflect the clinical behavior [9]. The mainstay treatment of phyllodes tumor is surgery, with an adequate

margin of at least 1 cm [10]. In some cases where the mass was large, immediate reconstruction was required to improve the cosmetic outcome [10, 11].

The prognosis of phyllodes tumor is quite good. In a retrospective study of 101 patients treated between 1944 and 1998, the overall survival rate of patients with benign and borderline tumors was 91% at 5 years. The five-year survival rate for malignant phyllodes tumors was 82% [12].

To date, the local recurrence rate in phyllodes tumor is approximately 15% [13–15]. Local recurrence usually occurs within the first few years following surgery, especially if it was with incomplete excision [7]. Tumors typically recur locally within 2 years of initial excision [16]. Approximately 15% have a propensity to recur locally and about 10% chance of distant recurrence [16].

Malignant transformation of phyllodes tumor is a very rare form of breast cancer. Only some reports show malignant transformation from a benign phyllodes tumor [13, 17–20]. We report one case of a benign phyllodes tumor that transformed into a malignant phyllodes tumor during its recurrence.

Case Report

A 54-year-old female presented to a private hospital in Bangkok, Thailand, in October 2015 with a 3-cm lump in her left breast. Her mammogram in October 2015 showed a mass at the upper outer quadrant of the left breast without calcification (Fig. 1). A focused ultrasound revealed a shaggy border mass size 2.5 cm. Core needle biopsy was performed, and the histopathological report was spindle cell lesion. The mass was excised in October 2015. Gross examination revealed an ill-defined firm gray-white mass, measuring 2.8 × 2.4 × 2.2 cm, close to resection margin. Microscopic examination showed a relatively circumscribed fibroepithelial lesion with stromal expansion. Multifoci of infiltration into the surrounding adipocytes and entrapment of normal mammary lobule were also noted. The stroma showed moderate hypercellularity and moderate nuclear atypia. No stromal overgrowth was detected. The margin displayed small tumor buds protruding into the surrounding tissue. Mitotic count is 2/10 high power field (HPF) (Fig. 2). The final pathological reported was benign phyllodes tumor. The result of molecular study was CD34 negative, CD117 positive, p53 weak-to-moderate staining in approximately 50%, Ki67 = 3%, EGFR moderate membranous straining in approximately 60%, Beta-catenin no nuclear staining, Bcl2 positive in few cell (<1%), and ER negative.

In April 2017, she revisited the hospital due to a rapidly growing mass at the site of prior excision for 3 month. On physical examination, the patient was found to have a 7-cm firm mobile mass in the 2 o'clock position of the left breast without evidence of any lymphadenopathy. Mammogram in April 2017 showed a large lobulated mass at the upper outer quadrant of the left breast (Fig. 3). A focused breast ultrasound also showed a large lobulated solid-cystic mass at the surgical bed (8.3 × 5.9 × 7.2 cm in size). We review the previous histopathology specimen from 2015, and our pathologist suggested that it could have been borderline instead of benign phyllodes tumor. The patient underwent wide local excision with wedging of pectoralis major muscle. Pathology revealed phyllodes tumor 7.5 cm in maximum diameter, invading the pectoralis major muscle with free all margins at least 1 cm. The tumor showed moderate-to-marked stromal hypercellularity, moderate-to-marked stromal atypia, focal ill-defined border, prominent stromal overgrowth, and mitotic count 5/10 HPF (Fig. 4). The final pathological reported this time is malignant phyllodes tumor. The result of molecular study was CD34 negative, CD117 negative, p53 moderate-to-strong staining in approximately 80%, Ki67 = 7%, EGFR moderate membranous straining in approximately 60%, Beta-catenin no nuclear staining, Bcl2 negative, and ER negative.

Discussion

Local excision with close margin is the treatment for most women diagnosed with benign phyllodes in order to preserve the breast parenchyma. Therefore, some residual tumor cells may still remain. It had been suggested that mutation of residual benign phyllodes tumor cell caused malignant transformation [21]. Generally, recurrent tumors are histologically similar to the primary tumors, but they are often more cellular, with focal area of atypical cell [21]. It is important that clinicians are aware that not only benign phyllodes tumor may recur but the recurrences will also occasionally show sufficient atypia to warrant the diagnosis of malignant phyllodes tumor [21]. In our case, the tumor recurred with increased degree of stromal atypia, stromal cellularity, mitotic count, and prominent stromal overgrowth.

Fibroepithelial tumors of breast, including fibroadenoma and phyllodes tumor, are biphasic neoplasms characterized by proliferation of both epithelial and stromal components. Phyllodes tumor of various grades shares some overlapping morphology, but they are significantly different in clinicopathologic features and clinical behavior [22] (Table 1). In our case, the clinicopathologic features of the primary tumor include moderate stromal hypercellularity, moderate stromal atypia, focally ill-defined border, no stromal overgrowth, and a mitotic count of 2/10 HPF. These findings are compatible with those of benign-to-borderline phyllodes tumor. The clinicopathologic features of the recurrent tumor include

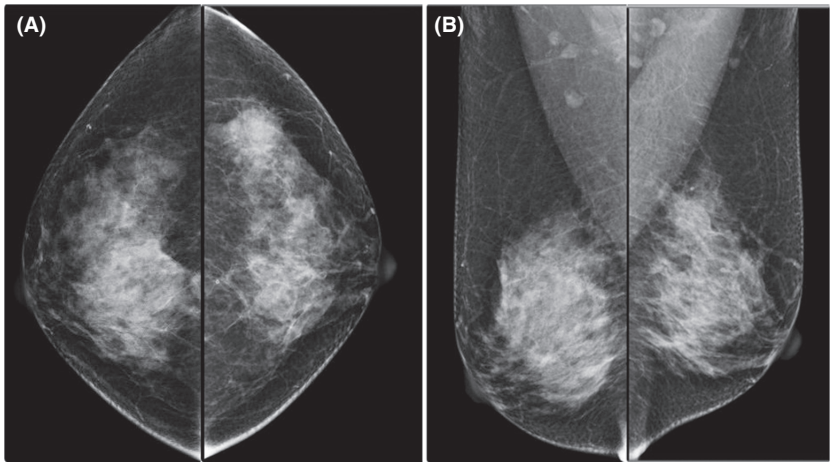

Figure 1. Mammogram in October 2015 (A, CC view; B, MLO view), demonstrating a mass shadow in left upper outer quadrant without calcification.

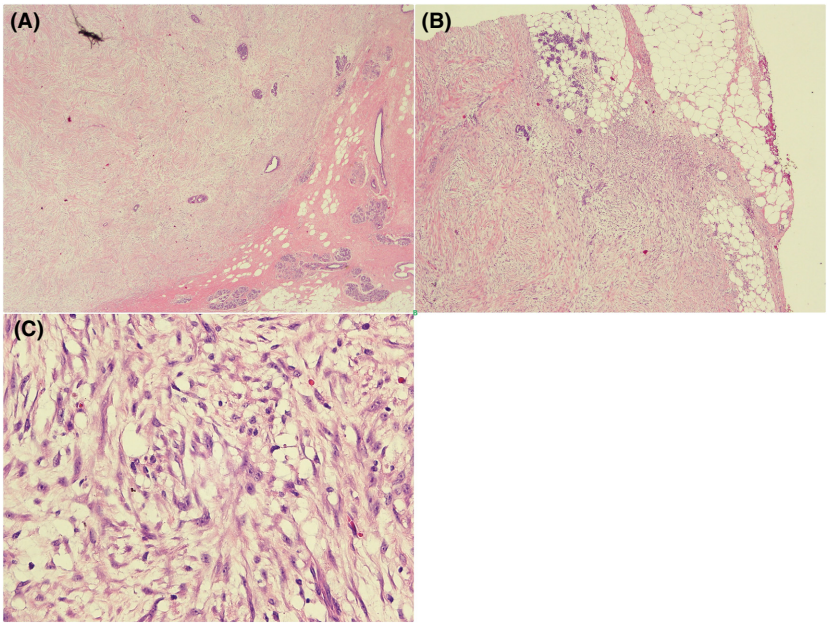

Figure 2. Histology slide from October 2015 showed. (A) Relatively circumscribed fibroepithelial lesion with stromal expansion (H&E, 4). (B) Infiltration into the surrounding adipocytes (H&E, 10). (C) The stroma shows moderate hypercellularity and moderate atypia (H&E, 400).

moderate-to-marked stromal hypercellularity, moderate-to-marked stromal atypia, focally ill-defined border, prominent stromal overgrowth, and a mitotic count of 5/10 HPF which is mostly compatible with the diagnosis of malignant phyllodes.

Some studies had described the mechanism of malignant transformation [23, 24]. A clonal analysis of phyllodes tumors showed that it consists of polyclonal epithelial cells and monoclonal stromal cells. The stromal cellularity of phyllodes tumor with high malignant potential increases, and its epithelial cellularity decreases as the size of tumor increases. Therefore, phyllodes tumor can be regarded as stromal cells neoplasm. A single stromal cell can undergo mutation and develops into a malignant phyllodes tumor composed mainly of monoclonal stomal cells and partially of polyclonal epithelial cells [23, 24]. In our case, the tumor was composed of both epithelial and stromal cells, but mainly of stromal cells.

Molecular profile of the tumor may help in evaluating malignant transformation. In benign phyllodes tumors,

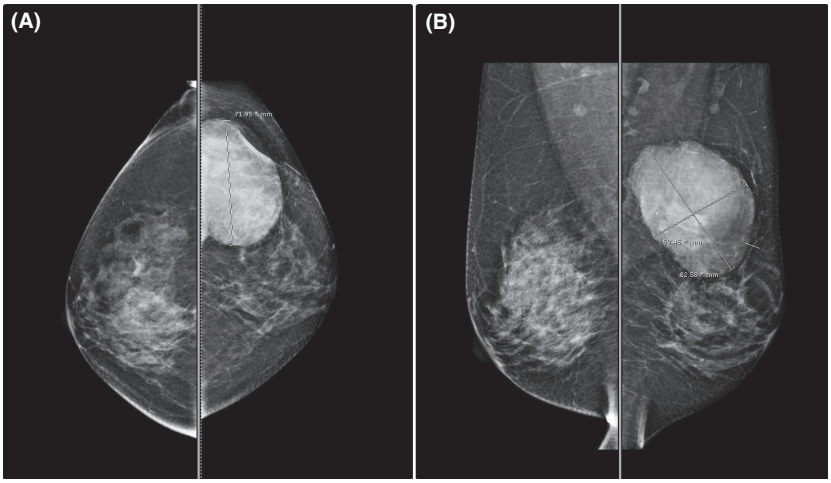

Figure 3. Mammogram in April 2017 (A, CC view; B, MLO view), demonstrating a large lobulated mass at upper outer quadrant of the left breast, 8.3 × 5.9 × 7.2 cm in size corresponding to the palpable mass.

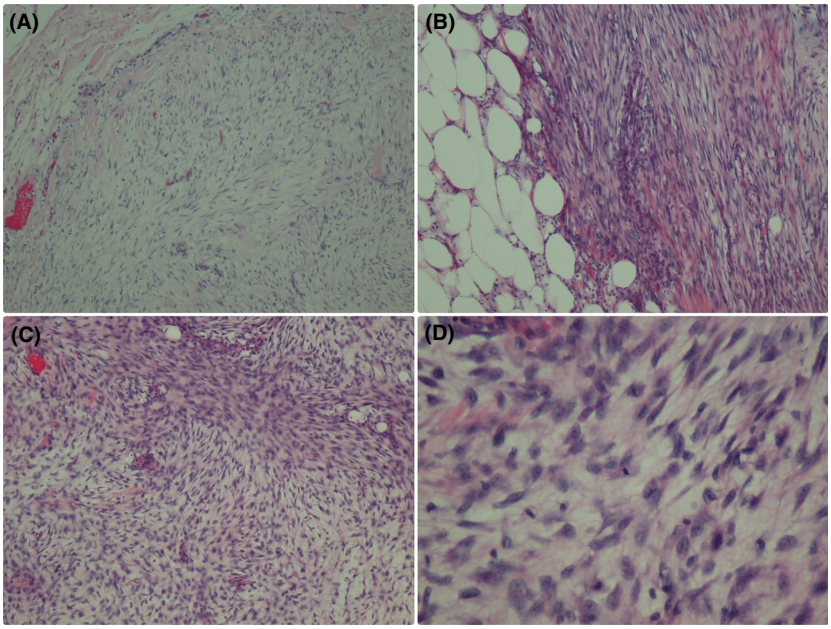

Figure 4. Histology slide from April 2017 showed. (A) Stromal overgrowth (H&E, 4). (B) Infiltration into the surrounding adipocytes (H&E, 10). (C) Moderate-to-marked stromal hypercellularity, moderate-to-marked stromal atypia, and increased mitotic figures (H&E, 40). (D) Moderate-to-marked stromal hypercellularity, moderate-to-marked stromal atypia, and increased mitotic figures (H&E, 400).

the presence of mitotic figures within the periductal stroma was opposed to stroma away from the epithelium. It is believed that the growth of tumor comes from the epithelial–stromal interaction process including Wnt-APC-Beta-catenin pathway and Estrogen receptor pathway [25]. Molecular studies have shown that the increase in the expression of Beta-catenin or estrogen receptor is associated with benign phyllodes tumors, but if there is a decrease in the expression, it is associated with malignant phyllodes tumors [26, 27]. In our study, both Beta-catenin and estrogen receptor were negative for both the primary and the recurrence tumors. In our study, bcl-2 is an inner mitochondrial membrane protein that inhibits apoptosis [28]. It was first recognized in follicular lymphoma in which a 14;18 translocation results in overexpression of bcl-2 [29], and expression was subsequently shown in other types of lymphoma and in some normal lymphocytes [30]. bcl-2 expression is associated with

Table 1. Clinicopathologic features of benign, borderline, and malignant phyllodes tumor.

Clinicopathologic features	Benign	Borderline	Malignant
Mitoses/10HPF	1–3	4–9	≥10
Cellularity	Modest	Modest	Mark
Pleomorphism	Little	Moderate	Mark
Border	Pushing	Intermediate	Infiltrating
Stroma	Uniform	Heterogeneous	Overgrowth
Ki67 index	Low	Intermediate	High

epithelium that undergoes hyperplasia and atrophy usually under hormonal control including breast and prostate. In the normal breast and benign phyllodes tumor, there were strong staining of lymphocytes and moderate-to-strong staining of normal epithelium [30]. In the one studied: 26 phyllodes tumors (15 benign, 4 borderline, 9 and 7 malignant), there was less bcl-2 expression in malignant (median 1.5%) than in benign and borderline phyllodes tumors [31]. In our study, bcl-2 was positive in few cell (<1%) in primary tumor and negative in recurrence tumor.

In malignant phyllodes tumor, the growth depends on the stromal component, which is molecular profile, and gene mutation like other types of cancer includes p53, Ki67, CD117 (c-kit), EGFR, and CD34.

P53

The p53 is a product of a tumor suppressor gene, located on chromosome 17p13.1 [32]. Its mutations are one of the most common genetic abnormalities in cancer, for which it is deemed a useful prognostic predictor, and its mutant forms are reflected by increased p53 staining on immunohistochemistry [32]. Stromal p53 expression has almost consistently been reported to increase significantly with malignant phyllodes tumor [33], which is represented mainly by stromal hypercellularity and overgrowth [32]. No study reported any correlation with recurrent disease [32, 33]. The significant increase in p53 expression would mostly be between benign phyllodes tumors and borderline-to-malignant tumors, with no significant difference in the latter two categories [32, 34]. In our study, p53 was weak-to-moderate staining in approximately 50% in primary tumor and moderate-to-strong staining in approximately 80% in recurrence tumor.

Ki-67

The nuclear protein Ki-67 is a cell proliferation marker expressed only in cycling cells. As a result, quantitative assessment of Ki-67 nuclear staining on tumor samples provides a good estimate of the proliferation index of individual tumors. Ki-67 index increased in borderline and especially in malignant PTs [35]. Ki-67-labeling indices have ranged from 1.3% to 4.7%, 6% to 26%, and 12% to 50%, for benign, borderline, and malignant phyllodes tumors, respectively [36]. Ki-67 proliferation index has been significantly correlated with disease-free and overall survival rates [37]. In our study, Ki67 was 3% in primary tumor and 7% in recurrence tumor.

CD117 (c-kit)

CD117 is a transmembrane protein of the type III receptor tyrosine kinase family. It is crucial in regulating cell survival, proliferation, and differentiation. It is recognized as a protooncogene with frequent activating mutations and/or overexpression in several types of neoplasms, including gastrointestinal stromal tumors, seminomas, melanomas, and hematopoietic malignancies. CD117 has thus been considered another possible contributor to stromal proliferation in the phyllodes tumors [32, 33, 38, 39] presumably participating in the process of cell cycle progression, and synergistic with p53 protein, with which its immunohistostaining has also been significantly correlated [32, 38, 40]. In other studies found, there is no association between CD117 expression and tumor grade, and furthermore, KIT-activating mutations have not been found in PTs [41–43]. In our study, CD117 was positive in primary tumor and negative in recurrence tumor.

CD34

CD34 is a type I transmembrane glycoprotein expressed on hemopoietic stem and progenitor cells, endothelial cells, and a subset of fibroblast and bone marrow progenitor cells, and is expressed in many mesenchymal tumors. CD34 coexists with c-kit in GIST and its possible coexistence with c-kit in phyllodes tumors [40]. In one study, it has shown that CD34 expression in 8 of 12 malignant tumors and only one in benign tumor [40]. Just like p53, Ki-67, and c-kit, the ability of CD34 to predict outcome,

Table 2. Correlations of molecular profile changes in the progression of malignant phyllodes tumors.

Increase expression	Decrease expression
p53	Bcl2
CD34	Estrogen receptor
EGFR	Beta-catenin
c-kit	
Ki67	

however, was also described as questionable [40]. In our study, CD34 was negative in both primary tumor and recurrence tumor.

EGFR

Epidermal growth factor receptor (EGFR) is said to mediate tumor formation and progression pathways intracellularly, via ras-activated mitogen-activated protein kinase, phosphatidylinositol 3-kinase/AKT, and phospholipase C pathways that modulate cell motility, adhesion, and proliferation [44]. EGFR was further associated with stromal cellularity and overgrowth, nuclear pleomorphism, mitosis, infiltrative margins, and size [45]. Immunopositivity for EGFR in the stromal cells was detected in 19% of 58 phyllodes tumors (75% of all malignant tumors) [46]. In our study, EGFR was moderate membranous straining in approximately 60% in both primary tumor and recurrence tumor. Conclusion of molecular profile of malignant transformation of phyllodes tumor is shown in Table 2.

The treatment of phyllodes tumor is local excision to obtain adequate margin. According to most studies, the margin at least 1 cm is considered adequate. The most evidence comes from retrospective studies [5, 12, 14, 47]. If inadequate margin after resection, about 20% of the phyllodes tumor will be local recurrence and may be lead to malignant transformation [48]. According to the NCCN guideline, a margin 1 cm or more is considered adequate and does not relate to the histology subtype of phyllodes [49]. In our study, the primary tumor was close resection margin after excised in October 2015. It may be the cause of local recurrence and malignant transformation.

Phyllodes tumors, that are local recurrence after excision. The treatment is re-excision if it is possible to achieve an adequate margin of 1 cm and acceptable cosmetic outcome. However, if the surgery affects the cosmetic outcome, mastectomy should be considered [49]. In some cases, that mastectomy cannot cover the defect. The another option may be considered including skin graft, local flap, pedicle flap, or free flap to close the defect [10]. In our study, the recurrence tumor was cleared free all margins at least 1 cm after wide local excision with wedging of pectoralis major muscle in April 2017**.** In October 2017, this patient is not recurrence.

Conclusion

Based on the data from previous literature and the case presented in this paper, it can be concluded that benign or borderline phyllodes tumor can progress to malignant phyllodes tumor after local excision, as mutation of residual tumor cell is the source of malignant transformation. The most widely accepted theory is p53 mutation. Complete surgical excision with adequate margin is essential to decrease the risk of recurrence and malignant transformation of phyllodes tumors.

Conflict of Interest

None declared.

Authorship

SP: collected data, writing of the manuscript, literature review, submitted the manuscript for publication. PC: reviewed and recommended edits of the manuscript, supervised the whole study process, and approved the final manuscript. WP: revised pathologic images, data and interpretation molecular profile, supervised the whole study process, and approved the final manuscript. WV: revised the English version of the manuscript. PL, CS, YK, TS, and ML: supervised the whole study process and approved the final manuscript.

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