Phyllodes tumors of the breast in 2 sisters

Case report and review of literature

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1. Introduction

Phyllodes tumors (PT) are unusual neoplasms of the breast, accounting for <1% of breast tumors.[1] They are most commonly found in women aged 35 to 55 years.[2,3] These tumors are fibroepithelial neoplasms characterized by monoclonal neoplastic stromal cells and epithelial cells.[4] PT are classified as benign, borderline, and malignant based on cellularity of the stroma, the number of mitosis, and degree of stromal atypia.[5] PT are uncommon, with an estimated incidence of 1 in 100,000 women in the general population.[6] Most tumors are detected as a palpable mass, and tumor size at presentation is highly variable. Wide excision with clear margin is definitively primary treatment.[7,8] The prognosis of benign PT is favorable. Although local recurrence is more frequent in the borderline and malignant PT, local recurrence rates ranging from 15% to 20% are associated with positive excision margins. Malignant PT developed distant metastasis commonly with a rate <5% overall.[9,10] A review of literature suggested that genetic predisposition may be responsible for PT development, but the mechanisms still remain unclear.[11-14] Only 2 published studies have shown the association between family relatives and PT. Birch et al[15] reported that the germline TP53 mutations (Li-Fraumeni syndrome) were associated with malignant PT development. Foucar et al[16] reported that PT of the breast occurred in 2 first-degree relatives: mother and daughter. To our knowledge, this is the second reported case of PT in 2 first-degree relatives: 2 sisters, suggesting genetic predisposition may have a role in the risk of PT of the breast.

2. Case reports

2.1. Younger sister

A G3, P2 49-year-old woman presented to the West China Hospital, Sichuan University, for a 3-month history of palpable lump in the right breast. She denied other symptoms related to breast problem. She had negative personal or family history for breast cancer or ovarian cancer. On physical examination of the right breast, a firm and mobile mass measuring approximately 3 cm in diameter was identified in upper inner quadrant. There was no skin dimpling and no nipple change was present. No abnormal findings were detected on examination of the left breast, axillary fossa, and supraclavicular space.

Ultrasound of the right breast revealed a 3.6 \times 2.0 \times 3.9 \text{ cm} hypoechoic, ill circumscribed mass in the right breast (Fig. 1). An ultrasound-guided core needle biopsy showed fibroepithelial...
tumor with stromal cell hyperplasia. The patient underwent wide excision of the mass in the right breast. The result of intraoperative frozen section sampling was consistent with the pathology of core needle biopsy. Final histopathology revealed a malignant PT with liposarcoma component (Fig. 2). Immuno-histochemistry results are as following: P53 (+) for stromal cells (Fig. 3), CD 10 (+), Ki-67 (20%+), CD34 (+) for vascular endothelial cells, CD117 (+), CK 5/6 (+), P63 (+), Desmin (–), SMA (–), S-100 (–). Ten days after operation, the patient asked for a right mastectomy. Target area capture sequencing (by Genplus Technology, Beijing, China) showed low frequency mutation (0.7%) of CCND1 (Cyclin D1).

2.2. Elder sister

A G4, P3 51-year-old female presented to West China Hospital for 7-month history of palpable mass in the left breast. She did not have any other symptoms related to her breast. She did not have a personal or family history of cancer other than her younger sister’s diagnosis of malignant PT of the breast 10 days...
ago. Physical examination revealed a 3 cm lump in upper outer quadrant of the left breast without any nipple retraction or skin dimpling. Ultrasound revealed a well-circumscribed hypoechoic lesion measuring 3.0 × 2.5 × 2.6 cm with internal anechoic area in the left breast (Fig. 1). She underwent a wide excision with clear margin of the mass in the left breast, due to the result of intraoperative frozen section sampling which showed fibroepithelial tumor, prone to PT. Histopathology of the resected specimen revealed borderline PT (Fig. 2). The immunohistochemical analysis was as follows: P53 (−), SMA (+), Desmin (−), Myogenin (−), S-100 (−), P63 (−), and Ki-67 (5%) (+). Target area capture sequencing (by Geneplus Technology, Beijing, China) showed low frequency mutation (0.48%) of DNA methyltransferase 3 alpha (Dnmt3A).

After a follow-up of 23 months, no local or distant recurrence was observed. The study was approved by the ethics committee of the West China Hospital, Sichuan University, and written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

3. Discussion

Up to date, genetic risk factors for the PT of the breast are still under investigation. It has been reported that the genetic changes in chromosomal region of +1q, +5p, +7, +8, −9p, −10p, −6, and −13 correlated with borderline and malignant PT of the breast. Gene such as p16INK4a in malignant PT was associated with 9p deletion. MED12 exon 2 mutations may play a critical role in the pathogenesis of PT of the breast, except for a reported association between germline TP53 mutations (Li-Fraumeni syndrome) and malignant PT development in affected families. Tan et al reported that PT exhibited mutations in Filamin A (FLNA), SET domain containing 2 (SETD2), and histone-lysine N-methyltransferase 2D (KMT2D), suggesting a role in driving PT development. Borderline and malignant PT harbored additional mutations in cancer-associated genes, including TP53 and epidermal growth factor receptor (EGFR). All these findings suggested that genetic abnormalities might associate with PT of the breast. Foucar et al first reported PT of the breast in 2 first-degree relatives, mother and daughter. In addition, to our knowledge, our report is the first reported case of PT in 2 sisters. 1p21 Dnmt3A and CCND1 mutation in malignant and borderline PT in these 2 sisters. Dnmt3A encodes a DNA methyltransferase that is thought to function in de novo methylation. Somatic mutations of DNMT3A gene were recently reported in acute myelogenous leukemia, as well as other solid tumors such as lymphoma, gastric cancer, and lung cancer. Mutations, amplification, and overexpression of CNND1, which altered cell cycle progression, were observed frequently in a variety of tumors and may contribute to tumorigenesis. However, mutation of these 2 genes had not been reported in PT. Future genetic investigations should be done among more PT patients to confirm the genetic predisposition in the development of PT.

It has been documented that immunohistochemistry can distinguish benign, borderline from malignant. Previous studies showed the expression of p53 protein and Ki-67 was associated with the grading of PT. P53, known as a tumor suppressor gene, involves in regulation of the cell cycle, cell differentiation, and DNA repair. Niezabitowski et al observed 0% (0/23) borderline and 14% (6/42) malignant PT of the breast were >9% positive for p53. However, Kleer et al found no significant difference between p53 expression and the phyllodes grade. It has been shown that p53 was more likely to be positive in the stromal cells in aggressive PT of the breast. But other report showed that p53 was positive in epithelium but not stromal cells in 2 benign PT patients. In our cases, p53 was expressed in stromal cells of the patient with malignant PT, which was in concordance with Niezabitowski’s study.

Ki-67, a proliferation marker, has been studied among breast carcinomas as well as PT of the breast. It was reported that 85% malignant PT of the breast tended to be positive for Ki-67 expression >10%, but Ki-67 was positive only in 16% of benign PT. Kleer et al found a statistically significant difference in Ki-67 expression among benign, low-grade malignant, and high-grade malignant PT. In agreement with these results, we found that Ki-67 expression in the case of malignant and borderline PT was 20% versus 5%.

Because of the small sample size of our case report, it is hard to draw a conclusion that p53 or Ki-67 expression was correlated with PT malignancy. We need to collect more PT samples to make further genetic investigation and p53 and Ki-67 examination in our future work.

With regard to treatment of PT of the breast, surgical excision, including local excision, wide local excision and mastectomy, plays a critical role in the management of PT. It is recommended that wide local excision with surgical margins >1 cm was the primary approach because of the insufficient clearance of resection margins related to local recurrence. Mastectomy was indicated for larger tumors, recurrent tumors, and malignant PT. It is generally agreed that PT of the breast did not need axillary dissection, which can be explained by the low lymph node metastasis. Moreover, the effect of the adjuvant radiotherapy and chemotherapy remains unclear, which can be explained by the rarity of malignant PT and small number of those patients for adjuvant radiotherapy. Based on above statements, in our report, one case with borderline PT underwent wide local excision, and the other case with malignant PT was performed for mastectomy. Neither of the 2 patients received adjuvant radiotherapy or chemotherapy.

4. Conclusions

We reported 2 cases of PT of the breast in 2 sisters, which indicated that genetic factors might contribute to the risk of PT of the breast. Markers such as p53 and Ki-67 may have some correlation with PT malignancy. Further genetic investigations among first-degree relatives are required to confirm our speculation.

References

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